The life of advanced therapies: from academia to prescription

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CERTIFIQUEM:

Que la graduada Carolina Iglesias-Lopez ha dut a terme sota la nostra direcció de la Universitat Autònoma de Barcelona, el treball que, amb el títol *"La vida de les teràpies avançades: de l'academia a la prescripció"*, es presenta en aquesta memòria, la qual consisteix la seva Tesi per optar al grau de Doctor en Farmacologia.

I perquè en prengueu coneixement i tingui els efectes que corresponguin, presentem davant de l'Escola de Doctorat de la Universitat Autònoma de Barcelona l'esmentada Tesi, signada aquesta certificació a

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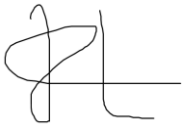
Alumna Carolina Iglesias-Lopez 

“It always seems impossible, *until it's done”*.

Nelson Mandela

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SUMMARY

Background: Advanced therapy medicinal products (ATMPs) are a medicinal class of products that contain recombinant nucleic acids or engineered cells and/or tissues. ATMPs comprise a category of innovative and complex biological products, constituting a fast-growing field and the future promise of medicine. To date, the introduction of ATMPs has made possible to cover unmet medical needs, potentially cure life-threatening diseases or significantly improve patient´s quality of life.

Objective: The aim of this work is to analyse the current development of ATMPs from three core pillars - regulatory, clinical and market access - to determine the particularities of this type of therapies, how the development challenges played a role in marketing authorisation and market access of these drugs, and how the field is moving forward. The analysis of these challenges at regulatory, clinical and market access level has allowed to: identify the causes of differences between regions regarding the definition and regulatory development of ATMPs, determine the quality and strength of clinical evidence associated with ATMPs authorization, and analyse the public national health authorities assessment procedures in several European countries and their subsequent reimbursement decisions.

Results: ATMPs are heterogenous class of products and a global harmonised classification framework would facilitate the development of these drugs. Half of the approved ATMPs obtained an orphan drug designation, mostly targeting serious conditions, unmet medical needs and paediatric populations. Flexibility on conventional regulatory requirements was implemented, and there is a trend toward an adaptive approach to licensing or a life-cycle approach. In general, the marketing authorisation application procedure was complex for most of the products approved and there was the need for an ad-hoc expert group consultation. The United States (US) had a shorter time of approval procedure than the European Union (EU). Development designations and expedited review processes were granted for these therapies in the EU, US and Japan. Twenty-three (23) main trials that supported the EU approval of seventeen (17) drugs were analysed. The pivotal studies of approved ATMPs were small, open-label, non-randomised, single-arm studies without control or using historical ones and assessing intermediate and single variables to evaluate the primary efficacy outcome. A total of fourteen (14) main trials to support the marketing authorisation for these therapies specifically developed in Japan (9) were also analysed. With a similar trend as in the EU, the pivotal studies that supported the product approval were based on small exploratory Phase I/II, uncontrolled,

single-arm trials. However, it was noted that more notable non-significant trends of efficacy and uncertain safety supported the approval of these drugs in Japan. The current landscape of the field shows that the hot spots of ATMP development are basically in terms of clinical and product´s quality development, where both are linked into each other. The majority of the ATMPs were reimbursed in the analysed countries, although complex and long negotiations were required. Managed entry agreements such as payment by results were essential to ensure market access. There is a divergent classification of added therapeutic value across the EU Member States. No major significant differences were found when the added therapeutic value for the approved ATMPs was compared among the eight (8) analysed countries (EU8), but there were differences in how the magnitude of the benefit was considered. The type of approval does not seem to have an influence on the reimbursement decision. The estimated incremental cost-effectiveness ratio among countries reveals high variability. Overall, the median time to reimbursement recommendation for the EU8 was in the range of 9-17 months.

Conclusions: Although EU, US, and Japan regulatory procedures may differ, the main regulatory milestones reached by the approved ATMPs are similar in these regions. Currently, most of ATMPs haven been authorized based on limited clinical evidence. Although uncertainties on added therapeutic value, most of approved ATMPs were reimbursed in the analysed European countries with managed entry agreements. More global regulatory convergence might further facilitate the current ATMP development, approval and reimbursement in these regions. In addition, more robust clinical designs and a more transparent and efficient economical assessments might raise patients' access of these therapies.

RESUMEN

Antecedentes: Los medicamentos de terapia avanzada (ATMP, por sus siglas en inglés) son una clase de productos medicinales que contienen ácidos nucleicos recombinantes o células y/o tejidos modificados genéticamente. Los ATMP comprenden una categoría de productos biológicos innovadores y complejos, que constituyen un campo de rápido crecimiento y la futura promesa de la medicina. Hasta la fecha, la introducción de los ATMP ha permitido cubrir necesidades médicas no satisfechas, curar potencialmente enfermedades mortales o mejorar significativamente la calidad de vida de los pacientes.

Objetivo: El objetivo de este trabajo es analizar el desarrollo actual de los ATMP a partir de tres pilares fundamentales: regulatorio, clínico y de acceso al mercado, para determinar las particularidades de desarrollo de este tipo de terapias, cómo los desafíos del desarrollo tuvieron un papel en la autorización de comercialización y el acceso al mercado de estas terapias, y cómo está avanzando el campo. El análisis de estos desafíos a nivel regulatorio, clínico y de acceso al mercado ha permitido: identificar las causas de las diferencias entre regiones en cuanto a la definición y desarrollo regulatorio de los ATMP, determinar la calidad y robustez de la evidencia clínica asociada a la autorización de estos productos, y analizar los procedimientos de evaluación de las autoridades sanitarias públicas nacionales en varios países europeos y sus posteriores decisiones de reembolso.

Resultados: Los ATMP son una clase heterogénea de productos y un marco de clasificación armonizado global facilitaría su desarrollo. La mitad de los ATMP aprobados obtuvieron una designación de medicamento huérfano, en su mayoría dirigidos a afecciones graves, necesidades médicas insatisfechas y poblaciones pediátricas. Se ha implementado flexibilidad en los requisitos reglamentarios convencionales y existe una tendencia hacia un enfoque adaptativo para la autorización de comercialización o un enfoque de ciclo de vida. En general, el procedimiento de solicitud de autorización de comercialización fue complejo para la mayoría de los productos aprobados y hubo la necesidad de una consulta de un grupo de expertos ad-hoc. Estados Unidos (EE.UU.) tuvo un tiempo de procedimiento de aprobación más corto que la Unión Europea (UE). Se otorgaron designaciones de desarrollo y procesos de revisión acelerados para estas terapias en la UE, EE.UU. y Japón. Se analizaron veintitrés (23) ensayos principales que apoyaron la aprobación en la UE de diecisiete (17) fármacos. Los estudios pivotales de los ATMP aprobados fueron estudios pequeños, abiertos, no aleatorizados, de un solo brazo sin control o que utilizaron estudios históricos y variables intermedias y únicas para

evaluar la variable principal de eficacia. También se analizaron un total de catorce (14) ensayos pivotales para respaldar la autorización de comercialización de estas terapias desarrolladas específicamente en Japón (9). Con una tendencia similar a la de la UE, los estudios fundamentales que respaldaron la aprobación del producto se basaron en pequeños ensayos exploratorios de Fase I/II, no controlados, de un solo brazo. Sin embargo, se observaron tendencias no significativas de eficacia y seguridad incierta para respaldar la aprobación en Japón. El panorama actual del campo muestra que los puntos calientes del desarrollo de los ATMP son básicamente en términos de desarrollo clínico y de calidad del producto, donde ambos están vinculados entre sí. La mayoría de los ATMP fueron reembolsados en los países analizados, aunque requirieron negociaciones largas y complejas. Los acuerdos de entrada gestionada, como el pago por resultados, fueron esenciales para garantizar el acceso al mercado de estas terapias. Existe una clasificación divergente del valor terapéutico añadido en los Estados miembros de la UE. No se encontraron grandes diferencias significativas al comparar el valor terapéutico añadido de los ATMP aprobados entre los ocho (8) países analizados (EU8), pero sí en cómo se considera la magnitud del beneficio. El tipo de aprobación no parece influir en la decisión de reembolso. La relación costo-efectividad incremental estimada entre países revela una alta variabilidad. En general, el tiempo promedio de recomendación de reembolso para la UE8 estuvo en el rango de 9 a 17 meses.

Conclusiones: Aunque los procedimientos regulatorios de la UE, EE. UU. y Japón pueden diferir, los principales hitos regulatorios alcanzados por los ATMP aprobados son similares en estas regiones. Actualmente, la mayoría de los ATMP han sido autorizados en base a una evidencia clínica limitada. A pesar de las incertidumbres sobre el valor terapéutico añadido, la mayoría de los ATMP aprobados fueron reembolsadas en los países europeos analizados con acuerdos de entrada gestionada. Una mayor convergencia regulatoria global podría facilitar aún más el actual desarrollo, aprobación y reembolso de los ATMP en estas regiones. Además, diseños clínicos más robustos y evaluaciones económicas más transparentes y eficientes podrían aumentar el acceso de los pacientes a estas terapias.

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I can't believe that this journey officially started in September 2018 and is now coming to an end. A journey of ~4.5 years, over 3,600 spent hours, ~ 400 written pages, over 70 versions to publish the 7 manuscripts, ~110 hours of meetings, ~626 hours of doctoral activities, and enormous personal sacrifice invested. But... what an experience and what a wonderful memory that will remain in my mind!

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DISCLOSURE OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The findings and conclusions in this article should not be construed to represent any agency determination or policy.

ABBREVIATIONS

ATMPs	Advanced therapy medicinal products
AA	Accelerate assessment
AAV	Adenovirus-associated virus
ADA	Adenosine deaminase
ADA- SCID	Severe combined immunodeficiency
ALL	Acute lymphocytic leukaemia
ARM	Alliance for Regenerative Medicine
ASGCT	American Society of Gene & Cell Therapy
ATMP	Advanced therapy medicinal products
ATU	Temporary Authorisation of Use
ATV	Product´s added therapeutic value
BLA	Biologics License Application
BSC	Best supportive care
CAR	Chimeric antigen receptor
CAs	Competent authorities
CAT	Committee for Advanced Therapies
cATMPs	Combined ATMPs
CAV	Clinical added value
CBER	Centre for Biologics Evaluation and Research
CE	European Conformity mark
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
COVID-19	Coronavirus disease 2019
CR	Complete response
CRISPR/Cas9	Clustered regularly interspaced short palindromic repeats associated to Cas protein 9
CT	Clinical trials
CTA	Clinical trial application
DLBCL	Relapsed or refractory diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EBE	European Biopharmaceutical Enterprises

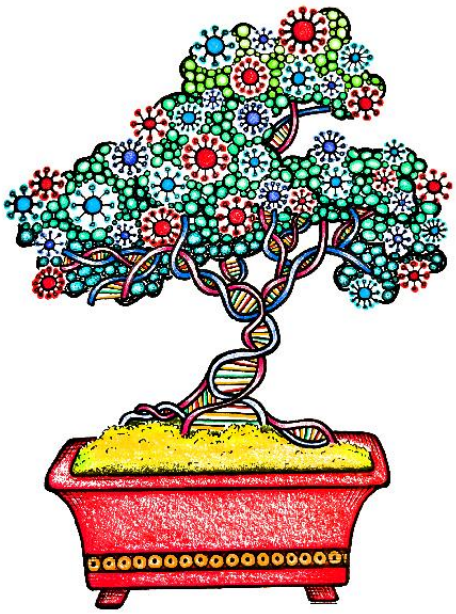
EBMT	European Blood and Marrow Transplant
EC	European Commission
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EP	Expedited programs designations
ERA	Environmental risk assessment
ESGCT	European Society of Gene Therapy
EU	European Union
EUnetHTA	European network for Health Technology Assessment
EuropaBio	European Association for Bioindustries
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
GMMs	Genetically modified micro-organisms
GMOs	Genetically modified organisms
GMP	Good Manufacturing Practices
GTMP	Gene therapy medicinal products
HCC	hepatocellular carcinoma
HCT/Ps	Human cells, tissues and cellular and tissue-based products
HIV	Human immunodeficiency virus
HMA	Heads of Medicines Agency
HRQoL	Health-related quality of life
HST	Highly Specialised Technology evaluation
HTAb	Health Technology Assessment bodies
HTAs	Health Technology Assessments
ICD-11	International Classification of Diseases 11th Revision
ICER	Incremental cost-effectiveness ratio
ICH	International Council for Harmonisation
IND	Investigational new drug
INTERACT	Initial Targeted Engagement for Regulatory Advice
IQR	Interquartile range
IQWiG	Germany's health technology appraisal institute
IRDiRC	The International Rare Diseases Research Consortium

ITF	Innovation Task Force
ITT	Intended to treat
LMO	Living modified organisms
LPL	Lipoprotein lipase
MA	Marketing authorization
MAA	Marketing authorisation application
MEAs	Managed entry agreements
MHLW	Ministry of Health, Labor and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intended to treat
mRNAs	Messenger ribonucleic acid
MVA	Modified vaccinia virus Ankara
NCAs	National Competent Authorities
NEPA	National Environmental Policy Act
NHAs	Competent national health authorities
NHI	National Institute of Health
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
OCTGT	Office of Cellular, Tissue and Gene Therapies
OCTP	Office of Cellular and Tissue-based Products
ODD	Orphan drug designation
ORR	Objective overall response rate
OS	Overall survival
OTAT	Office of Tissues and Advanced Therapies
OVRR	CBER/Office of Vaccines Research and Review
PACE	Patient and Clinician Engagement
PBO	Payment based on outcomes
PHSA	Public Health Services Act
PMD Act	Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act
PMDA	Japanese Pharmaceuticals and Devices Agency
PMS	Post-marketing clinical studies
PNCR	Paediatric Neuromuscular Clinical Research

PP	Per protocol set
pre-BLA	Pre-biological license applications
pre-IND	Pre-investigational new drug applications
PRIME	PRIority Medicines designation scheme
PRO	Patient-reported outcome
PROs	Patient-reported outcomes
QALY	Quality Adjusted Life Year
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
R&D	Research and development
RAC	Recombinant DNA Advisory Committee
RM Act	Safety of Regenerative Medicine
RMAT	Regenerative Medicine Advanced Therapy
RPs	Regenerative medicine products
RWE	Real-world evidence
SA	Scientific advice
SBB	Service Biosafety and Biotechnology
SCID-X1	X-linked severe combined immunodeficiency
SCT	Human somatic cell therapy
SCTMP	Somatic cell therapy medicinal products
SD	Standard deviation
siRNAs	Small interfering ribonucleic acid
SMA	Spinal muscular atrophy
SMC	Scottish Medicines Consortium
SNSA	Simultaneous scientific advice
SoC	Standard of care
SoHO	Substances of human origin
TALENs	Transcription activator-like effector nucleases
TEP	Tissue engineered products
TPP	Target product profile
US	United States of America
USDA	US Department of Agriculture
WHO	World Health Organisation

ZFNs	Zinc-finger nucleases

Chapter 1: Introduction



Long story short

Advanced therapy medicinal products (ATMPs) are a medicinal class of products that contain recombinant nucleic acids or engineered cells and/or tissues. ATMPs comprise a category of innovative and complex biological products, constituting a fast-growing field and the future promise of medicine. To date, the aim of ATMPs introduction into the market is to cover unmet medical needs, potentially cure life-threatening diseases or significantly improve patient´s quality of life. Given the potential observed with these therapies, many scientific efforts are focused on improving and promoting their development.

In the last decade, the first advanced therapies reached the market and several achievements have had to occur throughout history for this to happen. While deoxyribonucleic acid (DNA) was first identified in the late 1860s by Swiss chemist Friedrich Miescher [1], the concepts of gene therapy arose during the 1960s and early 1970s with the development of cell lines allowing to demonstrate that DNA could be introduced permanently into transformed mammalian cells [2]. In 1965, the journey of one of the most used viral vectors began – then adenovirus-associated virus (AAV) were discovered contaminating cultures of simian and human adenoviruses [3]. It was not until 1983 when Arun Srivastava completed the DNA sequencing of the AAV2 genome [3][4]. In 1968, Rogers and Pfuderer demonstrated that virus-mediated gene transfer was possible using tobacco mosaic virus as a vector vehicle [5]. Three years later, Berg's gene-splicing experiment resulted in the recombinant simian virus SV40 vector introducing genetic material into a mammalian cell [6]. In 1972, during this recombinant DNA era, Friedmann *et al*., posed the idea of "gene therapy", publishing in Science journal what is considered the foundational article in the ATMPs field under the heading "Gene therapy for human genetic disease?" [7].

In 1980, Martin Cline performed the first gene therapy attempt by infusing bone marrow cells from two patients with thalassemia after their transfection with plasmids containing human globin gene. Without clinical benefit to patients and the experiment being conducted without permission, the first gene therapy ethical debate was triggered [8][9][10]. In the late 1980s, an extensive regulatory process was then established, including the creation of the Recombinant DNA Advisory Committee (RAC) within the National Institute of Health (NIH) in the United States (US), to provide advice and oversight of research involving recombinant DNA

[10][11][12]. The RAC set guidelines for DNA research, as well as the review and approval of human gene therapy clinical protocols [13].

Human gene therapy clinical research officially commenced ten years later (1990) through viral vector delivery via gamma-retroviruses, lentiviruses, adenoviruses and AAV. French Anderson and Michael Blaese formally submitted a gene therapy protocol to test the retroviral-mediated transfer of the adenosine deaminase (ADA) gene into the T-cells of two children with severe combined immunodeficiency (ADA- SCID). The results were mixed, with clinical response in one patient and limited response in the other patient [14][15]. Similar trial targeting ADA-SCID was also started in the European Union (EU) [16].

The same year (1990), Doctor Anderson created and became editor-in-chief of the first journal devoted to cover the gene therapy field, Human Gene Therapy. This new journal published not only original scientific research papers, but also articles on ethical and regulatory issues relating to gene therapy [17].

In 1995, the feasibility and safety of in vivo gene transfer was demonstrated using replication-deficient retrovirus and adenovirus in human malignant glioma, by transferring the vector via catheter inserted into the tumour in ten patients [18]. Some years later (1999) the worst-case scenario in the field came with the first dead in a gene therapy clinical trial. Jesse Gelsinger, an 18-years-old boy, was given an infusion of recombinant adenoviral vector to correct ornithine transcarbamoylase deficiency. The patient experimented a severe immune reaction to the vector, dying 4 days after receiving the injection. This death slowed down gene therapy research, and in early in 2000 the Food and Drug Administration (FDA) and the NIH decided to enhance patient protection through the Gene Therapy Clinical Trial Monitoring Plan and the Gene Transfer Safety Symposia [19]. By the same time, European researchers reported the gene therapy success for X-linked SCID (SCID-X1) using gamma-retroviral vector-based [20], but in 2002 four of these patients developed leukaemia triggered by insertional mutagenesis [21]. With all these successes, the need for improved viral vectors became even more patent.

While in 1996, the first generation of lentiviral vectors was created through three plasmids [22], it was not until 2003 when the first clinical trial with a lentiviral vector started; CD4+ T-cells from patients with human immunodeficiency virus (HIV)-1 were transduced with a lentiviral vector containing an antisense sequence against the HIV-1 envelope. This Phase I trial was successfully completed demonstrating safety and opening the doors for Phase II trials with

lentiviral vectors [23]. Lentiviral vector-based gene transfer was subsequently applied in the treatment of several genetic diseases, including β-thalassemia, X-linked adrenoleukodystrophy, metachromatic leukodystrophy, and Wiskott-Aldrich Syndrome [24].

In the meantime, the completion of the Human Genome Project culminates the same year (2003) after more than one decade of research, resulting in a complete sequence human genome and leading to better understanding of the genetic causes and predispositions for a number of diseases and opening the field of individualized medicine [25].

In addition to viral vector-based therapies, other several gene editing systems were also being developed, such as zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) or CRISPR/Cas9 systems.

In 1985 the zinc finger motifs were discovered and in 2003 it was reported its first use, which established the basis for efficient site-specific genomic manipulation in mammalian somatic cells [26][27]. In 2005 took place the first modification of an endogenous gene in human cells through ZFNs, to correct inherited mutations in the IL2RG gene that causes severe immune deficiency [28]. Advances on ZFNs led to the first clinical trial in 2014, by editing the CCR5 gene in autologous CD4 T cells of persons infected with HIV [29]. Towards the end of 2017, the first report of *in vivo* gene editing with this tool become real with the delivery of the intact target gene and the ZFNs via an AAV for patients with Hunter's syndrome [30][31].

In addition, transcription activator-like effector nucleases (TALEN) motifs were described in 2009, and in 2011-2013 novel methods of genome editing TALEN and CRISPR/Cas9 systems marked the beginning of new era [32]. The first reported application of TALENs into the clinic (2015) enabled "off-the-shelf"' therapy of chimeric antigen receptor (CAR)19 T-cells with mismatched donor, using TALENs to overcome HLA barriers [33].

The golden age of CRISPR/Cas technology is now upon us. Although the "CRISPR" repeat sequence was reported in 1987, it was not until 2013 when the Cas system was applied to the cutting of DNA in mammalian cells, which paved the way for the application of this system for gene editing. Since then, the CRISPR/Cas9 technology is rapidly evolving. In November 2018, He Jiankui announced the birth of twin girls with edited genomes through CRISPR engineering triggering a huge ethical debate. The human embryos were edited by removing the CCR5 gene in order to confer them resistance to HIV [34]. In response to Jiankui 's work, the World Health

Organisation (WHO) urged to regulate genome editing and announced the creation of a global registry to track all human genome editing research [35][36]. The same year, Crispr Therapeutics became the first company to file an application to the regulatory authorities, with the aim to begin clinical trials for a CRISPR therapy (CTX001) in subjects with severe sickle cell disease [37]. In 2020, the first attempt to use the CRISPR gene-editing to treat blindness showed hints of success [38][39]. Gene editing has not only human clinical applications, but the research is also focused on developing disease control strategies, e.g., using CRISPR/Cas in mosquitoes to eradicate malaria [40]. In March 2021, the European Commission released a position paper with recommendations to foster responsible use of genome-editing technologies, such as CRISPR/Cas [41].

The time for the first ATMP approvals arrived in 2003. China became the first country to approve a gene therapy (i.e., Gendicine®), an adenoviral vector with human p53 cDNA for the treatment of head- and neck squamous cell carcinoma [42][43]. One year later (2004), Ark Therapeutics Group received the first commercial Good Manufacturing Practices (GMP) certification in the EU to manufacture Cerepro®. Cerepro® was a novel gene-based therapy for operable malignant glioma (brain cancer) based on an adenoviral vector, which contained the Herpes simplex virus thymidine kinase gene [44]. Finally, in November 2008, the marketing authorisation application (MAA) for this product was filed to the European Medicines Agency (EMA) and undergone a formal review. Cerepro® became the first and the only adenoviral vector that completed a Phase III clinical trial at that time [44]. The product did not obtain the approval given major objections to determine efficacy through the chosen primary endpoint [45][46]. While in 2005, the second gene therapy was approved in China, Oncorine® (a replicative adenovirus for the for the treatment of late-stage refractory nasopharyngeal cancer), it was not until July 2012 when Glybera® (AAV-lipoprotein lipase) was approved by the EMA. Glybera® was the first advanced therapy product that reach the European market after a long and complex procedure. The first gene therapy product approval in the US did not come until October 2015 with Imlygic®, a recombinant herpes simplex virus type 1 carrying the effector gene of granulocyte-macrophage colony-stimulating factor for the treatment of melanoma. In 2016, after years of research to target ADA-SCID, the EMA approved Strimvelis®, the first *ex vivo* hematopoietic stem cell gene therapy with a gamma-retroviral vector. The application was based on data from 17 ADA-SCID children treated from 2000 to 2011 and 7 years of evidence of long-term gene correction [47].

The development of CAR T-cell products has also been a decades-long journey, being now the booming of the field. The first engineered T-cell with chimeric molecule was developed in 1993 [48][49], although it was not clinically effective. Over next thirty years, CAR-T cells would evolve into fourth generations of engineered T-cells depending on their composition. In 2002, the second generation of CAR-T were able to kill prostate cancer cells [48]. Carl June led the first administration of CAR-T cells in patients with acute lymphocytic leukaemia (ALL) in 2011 [50] and B-cell acute lymphoblastic leukaemia (DLBCL) in 2012 [51][52]. After the disease remission of Emily Whitehead, the first child with ALL who received CD19 CAR-T therapy, the CAR-T field began a new stage [53]. Nonetheless, the field also experienced ups and downs; in 2017, clinical trials conducted by Juno Therapeutics reported the death of three patients from cerebral oedema linked to CAR T-cell therapy [54][55]. One year later, the first two CAR T-cell therapies directly targeting CD19 (Yescarta® and Kymriah®) were approved for the treatment of refractory ALL and in relapsed or refractory DLBCL, both in the EU and the US. CRISPR-Cas9 are currently being used to establish "off-the-shelf" CAR-T cells with robust resistance to immune cell-suppressive molecules [56][57].

The harmonisation efforts in the field have been always considered a need. In 1992 and 1996, the European Society of Gene Therapy (ESGCT) and the American Society of Gene & Cell Therapy (ASGCT) were founded respectively. The establishment of international guidelines in the context of the International Conference on Harmonization (ICH) for biotechnology products were a reality from 1997 [58]. As knowledge evolves, new ICH guidelines have been released along the years, with the latest one focused on nonclinical biodistribution considerations for gene therapy products (June 2019) [59]. In parallel, throughout all these years regional guidelines have also been released, as the field has advanced and more experience has been gained from regulatory agencies.

These are just some of the key milestones that the ATMPs field had to reach to be where it is today. What sounded like science fiction in the 90s, it is now a reality. As of Q2 2022, 3.633 therapies are in development ranging from preclinical through pre-registration [60], and as October 2022 there are 21 approved advanced therapies in the EU and 17 in the US. The technology, science and the regulatory environment are evolving to accommodate this growth.

What does the future hold for this field? To date, many challenges are associated with the development of these therapies in terms of manufacturing, nonclinical and clinical development, regulatory procedures, and market access. Some of these hurdles are translated

in product withdrawn or non-approval, which at the end affects access to potential new drugs: inefficient manufacturing processes and issues with manufacturing capacity, less standards compared with more mature medical fields, the constantly evolving landscape in cell and gene therapy which challenges the regulatory agencies, the difficulties with the drug market access due to the uncertainties associated with the available evidence and the associated high budgetary impact, etc. What is the current picture of ATMP landscape and how should we move forward to be prepared for the coming future?

Justification of the project

The delay between the theoretical concept of an ATMP to treatment approval are due to the multiple challenges that arise from the nature of ATMPs, including scientific, technical, and regulatory challenges [61]. The field of advanced therapies is booming but many gaps remain to be resolved, to the point that the treatment with these therapies becomes the standard. There is a need of better understanding of ATMPs at manufacturing, nonclinical and clinical level, as well as change of paradigm on this type of product´s development from several stakeholders [62][63]. Some of the identified gaps comprise comprehensive knowledge of product´s efficacy and safety profile at short and long-term, its clinical benefit over standard of care (SoC), more robust and predictable manufacturing processes and the ability to reduce product's cost, the optimisation of real world evidence to improve the quality of post approval commitments, the science iteration and development of standards to ensure consistency at quality, nonclinical and clinical level and the reproducibility of knowledge, the administrative simplification of regulatory processes to speed up development, and more alignment on market access evaluation procedures and decisions [64][65].

So far, the current picture of the ATMP field consist of most of the products being fit for the patient in an individualised manner or addressing rare diseases. It has been recognised the hurdles of drug development for small populations and the difficulties to conduct adequate and feasible clinical trials. On the other hand, the regulatory agencies have recognised that ATMPs requires specific expertise for their evaluation, which goes beyond the traditional pharmaceutical field [66]. The marketing authorization (MA) of these therapies in the last years has been crucial to the growth of clinical research in this field, however the clinical developments of the approved ATMPs are usually non-controlled, abbreviated, and based on cohort studies with small numbers of patients. In addition, the duration of benefit of an ATMP

is usually not possible to prove in a randomised clinical trial as the effect is expected to last beyond the end of a clinical trial by years or even decades. This limited evidence at the time of MA has been questioned since may lead to uncertainties in the product´s benefit/risk balance and delay patient access to the medicine. Therefore, the type of target diseases by these therapies (i.e., serious conditions and unmet needs), the inherent complexity of ATMPs and the accelerated and alternative developments have opened a current debate within the patients and advocates, industry and the regulatory agencies [67]. There are no exhaustive reviews that analyse the methodological characteristics of the studies that underpin the approval of ATMPs.

This type of clinical developments has also an impact on market access. Another opened discussion with the public national health authorities, is the need for suitable systems that incorporates better methodologies for indirect comparisons and that consider the one-off treatments and the innovative features of ATMPs. The transformative nature of ATMPs relies on the fact that exhibit the potential to cure diseases by addressing their root cause rather than symptomatic treatment [68]. The development of robust real-world evidence is also under debate, since can contribute to solve the uncertainties over long-term effectiveness and support the initial claims and market access decisions. Furthermore, how to balance the interests of the industry, patients and health care systems, and how countries can face the high-priced of these therapies, whose actual benefits are still uncertain, is one of the major current hurdles [69]. The financing of ATMPs is a challenge for public health systems. Only few studies have analysed the reimbursement decisions and the added therapeutic value evaluation across several European countries for the approved ATMPs, including a low number of drugs and European countries. A more comprehensive comparative analysis of the health technology assessments (HTAs) and recommendations issued by several EU national health authorities (NHA) for the approved ATMPs was considered of value.

Finally, there is a global recognition of the need of actions to promote the development of innovative therapies, as well as the need for development convergence needs. Divergencies on the regulatory requirements between regions and even within the committees of the same regulatory bodies are known and have been attributed as potential hurdle of ATMP development [67]. There are no studies that have compared the ATMP regulatory development to assess the differences between the different regions. Innumerable number of efforts are being made by all stakeholders to advance and achieve greater harmonization and optimization of ATMP development at a global level [70].

Overall, it is not trivial to find the balance between the ethical and unethical for the ATMPs clinical development and the respective market access decisions. The estimated global growth rate of the ATMPs market from 2021 to 2028 is around 12%, with an estimated value from $9.5 billion in 2021 to $21.2 billion by 2028 [71]. In 2024, 21 cell therapy launches and around 31 gene therapy launches are expected in the US [72]. To be prepared for the coming future is imperative to continue with the research, optimizing strategies, global harmonisation and achieving the agility of the different pillars that constitute drug development - quality, nonclinical, clinical, regulatory and market access - with the main aim of translational success in the field.

Hypothesis

The hypothesis of this work are as follows:

1. The development of ATMPs have been associated with regulatory challenges due to differences between regions. However, the legislative framework and regulatory procedures followed by the approved ATMPs across regions are quite similar.

2. Most advanced therapies have been developed to address unmet medical needs for rare diseases and that is why accelerate development and approval has been justified.

3. The clinical developments of approved ATMPs have been generally based on cohort studies without a control group and with a small number of patients.

4. Only few ATMPs have obtained the MA so far, and even fewer were reimbursement at national level within the EU or entered into the market through managed entry agreements.

The analysis of these challenges at regulatory, clinical and market access level will allow to: identify the causes of differences between regions regarding the definition and regulatory development of ATMPs, determine which is the quality and strength of clinical evidence associated with ATMPs authorization, and analyse the current situation of health technology assessment procedures by comparing the evaluation processes in several European countries and their subsequent reimbursement decisions.

Thesis objectives

The aim of this work is to analyse the current development of ATMPs from three core pillars - regulatory, clinical and market access - to determine the particularities of this type of therapies, how the development challenges played a role in MA and market access, and how the field is moving forward.

The ***Chapter 2*** analyses the ATMPs development challenges from a regulatory perspective:

- ***Section 2.1*** systematically reviews and compares the regulatory framework and the criteria to classify a product as an ATMP in the EU and the US.

- ***Section 2.2*** analyses and compares the regulatory pathways followed by the approved ATMPs to identify the similarities and differences between EU and US regions.

- ***Section 2.3*** reviews and compares the regulatory framework for the environmental risk assessment (ERA) procedures in the EU and the US during clinical development and at MAA stage. This section also discusses the challenges attributed to divergences and considerations during clinical development of ATMPs in relation to genetically modified organisms' applications in the EU.

Chapter 3 analyses the ATMPs development challenges from a clinical perspective:

- ***Section 3.1*** analyses the pivotal trials' features that supported the ATMPs MA in the EU.

- ***Section 3.2*** aims to analyse the consequences of the results obtained in *Section 3.1*. This section reviews and discusses the current landscape and challenges for clinical development and approval of ATMPs, as well as the current efforts and potential future approaches to address these obstacles.

- ***Section 3.3*** examines the regulatory and clinical developmental strategies that supported the MA for approved ATMPs in Japan, comparing it with the EU and US landscape. This section gives insights and how to optimize the parallel regulatory and clinical development among regions.

Chapter 4 analyses the ATMPs development challenges from a market access perspective:

- ***Section 4.1*** provides a comparative analysis of the HTAs and recommendations issued by several NHA in the EU for the approved ATMPs. The section also analyses the considerations that might have played a role in the reimbursement recommendations. In addition, this section evaluates any relationship between the type of the EMA approval and reimbursement decision.

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Chapter 2: Regulatory development of advanced therapy medicinal products in the European Union and United States

2.1: Regulatory framework for advanced therapy medicinal products in the European Union and United States

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Abstract

ATMPs are a fast-growing field of innovative therapies. The EU and the US are fostering their development. For both regions, ATMPs fall under the regulatory framework of biological products, which determines the legal basis for their development. Sub-classifications of advanced therapies are different between regions; while in the EU there are four major groups, i.e. gene therapy, somatic cell therapy, tissue engineered therapies and combined advanced therapies, in US the sub-classification covers two major groups of products, i.e. gene therapy and cellular therapy. The inclusion criteria that define a gene therapy are equivalent in both regions, and the exclusion criteria are directly related to the indications of the product. In the EU, there is a clear differentiation between cell and tissue-based products regarding their classification as advanced therapies or coverage by other legal frameworks, whereas in the US there is a broader classification about whether these products can be categorized as biologic products. Both in the EU and in the US, to classify a cell or a tissue-based product as an advanced therapy, it must be ensured that the processing of the cells implies a manipulation that alters their biological characteristics, although the term of manipulation in the US differentiates between structural and non-structural cells and tissues. The regulatory terminology used to define ATMPs and their sub-classification reveals some differences between EU and US.

Introduction

ATMPs comprise a category of innovative and complex biological products, which in most cases require extensive and complicated preclinical and clinical development. This complexity has been observed since the idea of transferring genetic material to cure a genetic disease was foreseen decades ago. The first ATMP product approved in the EU came in 2009 with the authorization of Chondrocelect®, a tissue engineered product indicated for the treatment of cartilage defects [1]. In the US the first approved ATMP came out one year later with Provenge®, a somatic cell therapy for the treatment of some prostate cancers [2]. The first authorized gene therapy was launched in 2012, when Glybera® achieved MA in the EU [3].

The delay between the theoretical concept of an ATMP and the first clinical trials that lead to a new treatment approval may be due to the multiple challenges that arise from the nature of ATMPs, including not only scientific and technical challenges but also regulatory ones [4]. The first step in their development is the definition of the product, and consequently, its classification. Both in the EU and the US there is a broad legal framework, ranging from medicinal products consisting of chemical substances to biological substances, the latter including a wide range of possible products. In this sense, the classification of a potential biological product is often not so trivial, and in some cases, it may be difficult to discern the line between different biological subcategories. The correct classification of a product at an early stage of development is a critical point, since it will determine the regulatory framework and the European and American recommendations to follow throughout the whole development plan of the product in each region.

This article aims to review the legal frameworks in the EU and the US for ATMPs, as well as the criteria to be met to define a product as such. The similarities and differences that exist between both regions are discussed to identify those nuances that may affect the development of an ATMP. A specific search for official regulatory documents concerning medicinal products for human use with a specific focus on ATMPs, such as legislation, guidelines, presentations and reports, from the websites of the EMA and the FDA competent authorities was carried out until 31st December 2018. Key terms that covered the regulatory framework for advanced therapies and other products were used to navigate the websites of these competent authorities, including: terms describing advanced therapies (Advanced therapy, Advanced therapies, Regenerative medicine, Cell therapy, Cell-based therapy, Human cellular therapy, Stem cells, Gene therapy, Tissue engineering, Human Cell Therapy, Human Somatic Cell therapy),

information on the regulatory framework and the definition and classification of advanced therapies in the EU and the US.

Regulatory framework for the classification of advanced therapies

Medicinal products for human use in the EU are governed by Directive 2001/83/EC and Regulation 726/2004/EC. Biological products comprise many diverse product types, including immunological medicinal products (i.e. vaccines, toxins, serums and allergens), medicinal products derived from human blood and human plasma (i.e. albumin, coagulation factors, and immunoglobulins of human origin), biotechnology products such as antibodies, and ATMPs, which are the focus of this paper [5]. ATMPs consist of products that contain recombinant nucleic acids or engineered cells and/or tissues. These products are divided into four subcategories: somatic cell therapy medicinal products (SCTMP), tissue engineered products (TEP), gene therapy medicinal products (GTMP) and the combined ATMPs (cATMPs). These last ones consist of one of the first three categories combined with one or more medical devices as an integral part of the product [6]. In the EU there is a clear differentiation between cell-based products considered as advanced therapies, and cell-based therapies covered by other legal frameworks such as the blood system or transplant laws, where these cells are not considered a medicinal product and the active substance, i.e. human cells and tissues, cannot be commercialised or manufactured on an industrial scale for ethical and legal reasons [7][8][9]. The classification of an ATMP as a biological product will determine the wider regulatory framework by which the requirements of the development and the MAA are defined. These are to be read in conjunction with the specific framework for ATMPs, Regulation 1394/2007/EC, which came into force on December 30, 2008. This regulation provides the overall framework on ATMPs for those products, which are intended to be placed in the market of the EU Member States. In addition, Directive 2009/120/EC updated the definitions and detailed scientific and technical requirements for advanced therapies. The cATMPs are not only regulated under the guidelines of medicinal products but also of medical devices. On 25 May 2017 two new Regulations on medical devices came into force [10].

For the development of advanced therapies in the EU, the clinical trial applications are submitted individually to the national competent authorities where the trial will take place. However, for the MA, all ATMPs are evaluated via centralised procedure ensuring that they benefit from a single evaluation and authorisation applicable across the EU. There are two

committees responsible for the validation and scientific evaluation for product approval: the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP) [11]. The CAT is the EMA committee responsible for classifying, assessing the quality, safety and efficacy of ATMPs and following scientific progress in the field. This committee's main responsibility is to prepare a draft opinion on each ATMP application submitted to the EMA to support the final decision by the CHMP. This MA via the centralised procedure may be granted in three ways: standard MA, conditional MA (when an innovative medicine addresses an unmet medical need yet a positive benefit-risk balance by sufficient clinical data is demonstrated), and MA under exceptional circumstances in those extreme situations where a disease is rare or a clinical endpoint is difficult to measure [12]. Regarding classification, the CAT offers the confirmation that a medicine meets the scientific criteria to be classified as an ATMP. On the other hand, the regulatory authority in charge of medical devices is the national appointed bodies of each EU member. In the case of cATMP, the CAT interacts with the Notified Bodies to prepare the draft opinion on a cATMP [13].

In the US, like in EU, advanced therapies are regulated as biologic products. In legislative terms, biological products comprise the following categories: i) the group of allergenics that includes allergen extracts, allergen patch tests and antigen skin tests, ii) blood and blood products, iii) vaccines, iv) xenotrasplants, and v) Cellular and Gene Therapy Products (CGTs), which constitutes the group of advanced therapies and encompasses two sub-categories of products. Advanced therapies should not be confused with other legislative category of products called 'human cells, tissues and cellular and tissue-based products' (HCT/Ps) and defined as "articles containing or consisting of human cells or tissues intended for implantation, transplantation, infusion or transfer into a human recipient" [14]. HCT/Ps are not considered biological products. On the other hand, combination products include products that are comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic. The definition is broad and considers the packaging and whether all components of the product are needed to achieve the intended use, indication or effect [15]. In 2016, the 21st Century Cures Act (Cures Act) was signed into law to help accelerate medicinal product development and bring new therapies to the market faster and more efficiently. This Act established a new expedited product development program called the Regenerative Medicine Advanced Therapy (RMAT) [16]. Although is not a type of classification *per se*, yet a designation that offers a new expedited option for evaluation of the product, it is considered worth mentioning it here as a part of the US advance therapy

classification. A regenerative medicine therapy is defined as: i) a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, explicitly excluding HCT/Ps, ii) that is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and iii) if the preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition [17]. Therefore, this definition implicitly includes ATMPs. A combination product can also be eligible for RMAT designation when the biological product component provides the primary mode of action. These products would be denominated as RMAT-based combination products. More than 30 out of 90 RMAT designation requests have been granted until 2019 [18].

The US federal regulatory framework consists of two main statutes, Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Services Act (PHSA), that provide the Food and Drug Administration (FDA, the federal regulatory medicines agency in the US) with the legal authority to regulate human medicinal products including drugs, biological products and devices. Biological products, and therefore advanced therapies, are regulated under section 351 of the PHSA and under the FDCA, because most biological products also meet the definition of "drugs" cited in this Act. FDA regulations are contained in the Code of Federal Regulations (CFR), which provides details on how the FDA implements the activities that are defined in the PHSA and FDCA. Regulations for biological and medical devices are found in Title 21 of the CFR [19][20]. In the US the applicants need to submit an investigational new drug (IND) application to obtain a clinical trial approval [21], and Biologics License Application (BLA) to obtain a MA [22]. The MA can be standard, under a Priority Review procedure or under an Accelerated Approval. In the Priority Review the application is reviewed within 6 months compared to 10 months under standard review and it is addressed to those drugs that, if approved, would bring about significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications. An Accelerated Approval allows drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint, if clinical benefit has been demonstrated [23].

Within the FDA, responsibilities for drugs, biologic products and devices are organised in eight different centres. The Centre for Biologics Evaluation and Research (CBER) has jurisdiction over a variety of biological products, including blood and blood products, vaccines and

allergenic products, and cellular, tissue, and gene therapies, as well as some related devices. Within the CBER, the responsibility for advanced therapies falls to the Office of Tissues and Advanced Therapies (OTAT), formerly known as Office of Cellular, Tissue and Gene Therapies (OCTGT). OTAT comprises five divisions in addition to the Office of the Director [24]. Combination products are assigned to the FDA centre that will have primary jurisdiction for its pre-market review and regulation. For combination products, CBER usually regulates medical devices related to licensed blood and cellular products by applying appropriate medical device laws and regulations [25]. This assignment is performed by the Office of Combination Products through a designation process [26].

The current European and American legislation for biological products is summarised in Table 1. One of the main differences between the EU and the US is that the FDA oversees clinical trials, whereas the EMA does not. In terms of MA, each region has specific legislations depending on the legal categorisation of the product; in the EU they are licensed under article 8.3 of Directive 2001/83/EC, while in the US, ATMPs are licensed under section 351 of the PHS Act. Both Agencies have their own specialised committees to evaluate ATMPs. In the US, the approval time for a standard BLA may extend up to 10 months from receipt date [27], while in EU the assessment leads to an opinion from the CHMP by day 210 and European Commission by day 277 (around 7 months) [28]. However, these timelines depend on the different types of MA available in each region. Among advanced therapies, product sub-classifications are slightly different between regions. While in the EU an ATMP can be sub-classified into four major groups, i.e. GTMP, SCTMP, TEP or cATMP, in the US the sub-classification groups are broader, covering two groups of products, i.e. gene therapy and cellular therapy products. Given that the sub-classification in the EU is more precise, there are products that could fall into two categories, and in some cases, the assignment in a particular subtype is not so trivial. In the case of the US, the difficulty might arise when classifying the product as an HCT/Ps or as a biological product that falls beyond minimal manipulation and/or homologous use. Finally, another difference between regions is related with terminology; in the US the term “advanced therapy” is not a common term used in legislative and regulatory documents, and these products are collectively referred as “cellular and gene therapy (CGT) products”.

To ensure a correct classification, both the EMA and the FDA have made scientific advice available to the applicants to clarify or corroborate this classification prior to further advancing

the development. In the EU, one of CAT's activities is to clarify the classification of a given product, above all when the product could fall in two different categories [29]. It is always advisable to obtain CAT's opinion about a particular product, since the features of each product can be unique and the corroboration of a product as an advanced therapy might add value to attract potential investors. On the other hand, in the US, the Tissue Reference Group is the working group within the FDA that provides recommendations to stakeholders concerning the application of the criteria for HCT/Ps. For both consultations, a minimum of information on the product is required to obtain its proper classification, such as the source of the product, the intended use of the product or description of how the product is processed from the time of recovery to the point of use step-by-step [30]. Another consultation option at an early stage of development is to hold informal meetings with the Agencies to obtain informal exchange of information and receive advice and recommendations on the development process in terms of scientific, regulatory and legal issues. For complex products, this type of meeting might also be helpful to obtain the first legal and scientific feedback on the classification of the product. For EU, these meetings are called Innovation Task Force (ITF) briefing meetings [29], while the equivalent meeting in the US is called in Initial Targeted Engagement for Regulatory Advice (INTERACT) meetings [31]. The ATMP classification procedures are valuable to address questions on borderline classifications, commonly raised for combined ATMPs, to confirm the medicinal product framework and determine what type of ATMP a product is, and therefore, develop the product under the specific dossier requirements and quality guidelines.

Finally, it is worth noting that the main EU and US Agencies have launched expedited development programs to enable new medicines reach the market as early as possible. The medicines that are eligible to these programs are those that can justify a potential major public health interest, i.e. they target conditions where there is an unmet medical need or have the potential to bring a major therapeutic advantage to patients. Since ATMPs usually offer new treatments for currently incurable conditions or improve existing treatments, most ATMP are eligible to this type of accelerate programs. The FDA has developed the Breakthrough Therapy and Fast Track designations programs [23], while the EU launched the adaptive licensing and afterwards the PRIME designation scheme. The difference between the Breakthrough Therapy and Fast Track designations falls on the qualifying criteria for the designation. In the latter, clinical or nonclinical data should demonstrate potential to address an unmet medical need, whereas in the former preliminary clinical evidence indicates that it may demonstrate substantial improvement over available therapies on a clinically significant endpoint(s). The

EU PRIME and the US Breakthrough Therapy designations share the same objective (timely patient access to innovative medicines) but have a different legal basis, hence comparison and harmonization is difficult. However, since late 2016, FDA and EMA have worked together to track submitted requests for PRIME and Breakthrough Therapy designations and compare final review outcomes, including specific reasons for a designation request denial [32]. Throughout 2019, a database to create a public list of RMAT recipients, as well as other expedited approval designations awarded in the US, the EU, and Japan is foreseen to be launched [33].

Classification criteria in Europe and United States

Gene therapies

Some examples of gene therapy products include *in vivo* therapies, such as nucleic acids or genetically modified microorganisms (e.g., viruses, bacteria, fungi), and *ex vivo* therapies like genetically modified human cells or human genome editing. In the EU, in order to classify a product as a gene therapy all of the following inclusion criteria must be met [34]: i) the product has to be a biological medicinal product according to Directive 2003/63/CE, ii) the product must contain recombinant nucleic acid(s), iii) the recombinant nucleic acids should be of biological origin, regardless of the origin of the vector system used, iv) the recombinant nucleic acid is used in or administered to human beings in order to regulate, repair, replace, add or delete a genetic sequence, and v) the recombinant nucleic acid(s) should be directly involved in the therapeutic, prophylactic or diagnostic effect of the product (Table 2). It should also be noted that, according to the ATMP Regulation [6], a product that may fall within the definition of a SCTMP or a TEP, and a GTMP, shall be considered a GTMP, since it is the one that can pose the most safety concerns.

In the US, the inclusion criteria that must be met are the following [35][36][37]: i) the product meets the definition of "biological product" in section 351(i) of the PHSA (42 U.S.C. 262(i)), ii) the product has to be applicable to the prevention, treatment, or cure of a disease or condition of human beings, iii) the product mediates its effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences, and iv) the product can work through several mechanisms: replacing a disease-causing gene with a healthy copy of the gene, inactivating a disease-causing gene that is not functioning properly, or introducing a new or modified gene into the body. Recombinant DNA materials used to

transfer genetic material for such therapy are considered components of gene therapy (Table 3).

Therefore, despite the different terminology used, the inclusion criteria that define a GTMP are equivalent in both regions: the product must be a biological product that contains "recombinant nucleic acid(s)" (term used in the EU) or "genetic material" (term used in the US), which through its action mechanism prompts the desired primary effect: addition, manipulation or modification of gene expressions on human beings. Two autologous CAR T cell therapies (Kymriah® and Yescarta®) were recently approved by the EMA and the FDA. These therapies are classified as a cell-based gene therapies in both regions since they consist of genetically modified T cells expressing a CD19-specific CAR in order to lyse CD19-positive targets (normal and malignant B lineage cells). The fact that the product must be a biological medicinal product is not a minor inclusion criterion, since chemically synthesized nucleic acid sequences will be excluded from being classified as ATMPs and will be considered chemical drugs that should be developed under another legal framework, as for example antisense oligonucleotides and aptamers approved by the EMA and FDA as chemical drugs. Unlike the US, in the EU one of the inclusion criteria for GTMP establishes that the recombinant nucleic acids should be of biological origin, regardless of the origin of the vector system used. On the other hand, in both regions the product must be applicable to the prevention or treatment of a human disease. However, diagnosis is not cited as one of the primary goals of these products in the US. Neither does the US definition of a biologic product, according to the PHSA Act, contemplate diagnosis as a purpose of the product [20]. In the EU there is one exclusion criterion that explicitly vetoed a product from being classified as a gene therapy: those products aimed at the treatment or prophylaxis of infectious diseases. These products would be classified as vaccines, even if the product meets all the necessary criteria to be considered an ATMP [34]. For instance, a modified vaccinia virus ankara (MVA) into which two genes have been placed for the treatment of non-small cell lung cancer is classified as a GTMP, but if these genes lead to foreign protein expression for the treatment of HIV disease, the product will not be considered an advanced therapy, but a vaccine [28][39]. The same principle applies to non-viral vectored products such as most plasmid DNA or RNA-based products. For instance, Trimix is a mixture of mRNAs encoding for antigen presenting cells activation molecules. If this mixture of mRNAs is combined with tumour associated antigens for the treatment of melanoma, the therapy is classified as a GTMP, but if these mRNA are combined with mRNA encoding for HIV antigens, the therapy will be considered a vaccine [40]. In the US, it is not specifically mentioned as an

exclusion criterion, but prophylaxis or therapeutic vaccines for infectious diseases have their own guidelines for development, and these products are typically reviewed by the CBER/Office of Vaccines Research and Review (OVRR) and not by the OTAT [41]. Therefore, the criterion for excluding a product from being classified as a GTMP in both regions is directly related to the indications of the product. Although some regulatory and development requirements for both types of products overlap, since these vaccines may be gene-based, for either region there are guidelines specifically addressed to the development of vaccines or gene therapy products independently. A consequence of this classification is that some of the available EU regulatory procedures that facilitate the development of ATMPs would not apply in the case of products classified as vaccines; for instance, the possibility of certifying the Quality and Non-clinical data for ATMP applications by the EMA [42].

Cell and Tissue therapies

In the EU, SCTMP are distinguished from TEP. However, both class-products share the same inclusion principle, i.e., the cells or tissues of the product must be 'engineered' and the difference lays in the indication. To consider a cell or tissue as '*engineered*', it must fulfil at least one of the following criteria [6]: i) the cells or tissues have been subject to substantial manipulation, or ii) the cells or tissues are not intended to be used for the same essential function(s) in the recipient and the donor, i.e. non-homologous use. Regarding the indication, in the case of SCTMP the product is administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues, whereas in the case of TEP the product is administered to human beings with a view to regenerating, repairing or replacing human tissue. The key to ascertain the most appropriate subcategory is based on the predominant mechanism of action of the active substance and the claimed intended function. A problem arises when the dividing line for classifying a product as SCTMPs or TEP is not clear. Such is the case when the product exerts a pharmacological action to regenerate, repair or replace a human tissue. For these cases, premises have been established to categorise a specific product: a product which may fall within the definition of a TEP and SCTMP, should be considered a TEP according to ATMPs Regulation, although the final classification should be considered on case-by-case basis, playing CAT's opinion a major role. In addition, those products that consist of engineered or manipulated cells that induce regeneration, repair or replacement in the native tissue via secretion of paracrine factors, also fulfil the definition of a TEP [34]. Finally, it is considered

that a TEP may contain cells or tissues of human or animal origin, or both, and that the cells or tissues may be viable or non-viable, considering viable cell those that have a functional cytoplasmic membrane. Two considerations in this regard are made: i) an inclusion criterion that automatically classifies a product as an ATMP applies when products contain or consist of animal cells or tissues, and ii) an exclusion criterion for not classifying a potential product either as a SCTMP or TEP includes those products containing or consisting exclusively of non-viable cells or tissues and which do no act principally through pharmacological, immunological or metabolic action (Table 2).

As mentioned, cell and tissue-based products can be sub-categorized in the US regulatory framework as biologic products or as HCT/Ps. The definition of cell and tissue-based products regulated as biologic products includes those that are "more-than-minimally manipulated", or for "non-homologous use", or have a systemic effect, or depend on its metabolic activity (except for autologous cells, allogeneic cells for 1st of 2nd degree relatives and reproductive cells) [43]. The group of advanced therapies referred to as "human somatic cell therapy products" fall within this definition. Note that in the US there is no product class defined for tissue-based advanced therapies. The definition and the inclusion criteria for human somatic cell therapy (SCT) include the following [35, 36]: i) SCT consists of administration to humans of autologous, allogeneic, or xenogeneic living cells, ii) the manufacture of products for somatic cell therapy involves the *ex vivo* propagation, expansion, selection or pharmacologic treatment of cells, or other alterations of their biological characteristics, and therefore considered "more-than-minimally manipulated", and iii) the aim of this cellular products is to be used for therapeutic, diagnostic, or preventive purposes (Table 3).

Therefore, the categorization or classification of human cells and tissue products between the EU and the US is different. On one hand, in the EU there is a differentiation between products considered TEP or, SCTMP, in which the difference lies in the claimed indication, while in the US cell and tissue products that constitute an advanced therapy will be labelled under the SCT term. For instance, MACI (Matrix Applied Characterised autologous cultured chondrocytes) is a product approved both in the EU and the US, which consists of autologous chondrocytes seeded on a collagen membrane of porcine origin indicated for the repair of symptomatic, full-thickness cartilage defects of the knee in adult patients. While in the US MACI is considered a cell therapy (a biologic-device combination product with the aim of being used for therapeutic purposes), in the EU it is classified as combined TEP, since the claimed primary mechanism of

action of the product is the regeneration, repair, and replacement action [44, 45]. Finally, the FDA classifies xenogeneic living cells as SCT, as well as in EU, where these therapies can be assumed to be automatically classified as ATMPs from a regulatory point of view [46, 47].

Manipulation and Homologous use

Both inclusion criteria, manipulation and homologous use, have their own definitions depending on the region.

In the EU, *"substantial manipulation"* means to modify the biological characteristics, physiological functions or structural properties relevant for the intended clinical use. For instance, cell separation, concentration or purification does not represent a substantial manipulation if the cells performed the same biological activity as in the human body, whereas cell-culturing leading to expansion or cell activation with growth factors does. A non-exhaustive list of manipulations that are not considered substantial for ATMP purposes is provided in Annex I of Regulation EC (No) 1394/2007, and includes: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing and cryopreservation.

On the other hand, the *"same essential function"* (or homologous use) means that the cells or tissues (whether substantially manipulated or not) are used to maintain the original function(s) in the same anatomical or histological environment. By contrast, *"different essential function"* (or non-homologous use) for cells or tissues (substantially manipulated or not) are those not intended to be used for the same essential function(s) in the recipient as the original cell/tissue would perform in the donor [34].

Allogeneic human islets of Langerhans for the treatment of severe forms of type 1 diabetes is a common example of cell/tissue products that might be regarded as non-ATMPs, since these cells/tissues might be isolated, purified and cultured by methods that do not result in a modification of the biological characteristics, and are re-administered to fulfil their same essential function. In 2011, CAT considered that autologous/allogeneic human islets of Langerhans were not an ATMP [48], but are considered to fall under the provisions of the Tissues and Cells legislation. Under this legislation, these cells are neither considered a medicinal product, since the active substance, i.e. human tissues, cannot be commercialised or manufactured on an industrial scale for ethical and legal reasons. However, in 2013, a product

that consisted of viable alginate encapsulated porcine pancreatic islet cells was classified as a SCTMP [49]. In this case, the porcine islets were isolated from pancreases of neonatal piglets and cultured during 30 days, in which cell differentiation occurs by increasing the amount of insulin released from the cells, this being considered a substantial manipulation. Nevertheless, it should be noted that, since this product is based on xenogeneic cells, it is automatically considered an ATMP, as previously discussed. Finally, in 2018 the CAT considered an encapsulated allogeneic pancreatic islets-based product a non-ATMP. The consideration here is whether the encapsulation itself might change the characteristics of the islet [50].

In the US, the definitions of manipulation and homologous use are defined for HCT/Ps, and by exclusion the products based on cells and tissues that do not comply with these criteria established for HTC/Ps could be considered a biological product, and consequently an advanced therapy [43]. The criteria for HCT/Ps include "*minimal manipulation*" and "*homologous use*", while "*more-than-minimally manipulated*" and "*non-homologous use*" are considered for cell and tissue-based products considered biological drugs.

Unlike the EU, in the US there is a differential definition of minimal manipulation depending on whether or not the product consists of structural tissue. "*Minimal manipulation"* is defined as: "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement" for structural tissues, and "processing that does not alter the relevant biological characteristics of cells or tissues" for cells or non-structural tissues [51]. For clarification, structural tissue is defined as human cells/tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion (e.g. amniotic membrane and umbilical cord). On the other hand, human cells/tissues that serve as metabolic or other biochemical roles in the body, such as hematopoietic, immune, and endocrine functions, are generally considered cells/non-structural tissues (e.g., hematopoietic stem/progenitor cells). It is considered that this differentiation between structural and non-structural tissues is required, since structural HCT/Ps generally raise different safety and efficacy concerns from those of cells or non-structural tissues.

As a result, the term "processing" is defined as any activity performed on a cell and/or tissue-based product other than recovery, donor screening, donor testing, storage, labelling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage. Processing includes cutting, grinding, shaping, culturing, enzymatic digestion, and

decellularization [51]. Cell expansion, encapsulation, activation, or genetic modification are considered to be more than minimal manipulations. The aforementioned or any other additional processing steps should be considered in determining whether a product is minimally manipulated or not.

For products that contain structural tissues, "*original relevant characteristics of structural tissues*" generally comprise the properties of that tissue in the donor that contribute to the tissue's function or functions; for instance, the original relevant characteristics of amniotic membrane generally include the physical integrity, tensile strength and elasticity of the tissue. Following with the same example, preserving and packaging amniotic membrane in sheets would be considered a minimal manipulation, yet more than minimally manipulated if the amniotic membrane is ground, lyophilised and packaged as particles, since it would imply the separation of structural tissue into components whose characteristics related to serving as a barrier are altered. However, ground bone adhered to form bone particles would generally be considered minimally manipulated since it can maintain its utility as a supporting structure. For products that contain cells (both structural and non-structural) and non-structural tissues, "*original relevant characteristics*" include differentiation and activation state, proliferation potential, and metabolic activity, e.g., for hematopoietic stem/progenitor cells, the ability to repopulate the bone marrow by self-renewal and by differentiating along myeloid and lymphoid cell lines. In this case, cell selection on peripheral blood apheresis products to obtain a higher concentration of hematopoietic stem/progenitor cells for transplantation would be considered a minimal manipulation, whereas differentiating the cells by culturing under specific conditions would be considered more than a minimal manipulation because the characteristics of multipotency and capacity for self-renewal are altered. The storage of the product should also be considered, since it can alter the original relevant characteristics of the cells and tissues. If a product is stored in a buffer solution or is cryopreserved, it would generally meet the minimal manipulation criterion.

Regarding "*homologous use*", there is also a differentiation between structural and non-structural tissue. The term of homologous use for a structural tissue defines that the tissue is intended to be used for a homologous function when used to replace an analogous structural tissue that has been damaged or otherwise does not function adequately. Therefore, it is defined as the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the

donor [51]. The Agency would consider structural tissue to be performing a non-homologous function when used for a purpose different from those that it fulfils in its native state, or in a location of the body where such structural function does not normally occur. Similarly, cellular products are considered to be used for a homologous function when they are used to perform their native function, and for a non-homologous function when they are used to perform other functions [43, 52].

As it has been discussed, it is important to have a product defined since, otherwise, the legal requirements for these could be violated. In the US, this was the case of some amniotic/chorionic-based products, used for wound healing, which were considered HCT/Ps by some companies, when in fact they were biological products. These products were therefore launched to the market without a premarket review. After an inspection of the CBER Office of Compliance and Biologics Quality, an appropriate clinical development was requested to demonstrate the safety and efficacy of the intended use of the product, as well as distribution of the product to test its clinical use in humans. An IND application and the subsequent submission of a BLA approval for its marketing was required. This implied that the cost of bringing this product to the market was very different from the one initially invested, given that the preclinical and clinical development is much broader than for HCT/Ps [53, 54].

Therefore, both in the EU and in the US, to consider a cell and tissue-based product an advanced therapy, it must be ascertained that the processing of the cells implies a manipulation that alters their biological characteristics. In the EU the concept is referred as a "*substantial manipulation*", while in US it is referred as "*more-than minimally manipulated*". Regarding this term of manipulation in the US, there is a nuance that differs from EU definitions and consists in the differentiation of structural and cells/non-structural tissues in the US. The European definitions of substantial manipulation and non-homologous use would encompass both structural and non-structural tissues under the same definition. Regardless of the examples of processing mentioned for either region, for both, it is key to determine if the processing changes the original characteristics of the product. This requires a characterisation of the product during the manufacturing process, as a part of development, to corroborate whether the phenotypic and physiological characteristics of a potential product have been altered. On the other hand, the European terminology uses the term 'engineered' to denominate those cells or tissues that are substantially manipulated and/or used for a different essential function (or non-homologous use), which is mandatory criteria to classify a product as an advanced therapy. In

the US, the term of non-homologous use is not explicitly mentioned in the definition of SCT, although it is to classify a product as biologic in the general definition of cell and tissue-based products. Note that the nomenclature of "*non-homologous use*" is common for both regions, although in Europe the term "*different essential function*" would also be the one harmonized according to the EMA guidelines. All these mentioned differences in terminology can be important when submitting documents to the respective Agencies, since it is advisable to use the specific terminology used in each region (Table 4).

Combined advanced therapy medicinal products

In the EU there is a specific category for those products that consist in an ATMP combined with a medical device. A medical device is defined as any instrument, apparatus, appliance, material or other article intended by the manufacturer to be used on human beings for the purpose of: i) diagnosis, prevention, monitoring, treatment or alleviation of disease, compensation for an injury or handicap, investigation, replacement or modification of the anatomy of a physiological process, or control of conception, and ii) which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but may assist its function by such means [55]. Examples of medical devices in cATMP could be scaffolds, matrices and encapsulation systems for cells, such as microspheres, among others. The criteria to meet in this category class is that the product must incorporate, as an integral part of the product, one or more medical devices. The medical device should be used in the combination, in the same way as its intended use without additional components. On the other hand, the cellular or tissue part of the product must contain viable cells or tissues, or if containing non-viable cells or tissues, it must be liable to act upon the human body with actions that can be considered primary to those of the devices referred to [34].

In US, there is no specific category for cATMPs, but there are nine different types of combined products including drug/device, biologic/device, drug/biologic, or drug/device/biologic. The definition takes into account how the product is packaged, i.e. together in a single package or packaged separately, and if all components of the product are needed to achieve the intended use, indication or effect. Among all of these categories, the type-5 combination product named “Device Coated or Otherwise Combined with Biologic” constitutes the biologic/device combination where the device has an additional function in addition to delivering the drug, and constitutes an “integral part” of the final product, e.g. live cells seeded on or in a device scaffold

[15]. In US, a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which has at least one of the following three characteristics: i) it is recognised in the official National Formulary or the United States Pharmacopeia, or any supplement to them, ii) it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease; or iii) is intended to affect the structure or any function of the human body or other animals, and does not achieve its primary intended purposes through chemical action within or on the human body or other animals and which does not depend on being metabolized for the achievement of its primary intended purposes [56, 57].

Therefore, while in EU cATMPs are the fourth subcategory of products within the group of advanced therapies, in the US the subcategory defined for combined products is very broad and includes drugs, biological and medical devices. The category of type-5 combined products would constitute a group equivalent to what defines cATMPs in the US, where the product is a single-entity combination product, or the device constitutes "an integral part of the product" according to European definition. For both EU and US, the final combined product will be a biological and a medical device, where the definitions of medical device are equivalent: the medical device assists in the primary function of the biological component. Following MACI's aforementioned example, for both regions the porcine collagen membrane is considered a device constituent of the product, in EU a CE-marked Class III device [44, 45].

The fact of combining a biological product with a medical product complicates its development, and in the US, unlike in the EU, there are guidelines with some considerations to be taken into account during the development of these products [58, 59].

General discussion and conclusion

Our analysis reveals a difference between the EU and the US in the sub-categorisation of advanced therapies and the regulatory terminology defining them. The criteria that must be met in both the EU and the US to classify a product as an advanced therapy is similar, although the EU presents a more precise sub-classification with more defined inclusion criteria between these subcategories. The criteria to determine if a product qualifies as a gene therapy may be simpler or more obvious than for cell therapies, although there are some relevant considerations for all defined subcategories of advanced therapies that can change the classification of the product both in the EU and the US.

The EU and the US are facing similar challenges regarding the regulation of ATMPs due to their inexperience in this specific medicinal product group, and because Europe covers a variety of overlaying jurisdictions and authorities on a member state level [4, 60]. European and American legislation and regulatory guidelines launched by the EMA and the FDA show similarities and differences in the ATMP classification for both regions. It is unknown if these differences can be translated into divergent final recommendations by the regulatory authorities. Currently, the number and type of ATMPs approved differ between the two regulatory Agencies. In the EU up to 12 ATMPs have been authorized from 2009, but four of them have been withdrawn throughout the past 10 years. In the US, 9 gene and cell therapies haven been authorized and only 6 of them match for both Agencies. The rationale behind these differences is unknown but it seems feasible that a worldwide harmonization of the procedures involved in the development of ATMPs may allow to reach similar ultimate decisions. It is acknowledged that the EMA and the FDA have been collaborating for the past 15 years with the aim to ameliorate regulatory excellence. An ATMP cluster has been created under the umbrella of the reinforced EU/US collaboration on medicines with the aim to facilitate regulatory excellence of the new medicinal products [61]. Yet, Agencies´ recommendations are evolving and being updated over time in a non-parallel manner. In 2018, the FDA launched several guidelines that include specific recommendations for the development of ATMPs aimed at certain types of diseases such as haemophilia or retinal disorders [62], while the EMA guidelines published to date are more generalist, encompassing only the development of ATMPs according to the three main groups of therapies, GTMP, SCTMP, TEP. In the future, it would be convenient to begin a progressive process of convergence between both Agencies in terms of terminology, legal recommendations and characterisation requirements. In this regard, some steps could be taken to reach this alignment between regulators - for example common guidelines, increased number of EMA/FDA parallel scientific advice from the beginning of the lifecycle of the medicinal product, as well as similar post-authorization monitoring of the products or real-world evidence data generation.

Tables

Table 1. Legal and regulatory framework of biological products in United States and European Union

European Union			United States		
Type of product	**Legal framework**	**Regulatory Organism**	**Type of product**	**Legal framework**	**Regulatory Organism**
Advanced therapy medicinal products: Gene therapy products Cell therapy products Tissue engineered products	Directive 2001/83/EC (relating to medicinal products for human use) Directive 2009/120/EC (relating to medicinal products for human use as regards advanced therapy medicinal products) Regulation 726/2004/EC (Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency) Regulation 1394/2007/EC (on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004)	Clinical trials are under national competent authorities of each member state where the clinical trial will take place. Product positive opinion: CHMP Draft opinion: CAT	**Human somatic cell therapy and gene therapy products**	Section 351 of the PHSA and FDCA and Title 21 CFR 600-680 (Regulation on Biologics) (21 CFR 1271; prevent the spread of infection diseases) RMAT designation: Section 3033 of the 21st Century Cures Act (21 U.S.C. 356(g)(8))	CBER and OTAT

CAT: Committee for Advanced Therapies; CBER: Centre for Biologics Evaluation and Research; CHMP: Committee for Human Medicinal Products; FDCA: Federal Food, Drug, and Cosmetic Act; OCTGT: Office of Cellular, Tissue and Gene Therapies; PHSA: Public Health Services Act; RMAT: Regenerative Medicine Advanced Therapy Designation.

Table 2. Inclusion/Exclusion criteria in European Union

Advanced Therapy medicinal products Product category	Active substance	Purpose	Inclusions	Exclusions
Gene therapy medicinal products (GTMPs)	Recombinant nucleic acid of biological origin.	Administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. Therapeutic, prophylactic or diagnostic effect that relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.	• Plasmids DNA • Viral vectors • Genetically engineered microorganisms • Human gene editing technology • Patient-derived cellular gene therapy products	• Non-biological products (e.g. chemical synthetized nucleic acids) • Vaccines against infectious diseases
Somatic cell therapy medicinal products (SCTMPs)	Cells or tissues that have been subject to substantial manipulation or not intended to be used for the same essential function(s) in the recipient and the donor	Treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.	• Products containing or consisting of animal cells or tissues • Cancer immunotherapies • Other autologous and allogeneic cells therapies • Xenogeneic living cells • Stem cells and stem cells-derived products	• Products containing or consisting exclusively of non-viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action

Advanced Therapy medicinal products Product category	Active substance	Purpose	Inclusions	Exclusions
Tissue engineered products (TEP)	Cells or tissues that have been subject to substantial manipulation or not intended to be used for the same essential function(s) in the recipient and the donor. The cells or tissues may be viable or non-viable.	Regenerating, repairing or replacing a human tissue	• Products containing or consisting of animal cells or tissues • Products may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices • Products for cartilage or cardiac defects, among others. • Stem cells and stem cells-derived products	• Products containing or consisting exclusively of non-viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action
Combined ATMPs (cATMPs)	Combines: - one or more medical devices within the meaning of or one or more active implantable medical devices and - its cellular or tissue part must contain viable cells or tissues, or - its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.	Therapeutic, prophylactic or diagnostic effect. Regenerating, repairing or replacing a human tissue.	-	-

Table 3- Inclusion/Exclusion criteria in United States

Cell and Gene Therapy Products				
Product category	**Definition**	**Purpose**	**Examples**	**Exclusions**
Human gene therapy	Administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use.	Prevention, treatment, or cure of a disease or condition of human beings	• Plasmids DNA • Viral vectors • Genetically-engineered microorganisms • Human gene editing technology • Patient-derived cellular gene therapy products	• Non-biological products (e.g. chemical synthetized nucleic acids) • Products that are destined for the treatment or prophylaxis of infectious diseases
Somatic cell therapy	Autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo*.	Therapeutic, diagnostic, or preventive purposes	• Cancer vaccines • Cellular immunotherapies • Other types of both autologous and allogeneic cells • Xenogeneic living cells • Stem cells and stem cells-derived products • Gene therapy modified cells	• HCT/Ps under section 361 of the PHSA
Combination products				
Product category	**Definition**	**Purpose**	• **Examples**	**Exclusions**
Combination products	Two or more regulated components, i.e., drug, device, biologic as a single entity or packaged together, packaged separately but intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect.	Therapeutic, diagnostic, or preventive purposes	• Drug/device • Biologic/device: cells combined with medical devices such as natural or synthetic scaffold • Drug/biologic, or • Drug/device/biologic	-

Regenerative medicine advanced therapy designation				
Product category	**Definition**	**Purpose**	**Examples**	**Exclusions**
Regenerative medicine advanced therapy (RMAT)	A cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products	To treat, modify, reverse, or cure a serious or life-threatening disease or condition To address unmet medical needs for such disease or condition	• AT132 (Audentes Therapeutics, Inc.) • Romyelocel-L (Cellerant Therapeutics, Inc.) • AmnioFix® (MiMedx) • CAP-1002 (Capricor Therapeutics)	Products regulated solely under section 361 of the PHSA are explicitly excluded.
Human Cells, Tissues, and Cellular and Tissue-Based Products				
Product category	**Definition**	**Purpose**	**Examples**	**Exclusions**
HCT/Ps[1]	Articles containing or consisting of human cells or tissues	Implantation, transplantation, infusion or transfer into a human recipient	• Bone • Ligament • Skin • Dura mate • Heart valve • Cornea • Hematopoietic stem/progenitor cells derived from peripheral and cord blood • Manipulated autologous chondrocytes • Epithelial cells on a synthetic matrix, • Semen or other reproductive tissue • Amniotic membrane (when used alone (-without added cells-) for ocular repair)	• Vascularized human organs for transplantation • Secreted or extracted human products (e.g. milk, collagen, and cell factors) • Minimally manipulated bone marrow for homologous use, • Ancillary products used in the manufacture of HCT/P • Cells, tissues, and organs derived from animals other than humans • *In vitro* diagnostic products

1: HCT/Ps that meet the criteria contemplated in 21 CFR 1721.10(a).

Table 4 – Terminology and definitions for cell- and tissue-based products as advanced therapies

European Union[1]		United States[2]	
Term	**Definition**	**Term**	**Definition**
Substantial manipulation	Biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function during the manufacturing process.	**More than "minimally manipulated"** *	For structural tissue, processing that alters the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement. For cells or non-structural tissues, processing that alters the relevant biological characteristics of cells or tissues.
Different essential function or Non-homologous use	Cells when removed from their original environment in the human body are not used to maintain the original function(s) in the same anatomical or histological environment.	**Non-homologous use**	Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor, including when such cells or tissues are for autologous use. Basic functions of a structural tissue would generally be to perform a structural function for example, to physically support or serve as a barrier or conduit, or connect, cover, or cushion. Basic functions of a cellular or non-structural tissue would generally be a metabolic or biochemical function, such as, hematopoietic, immune, and endocrine functions.
Manufacturing	Defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of active substance(s) and the related controls.	**Processing**	Any activity performed on an cell and/or tissue-based product, other than recovery, donor screening, donor testing, storage, labelling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.
List of manipulations	Provided in Annex I of Regulation EC (No) 1394/2007	**List of processing**	Provided in Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (2017) and Proposed approach to regulation of cellular and tissue-based products (1997), and the United States Pharmacopoeia (Cellular and Tissue-based Products: 1046)

European Union[1]		United States[2]	
Term	**Definition**	**Term**	**Definition**
-	-	**Original relevant characteristics**	For products that contain structural tissues, "original relevant characteristics of structural tissues" generally include the properties of that tissue in the donor that contribute to the tissue's function or functions.
			For products that contain cells (both structural and non-structural) and non-structural tissues, "original relevant characteristics" includes differentiation and activation state, proliferation potential, and metabolic activity.
Viable cell	A viable cell is a cell that has a functional cytoplasmic membrane. [The European Pharmacopoeia provides information on assays to demonstrate cytoplasmic membrane integrity and activity < 20729 >]	**Living cells**	- [The United States Pharmacopoeia Cellular and Tissue-based Products <1046>]
Tissues	Defined in Directive 2004/23/EC (Art 3.b) as 'all constituent parts of a human body formed by cells'.	-	-

[1]: Definitions provided in EMA/CAT/600280/2010 Rev.1, CPMP/ICH/4106/00 and Regulation EC (No) 1394/2007; [2]: Definitions provided in the Code of Federal Regulation (21 CFR 1271.3; 21 CFR 1271.10), *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (2017)* and *Proposed approach to regulation of cellular and tissue-based products (1997)*; *The definition provided is minimal manipulation. For advanced therapies the term that applies is "more than minimally manipulated".

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2.2: Comparison of regulatory pathways for the approval of advanced therapies medicinal products in the European Union and the United States

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Abstract

Regulatory agencies in the EU and in the US have adapted and launched regulatory pathways to accelerate the patient access to innovative therapies, such as ATMPs. The aim of this study is to analyse similarities and differences between regulatory pathways followed by the approved ATMPs in both regions.

***Methods**:* A retrospective analysis of the approved ATMPs by the EU and US regulatory agencies was carried out until 31st May 2020. Data was collected on the features and timing for the orphan drug designation (ODD), scientific advice (SA), expedited programs designations (EP) and MAA and authorisation for both regions.

***Results**:* In the EU a total of 15 ATMPs were approved (8 gene therapies, 3 somatic cell therapies, 3 tissue engineered products, and 1 combined ATMP), while in the US a total of 9 were approved (5 gene therapies and 4 cell therapies); 7 of those were authorised in both regions. No statistical differences were found on the mean time between having the ODD or EP granted to the start of pivotal clinical trial or to the MAA among the EU and the US, although the US required less time for the MAA assessment than the EU (5.44 difference; p=0.012). The MAA assessment was shorter for those products with a PRIME or breakthrough designation. No differences were found in the percentage of ATMPs with expedited MAA assessment between the EU and the US (33.3% vs 55.5%, respectively; p=0.285) or in the time required for the MAA expedited review (mean difference 4.41, P = 0.105). Approximately half of the products in both regions required an Advisory Committee during the MAA review, and 60% required an oral explanation in the EU. More than half of the approved ATMPs (67% and 55.55% in the EU and the US, respectively) were granted with an ODD, 70% by submitting preliminary clinical data in the EU. The mean number of SA and protocol assistance per product conducted by the EMA was 1.71 and 3.75, respectively, and only 13% included a parallel advice with the HTAs bodies. 53.33% of the products conducted the first SA after the pivotal clinical study had started, reporting more protocol amendments. Finally, of the 7 ATMPs authorised in both regions, only for 2 ATMPs (28.6%) the type of MA differed and 4 out of 8 products non-commercialised in the US had a non-standard MA in the EU.

***Conclusion**:* The current approved ATMPs mainly target orphan diseases. Although the EU and the US regulatory procedures may differ, the main regulatory milestones obtained for the approved ATMPs are similar in both regions, with the exception of the time for MAA

evaluation and the number of authorised products. More global regulatory convergence might imply to simplify and expedite even more the current ATMP development among regions.

Introduction

ATMPs feature cells, genes, or tissues. In the last decade, the first advanced therapies have been launched into the market and, as a result of their recent increase in research and development, the regulatory agencies have adapted and launched new regulatory pathways compatible with the novelty, complexity and technical specificity of these products. It has been recognised by the EMA and the FDA that the evaluation of ATMPs requires specific expertise, which goes beyond the traditional pharmaceutical field [1].

There are several optional and mandatory regulatory procedures to be followed throughout drug development (Figure 1). No studies have been conducted so far to analyse the regulatory steps taken in the EU and the US for the approved ATMPs; thus, the aim of this study is to analyse and compare the regulatory pathways followed by these therapies in both regions.

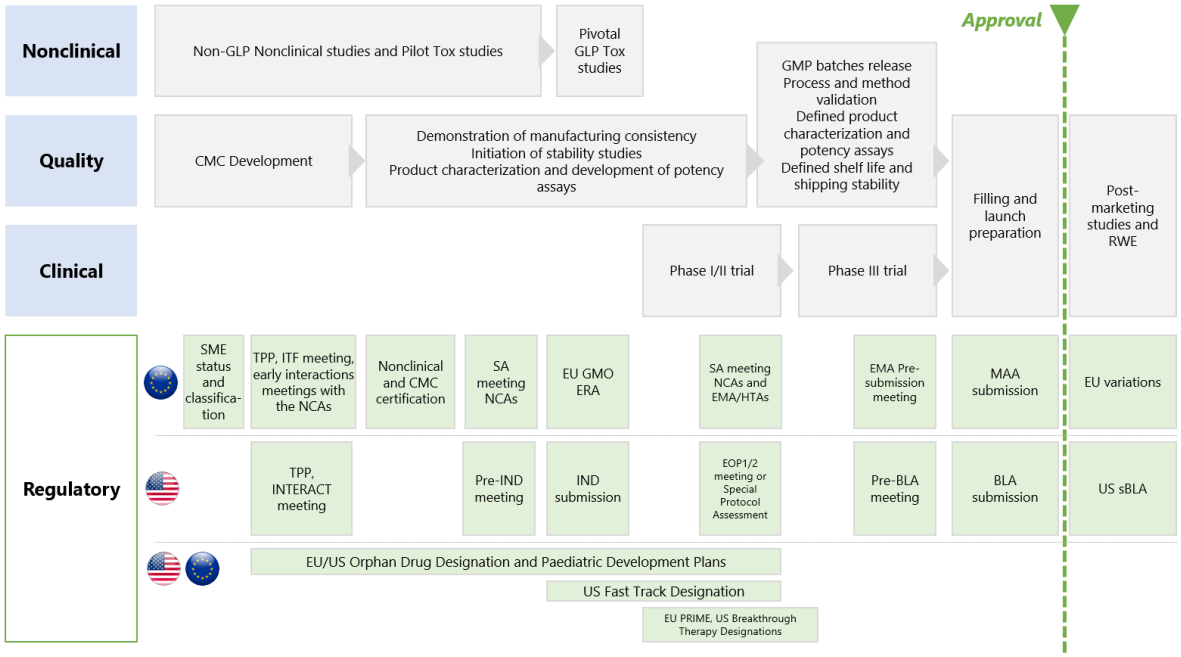

Figure 1. Overview of the EU and the US regulatory steps for advanced therapies during development

CMC: Controls Manufacturing Chemical; EOP1/2: End-of-Phase 1 or 2; EU: European Union; GLP: Good Laboratory Practices; GMO: Genetically Modified Organism; GMP: Good Manufacturing Practices; IND: Investigational New Drug; ITF: Innovative Task Force Meeting; INTERACT: Initial Targeted Engagement for Regulatory Advice; NCAs: National Competent Authorities; PD: Pharmacodynamic; SA: Scientific Advice; sBLA: Supplemental Biologics License Application; SME: Small and Medium Enterprise; Tox: toxicity; TPP:

target product profile; RWE: Real World Evidence; US: United States of America. In the US, the current good manufacturing practice (CGMP) for Phase 1 Investigational Drugs, which include biological drugs, are exempt from complying with 21 CFR part 211 (CGMP for finished pharmaceuticals) under 21 CFR 210.2(c) (referred to as phase 1 investigational drugs). However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in § 312.21(b) and (c), or the drug has been lawfully marketed. In the EU, cGMP requirements are detailed in EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice - Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.

Methodology

To perform the retrospective study of the approved ATMPs in the EU and the US the following approach has been used:

Search strategy: Data collection was primarily extracted from the EMA and FDA websites (www.ema.europa.eu; www.fda.gov). European data was gathered from European Public Assessment Reports, orphan designations product reports and publicly available EMA agendas, minutes and highlights. The US data were collected mainly from FDA drug summaries reports and "Summary Basis of Regulatory Action" documents and other approval history related documents published for the approved cellular and gene therapy products. The search was carried out until 31st May 2020. In addition, a search for the main clinical trials of the approved ATMPs was conducted using ClinicalTrials.gov database.

Eligibility criteria: The medicine products classified as ATMPs according to the EMA criteria and those classified as cellular and gene therapy products in the US were included in the study [2][3]. To compare only those products that are considered ATMPs in both regions, the approved hematopoietic progenitor cell cord blood products in the US have been discarded from this analysis since are not considered ATMPs products in the EU but under the transplantation laws. In addition, only product under centralised procedure in the EU have been considered, excluding those ATMPs approved under ¨hospital exemption", since these products are non-industrial manufactured and tailor-made for a single patient.

Data extraction and collected variables: We designed specific data extraction forms using Microsoft Excel 2019 to collect the information related to the approved ATMPs regulatory development: i) SA number and timing in the EU and US pre-investigational new drug applications (pre-IND) and pre-biological license applications (pre-BLA) meetings, along with Special Protocol Assessment procedure, ii) timing and features for the European and the US ODD, including significant benefit for the EU, iii) timing and features of expedited programs,

MAA and type of approval for the approved ATMPs in both regions. The expedited programs were classified as PRIME in the EU, and Breakthrough designation, Fast Track, RMAT in the US. Information on the expedited programs for other chemical and biological drugs was also collected. The types of MA were classified as standard approval, conditional approval, and exceptional circumstances in the EU, and standard approval and accelerated approval program in the US. The date for the EU approval was based on the CHMP positive opinion. Finally, the issues raised to the scientific advisory groups meetings during the MAA evaluation were collected for both regions, and its categorisation approach were sourced and adapted from Barkholt et al. [1]. ATMP classification and certification procedures have been exclude from the analysis since are European specific, as well as the ERA procedures as they differ among regions [2].

Statistical analysis: Statistical analysis of categorical and continuous variables was made by means of the distribution of frequencies, proportions, confidence intervals (CI) 95%, means, standard deviation (SD), median, interquartile range (IQR), and range (minimum and maximum). Statistical differences were evaluated using the chi-square test for categorical variables and paired student's t-test for continuous variables. Comparison of temporal variables were only made for common ATMPs approved in both regions. A two-tailed significance was set at a level of 0.05. The statistical analysis was performed using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In the EU a total of fifteen ATMPs were approved for sixteen different clinical indications, while in the US a total of nine therapies were approved for ten clinical indications. The ATMPs approved in both regions, the year of submission and approval, and the clinical indications authorised are shown in Table 1. A total of seven of these ATMPs were approved in both the EU and the US regions (five being GTMPs), eight therapies were only approved in the EU, and two were only approved in the US. In the EU, eight (53.33%) ATMPs were GTMPs, three (20%) were SCTMPs, three were TEP (20%), and one (6.66%) was a combined ATMP. In the US, five (55.55%) were GTMPs and four (44.44%) were cell therapies.

Orphan Drug designation

Ten out of fifteen approved therapies in the EU (67%) were granted with an ODD during their development (seven were GTMPs, two SCTMPs and one TEP), while in the US five GTMPs out of nine approved ATMPs (55.55%) obtained this designation. In the EU, Yescarta®, Kymriah® and Luxturna® received two ODD each product, while in the US Yescarta® received three ODD and Kymriah two (Table 2). For those seven products that were developed both in the EU and the US, four of them obtained an orphan designation in both regions (57.14%).

In the EU significant benefit did not need to be demonstrated for five medicinal products at the time of designation, as they targeted rare conditions lacking any approved therapies in the EU (33.3% of all approved ATMPs and 50% of those with an ODD). Only three ATMPs approved (30% of the approved products with an ODD) obtained the designation supported only by preclinical data (Glybera®, Luxturna® and Zynteglo®), for Alofisel® this information was not known, while the rest submitted preliminary clinical data (70%) (Table 2).

The mean (SD) time between having the ODD granted to the start of pivotal clinical trial in the EU was 3.16 (26.93) months (median -2.50; IQR -15.75, 30.25; Range -34, 41) and -7.57 (28.72) months for the US (median -15; IQR -25, 14; Range -49, 36), meaning that the main clinical trial started before having the ODD granted (Figure 2). When analysing the four ATMPs with an orphan designation in both regions, the mean (SD) time between having the ODD granted to start de pivotal clinical trial in the EU was 1.50 (16.37) months (median -2.50; IQR -11.25, 15.25; Range -15, 28) and -5 (30.57) months for the US (median -3; IQR -31, 19.50; Range -49, 36). This difference was not statistically significant (difference = 6.5 months; CI 95% -20.14, 33.14; p=0.558).

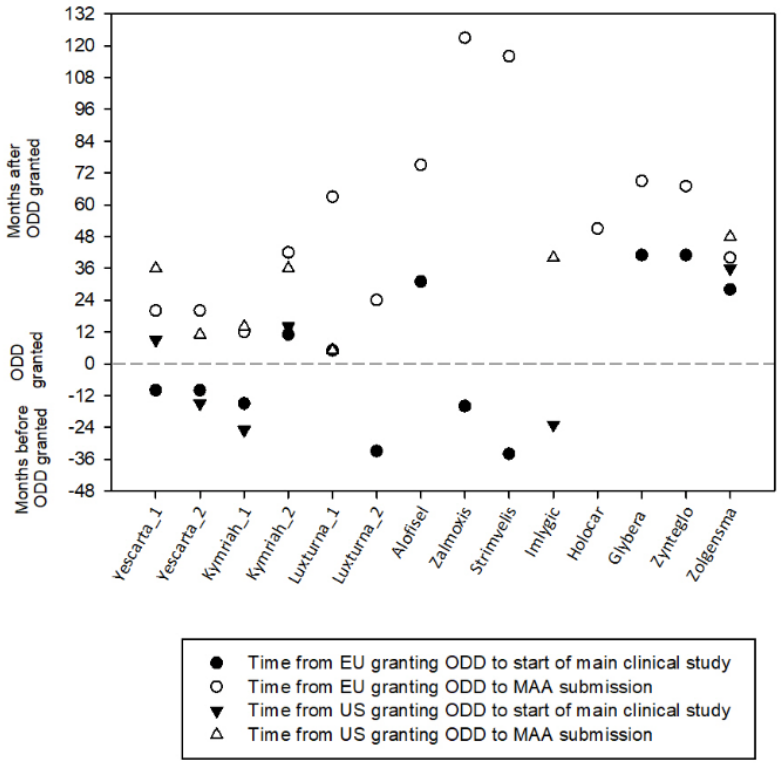

Figure 2. Relationship between date of granted ODD and start of main clinical study and MAA submission.

No prospective clinical trials were conducted in support of Holoclar MAA. Yescarta_1 and Kymriah_1: Treatment of diffuse large B cell lymphoma indication in the EU and the US; Yescarta_2: Treatment of primary mediastinal large B-cell lymphoma indication in the EU and the US; Kymriah_2: Treatment of B-lymphoblastic leukaemia/lymphoma in the EU and the US; Luxturna_1: Treatment of Leber's congenital amaurosis in the EU and treatment of inherited retinal dystrophy due to biallelic RPE65 gene mutations in the US; Luxturna_2: Treatment of retinitis pigmentosa in the EU. Yescarta received three ODD in the US: i) treatment of diffuse large B-cell lymphoma, ii) treatment of primary mediastinal B-cell lymphoma and iii) treatment of follicular lymphoma. The two latest indications have been clustered (Yescarta_2), since were granted almost at the same time. EU: European Union; MAA: Marketing Authorisation Application; ODD: Orphan Drug Designation; US: United States of America.

The mean (SD) time between having the ODD granted to the MAA submission in the EU was 55.53 (35.13) months (median 51; IQR 22, 72; Range 12, 123) and 27.14 (16.73) months for the US (median 36; IQR 11, 40; Range 5, 48) (Figure 2). When analysing the four ATMPs with an orphan designation in both regions, the mean (SD) time between having the ODD granted to MAA was 32.83 (19.02) months in the EU (median 30; IQR 20, 47.25; Range 12, 63) and 28.3 (14.29) months for the US (median 30.50; IQR 13.25, 39; Range 11, 48). This difference was not statistically significant (difference = 4.50 months; CI 95% -15.21, 24.21; p=0.583).

Of those therapies that were granted with an ODD, none of them lost the designation after their MA and only Alofisel® needed an oral explanation during the EU MAA procedure to maintain the designation. Finally, Kymriah® and Zolgensma® (13.33% of the approved products)

required the submission of a critical report addressing the possible similarity with other authorised orphan medicinal products in the EU.

Scientific advice procedures

In the EU, all authorized ATMPs followed a SA or a protocol assistance (in case of an orphan medicinal product) with the EMA. The mean (SD) number of SA per product was 1.71 (0.75) for product (median 2; IQR 1, 2; Range 1, 3) and the mean (SD) number of protocol assistances was 3.75 (1.05) for product (median 4; IQR 3, 4.75; Range 2, 5). The questions for all products pertained to quality, nonclinical and clinical development. A total of 6 (40%) of the approved therapies had the first EMA SA before the start of pivotal clinical study, while a total of 8 products (53.33%) had it later (Figure 3A). The mean (SD) time from the first SA to the conduct of the pivotal study was -2.50 (41.34) months (median 6; IQR –35, 15.5; Range -74, 85). The mean (SD) number of reported protocol amendments to the pivotal study for those products that had the SA after starting this main study was 5.60 (1.67) (median 6; IQR 4, 7; Range 3, 7), while for those products that had the SA before starting the main study was 3.75 (1.67) (median 4; IQR 2.25, 5; Range 1, 6). The mean (SD) time from the first EMA SA to the MAA was 55.86 (33.23) months (median 46; IQR 40, 70; Range 10, 129). Only Zynteglo® conducted a parallel advice with the HTA bodies, whereas Kymriah® benefited from the pilot version of this program (13.33% of the ATMPs approved products in the EU).

For the US, Kymriah®, Yescarta®, Luxturna® and Zolgensma® had pre-BLA meetings. The mean (SD) time from the pre-BLA meeting to the MAA was 7.40 (5.68) months (median 5; IQR 2.5, 13.5; Range 2, 14). Kymriah®, Luxturna® and Zolgensma® also had reported pre-IND meetings with a mean (SD) time from these meetings to the conduct of the pivotal study of 47.50 (34.78) months (median 46.50; IQR 15.50, 80.50; Range 13, 84) and 74.75 (47.30) months (median 63; IQR 36.75, 124.50; Range 34, 139) from the meeting to the MAA. The applicant of Kymriah® and Imlygic® applied for the Special Protocol Assessment procedure one year before the conduct of the main trial (Figure 3B).

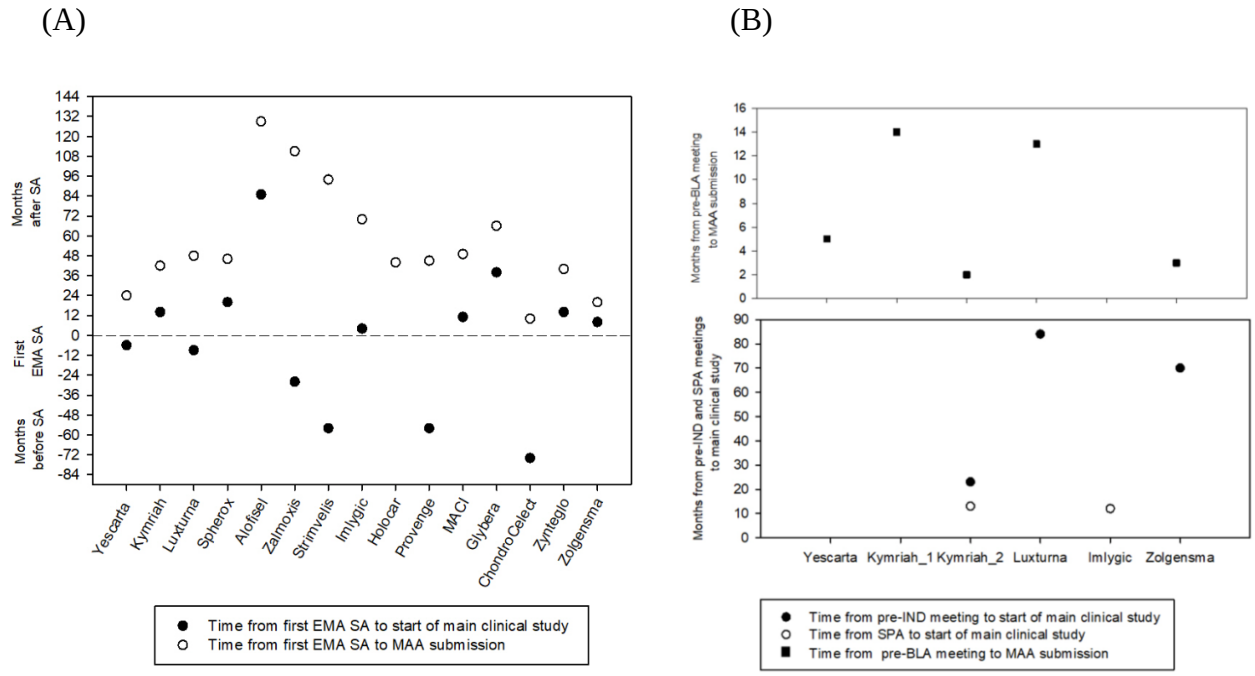

Figure 3. (A) Relationship between date of first EMA Scientific Advice and start of main clinical study and MAA submission. (B) Relationship between the reported meetings with the FDA and start of main clinical study and MAA submission.

No prospective clinical trials were conducted in support of Holoclar MAA. Kymriah_1: Treatment of diffuse large B cell lymphoma indication; Kymriah_2: Treatment of B-lymphoblastic leukaemia/lymphoma. EMA: European Medicines Agency; MAA: Marketing Authorisation Application; pre-IND: pre-Investigational New Drug; SA: Scientific Advice; SPA: Special Protocol Assessment.

Expedited programs designations

In the EU, four approved ATMPs obtained the Priority Medicines (PRIME) designation (26.67%), three of them the same year that the scheme was launched, Kymriah®, Yescarta® and Zynteglo®, and the following year for Zolgensma®. All the therapies, except for Zolgensma®, obtained the PRIME designation after having started the main clinical trial that was the base of the submission. The mean (SD) time from the start of the pivotal clinical trial to the PRIME designation was 5.25 (10.56) months (median 6.50; IQR -5.50, 14.75; Range -8, 16) (Figure 4A). The mean (SD) time from obtaining the PRIME designation to the MAA submission was 18.66 (4.46) months (median 20.28; IQR 14.61, 23.19; Range 14.04, 24.24). Both Kymriah® and Yescarta® obtained the designation just over a year before the MAA submission, and around two years before for Zynteglo® and Zolgensma® (Figure 4B). Although CAR-T products were approved for the same indication, i.e., "relapsed or refractory diffuse large B-cell lymphoma (DLBCL)" in adults, Kymriah® obtained the PRIME designation for the treatment of paediatric patients with relapsed or refractory B cell acute

lymphoblastic leukaemia (ALL) while Yescarta® obtained the designation for DLBCL indication.

In the US, four out of nine ATMPs approved were granted with the Breakthrough designation (44.44%) (Kymriah®, Yescarta®, Luxturna® and Zolgensma®). All these therapies obtained the Breakthrough designation after having started the main clinical trial that was the base of the submission, except for Zolgensma®. Kymriah® obtained two Breakthrough designations, one for the B-cell precursor ALL indication and the other for DLBCL indication. The mean (SD) time from the start of the main clinical trial to obtain the Breakthrough designation was 10 (15.13) months (median 11; IQR -2.50, 22; Range -15, 23) (Figure 4A). The mean (SD) time from obtaining the Breakthrough designation to the MAA submission was 20.2 (8.14) months (median 19.56; IQR 13.02, 28.50; Range 11.04, 30.96). Like in the EU, both Kymriah® and Yescarta® obtained the designation just over a year before the MAA submission, and over two years before for Luxturna® and Zolgensma® (Figure 4B). Three approved products (33.33%) received the Fast Track designation (Provenge®, Imlygic® and Zolgensma®). Zolgensma® obtained both Fast Track and Breakthrough designations consecutively. The mean (SD) time from the start of the main clinical trial to obtain the Fast Track designation was -8.33 (35.64) months (median 2; Range -48, 21). The mean (SD) time from obtaining the Fast Track designation to the MAA submission was 58.96 (15.57) months (median 60.12; Range 42.84, 73.92). None of the approved ATMPs have been granted with a RMAT designation and no product with this designation has been launched yet to the US market.

(A) (B)

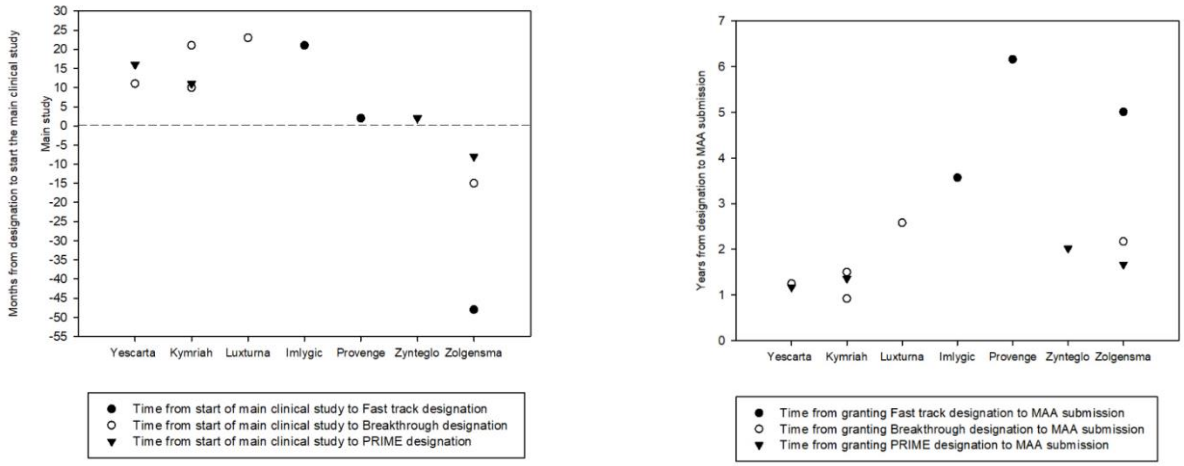

Figure 4. (A) Relationship between date of granting expedited programs and start of main clinical study. (B) Relationship between date of granting expedited programs and MAA submission.

(A)(B). Kymriah obtained the Breakthrough designation for the two following indications: i) treatment of adult patients with diffuse large B-cell lymphoma (DLBCL), and ii) treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory or in second or later relapse. MAA: Marketing Authorisation Application; PRIME: PRIority Medicines designation.

When analysing the three common ATMPs approved in the EU and the US, the mean (SD) time between having the expedited designation granted to start de pivotal clinical trial in the EU was 6.33 (12.66) months (median 11; Range -15, 28) and 5.66 (18.58) months for the US (median 11; Range -15, 21). This difference was not statistically significant (difference = -0.66 months; CI 95% -23.75, 22.42; p=0.912). The mean (SD) time between having the expedited designation granted to MAA in the EU was 16.80 (3.02) months (median 18; Range 14.04, 20.04) and 19.68 (5.70) months for the US (median 18; Range 15, 26.04). This difference was not statistically significant (difference = 0.24 months; CI 95% -0.32, 0.80; p=0.209).

The cumulative PRIME designations granted from May 2016 to May 2020 for ATMPs was 32 out of 76 (42.10%) designations requested, while for other chemical and biological drugs was 36 out of 199 (18.09%) requested (p<0.0001) (Figure 5). No cumulative data is reported for the Breakthrough designation. The reported cumulative RMAT requests received from December 2016 until May 2020 add up to a total of 139, and of those 48 were granted (34.5%), 76 were declined (54.67%) and 6 were withdrawn (4.3%). Since both RMAT and PRIME were launched in 2016, the cumulative data indicates that slightly more PRIME designations are granted than RMAT for ATMPs (42.1% vs 34.5%, respectively).

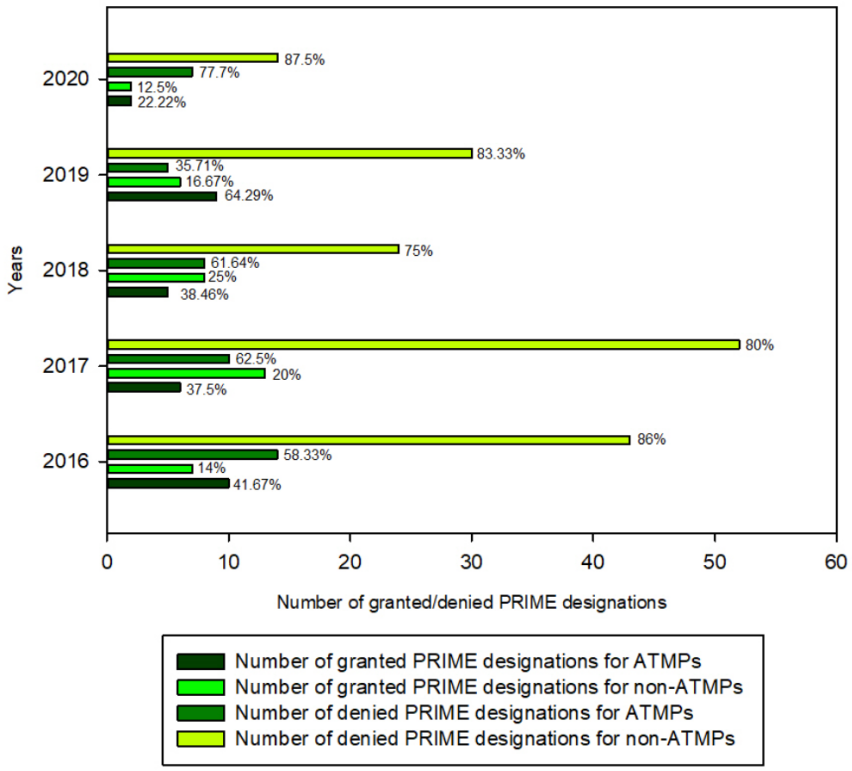

Figure 5. Number of PRIME designations granted and denied for ATMPs vs non-ATMPs (from May 2016 to May 2020).
ATMPs: Advanced Therapies Medicinal Products; PRIME: PRIority Medicines designation.

Marketing authorization application

The mean (SD) time required from submission of the MAA to its final approval in the EU was 17.96 (10.97) months (median 17.55; IQR 10.78, 21.42; Range 7.69, 53.49) and 10.96 (4.62) months for those therapies with a PRIME designation (median 9.30; IQR 7.72, 15.86; Range 7.69, 17.55). The mean (SD) time of the first clock stop for all approved ATMPs was 6.56 (9.81) months (median 3.65; IQR 2.16, 6.19; Range 0.85, 43.70), while for therapies with the PRIME designation was 1.59 (0.63) months (median 1.66; IQR 0.95, 2.16; Range 0.85, 2.20) and 9.03 ± 11.35 months for those without the PRIME designation (median, 5.55, IQR, 3.65–8.23, range, 2.86 - 43.70). The mean (SD) time for the second clock stop for all approved ATMPs was 2.03 (2.22) months (median 1.05; IQR 0.64, 2.38; Range 0.03, 7.75). After this clock stop, there were second rounds of outstanding issues for nine of the approved ATMPs analysed (60%), and even third and fourth rounds for ChondroCelect® and Zalmoxis® respectively (13.33% of the approved products). For Zynteglo®, at Day 180 there were no outstanding issues, although the European Commission requested clarifications on the label after the Committee for Advanced Therapies (CAT)/Committee for Medicinal Products for

Human Use (CHMP) positive opinion. Finally, nine of the approved products required an oral explanation (60%) to obtain the approval.

In the US, the mean (SD) time required from submission of the MAA to its final approval was 8.16 (3.05) months (median 6.98; IQR 5.95, 10.31; Range 5.13, 14.98) and 6.85 (1.10) for those products with a Breakthrough designation (median 6.63; IQR 5.49, 7.56; Range 5.13, 7.72). It took 7 months for Yescarta® and Luxturna® to obtain the approval through a rolling submission.

The mean (SD) time required from submission of the MAA to its final approval between approved ATMPs in both regions was 13.64 (4.58) months in the EU (median 13.76; IQR 8.56, 17.81, Range 7.82, 19.78) and 8.20 (3.29) months for the US (median 6.98; IQR 6.11, 10.40; Range 5.13, 14.98). The difference was statistically significant (difference = 5.44 months; CI 95% 1.63, 9.25; p=0.012).

A total of seven products (46.67%) in the EU and six products (66.66%) in the US required an Advisory Committee (AC) during the MAA. The issues raised to the advisory committees were different in the EU and the US and the most common questions are related with the target population, the evidence of clinical efficacy and clinical pharmacology (including dose and route of administration) (Table 3).

Expedited Marketing Authorisation assessments

The MAAs of Strimvelis®, Yescarta®, Kymriah®, Zynteglo® and Zolgensma® were reviewed under an accelerate assessment (AA) (33.33% of the approved products), being the mean (SD) time from submission to final approval 10.96 months in the EU (median 10.78; IQR 7.75, 14.29; Range 7.69, 17.55). Only Zynteglo® could keep the AA until the end of the procedure.

A total of 5 (55.55%) of the approved products obtained the priority review in the US, including all the approved therapies that were granted the Breakthrough designation (Yescarta®, Kymriah®, Luxturna® and Zolgensma®). Provenge® was granted with a Fast-Track designation, also obtaining the priority review, since at the time of its development the breakthrough designation was not available. The mean (SD) time for approval under priority review was 6.56 (0.91) months (median 6.73; IQR 5.74, 7.25; Range 5.13, 7.72).

There were not differences in the percentage of ATMPs with an expedited MAA assessment between the EU (33,3%; CI 95%: 15%, 58.5%) and the US (55.5%; CI 95% 26.6%, 81.2%) (p=0.285).

Kymriah®, Yescarta® and Zolgensma® obtained expedited MAA review in both regions (42.86% of ATMPs authorised in both regions). The mean (SD) time from submission to final approval of these products was 10.99 (4.58) months in the EU (median 9.3; IQR 7.82, 15.85; Range 7.82, 17.55) and 6.58 (1.07) months in the US (median 6.73; IQR 5.49, 7.50; Range 5.13, 7.72). The difference was not statistically significant (difference = 4.41; CI 95% -1.70, 10.53; p=0.105).

Types of marketing authorisation

In EU, ten (66.7%) ATMPs have been authorised under a standard approval, four (26.7%) under conditional approval and one (6.7%) under exceptional circumstances. In US, all therapies were authorised under standard approval. Four out of eight products non-commercialised in the US had a non-standard MA in the EU. Five therapies were withdrawn in the EU, while two of those are still authorised in the US (Table 1).

Discussion

The major finding of the current study is that the main regulatory milestones are similar between regions although there are some differences (Figure 6).

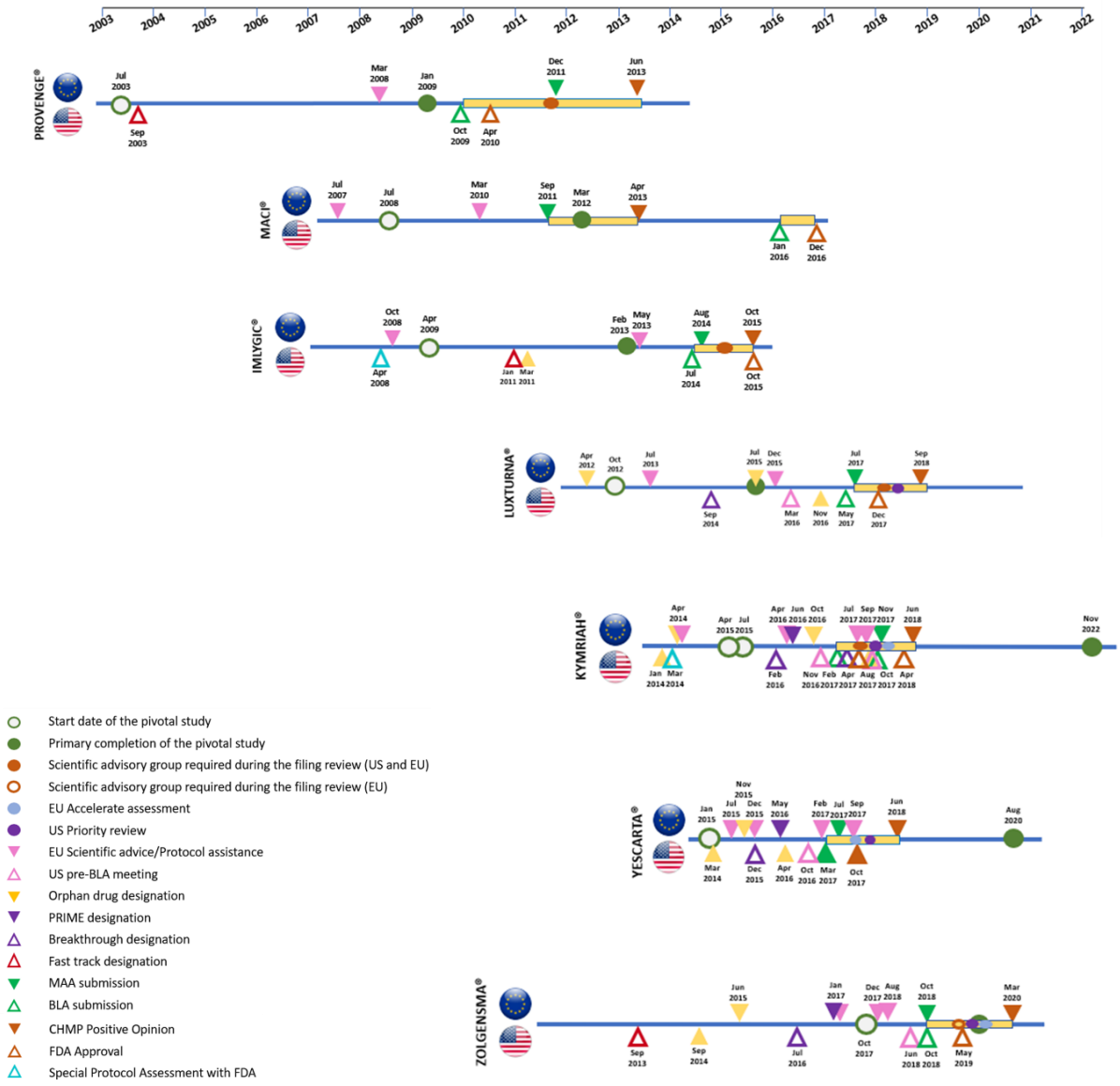

Figure 6. Comparison of regulatory pathways followed by ATMPs that were authorised in both regions.

Over the last years a constant effort has been made to develop ATMPs mainly focused on orphan conditions. Almost 2.100 clinical trials studying ATMPs were initiated between January 2014 and June 2019 worldwide, most of them cell and gene therapies in phase I or II of clinical development [6]. Interestingly, three times more of these interventional clinical trials were conducted in North America than in Europe. However, only 15 ATMPs in the EU and 9 in the US have achieved MA until May 2020, representing 1.6% of overall approved products in Europe from 2009. This data reveals the necessity to understand the gap between the large

number of investigational products and the approved ATMPs, and whether specific regulatory procedures were used to achieve their status in the EU and the US.

When analyzing all the steps involved in the procedure to achieve MA, the authors observed that more than half of the approved ATMPs obtained the orphan status. For the European and US ODD programs the medical plausibility needs to be demonstrated, as well as the prevalence of the disease. However, unlike the EU, in the US there is no need to proof significant benefit over standard of care [7][8]. Our study indicates that in the EU, half of the approved ATMPs with an ODD targeted unmet medical needs, avoiding significant benefit demonstration and in part contributing to an open label clinical designs. Moreover, the time analysis related to achieve orphan designation exhibits that there is no representative mean time to apply for the ODD and it is mainly product-specific and dependant on the duration of the clinical development. Most of the approved therapies applied to the ODD once preliminary clinical data in patients was available, maybe due to the fact that the conventional nonclinical toxicological packages are not applicable to these therapies because of their patient-specificity and the lack of preclinical models [9]. On the other hand, the therapies that have a short period between the ODD granted status and the MAA submission might be in part due to the abbreviated clinical development, common in the case of advanced therapies, whereas those products with prolonged periods were probably attributed to recruitment issues, common in the case of rare diseases.

SA is a non-binding regulatory procedure offered to the sponsors at any stage of the ATMP development program. Although SA is not mandatory, it has been previously shown that products following SA recommendations at early stages of the clinical development are more prone to achieve MA [10]. In the EU, an advice can be provided by the EMA or the National Competent Authorities (NCAs). The NCAs SA are related to the suitability of early clinical development, whereas the EMA SA will usually focus towards the pivotal clinical trials that will support the MAA. Interestingly, half of the approved products did not seek advice with the EMA before starting the main study and this did not imply an impact on approval success but a mean of two additional amendments to the protocol of the main study were observed. The fact that these therapies target unmet medical needs and the lack of clinical regulatory guidelines at that time for specific medical conditions might increase the need for this procedure. In 2020, the EMA has promoted a new pilot program to facilitate multiple SA with the NCAs [11]. It should be noted that the review will be independent among the NCAs and

diverging opinion may still occur. Other options prior to a formal SA include informal meetings with the NCAs in the EU focused on innovative therapies [12][13][14] or the called ITF and INTERACT meetings with the EMA and FDA, respectively [15][16].

On the other hand, the early development strategy should include discussions with the authorities regarding evidence generation. The abbreviated clinical developments and non-controlled trials that follow most of ATMPs, brings in uncertainty about long-term efficacy and safety, being the main constraint for obtaining product´s reimbursement [3]. Although approved through a standard authorisation, Provenge®, MACI® and ChondroCelect® were withdrawn due to poor commercial performance and/or lack of reimbursement in the EU countries [4][5][6]. Despite the importance of this point, only 13% of the products conducted a parallel advice with the EMA and with the European Network for HTA bodies [21].

In the US, limited information about meetings conducted with the FDA is available. Interestingly, in the case of ATMPs, Special Protocol Assessment procedure were also reported, where the sponsors might reach an agreement with the FDA on the design and size of a single clinical trial to support the MA [22]. End-of-phase 2 meetings with the FDA are aimed to obtain advice on pivotal study design and would be similar to the EMA SA when is conducted with the same purpose. No comparisons among regions can be done for these SA procedures since there is not publicly information about when End-of-phase meetings were conducted with the FDA for the approved ATMP products.

Another milestone of the regulatory pathway in the EU and the US is the possibility to apply for an expedited program (Table S1). These programs offer a continuous support and guidance from the agencies during the clinical development to optimise and speed up the drug development plans and evaluation. Expedited programs are mainly aimed for those products that target unmet medical needs, serious conditions or bring a major therapeutic advantage to patients without treatment options. The FDA has created three type of expedited programs: the Fast Track designation in 1997, the Breakthrough Therapy designation in 2012 and the RMAT in 2016, while the EMA launched the PRIME designation scheme in 2016 [7][8][9].

The present data points that more Breakthrough designations have been granted than PRIMEs for the approved ATMPs (44.4% vs 26.7%). Although a low number of approved ATMPs obtained PRIME designation, almost all the ATMPs that were under development when these programs were launched benefited from them except for Luxturna® in the EU. Our results also

demonstrate that the mean time from the start of the main clinical trial to obtain PRIME or Breakthrough designation or the mean time from obtaining these designations to the MAA submission was similar for both regions. However, the time for obtaining PRIME designation might be not representative, since it might have been granted earlier for these therapies based on exploratory clinical data, if this program was available at that time. Further analysis is required to conclude the mean timing to apply for this program, although for the current approved therapies was requested after the main clinical trial started. The fact that the Breakthrough designation was available but obtained later during the development, might be attributed to the qualifying criteria of this program, where clinical evidence that demonstrate substantial improvement over available therapies is required.

With respect to Kymriah®, Yescarta® and Zolgensma®, both PRIME and Breakthrough designations were obtained consecutively from each other. Although the Breakthrough Therapy and the PRIME designations would be equivalent among regions the development requirements and the regulatory guidance may differ. However, our data displays that the access of ATMPs to expedited programs are either approved or rejected similarly in both agencies.

In the US, RMAT designation includes all the benefits of the Fast Track and Breakthrough Therapy programs and does not require evidence to indicate that the drug may offer improvement over available therapies. Therefore, RMAT designation would have been an attractive option for these approved products, but it is assumed that the development was already too far advanced at the time the RMAT designation was put in place by the FDA.

In the EU, there is a notable difference between the number of PRIME designations that have been granted for ATMPs in comparison with other products, including chemicals and other biological drugs. This fact empathises again the type of disease that the current ATMPs target. Even if the clinical design for ATMPs is typically non-controlled, this fact does not seem to be an obstacle to get the expedited designations.

The final step to achieve MA is the MAA. The standard timelines for a BLA review comprise 11 months of the 60-day filing date and around 11 months for the CHMP Opinion in the EU (considering 210 days for the assessment and 4 months approx. for the clock stops). For priority reviews in the US or AA in the EU this standard timelines can be reduced to 6 months approximately (including clock stop of one month in the EU) [26][27]. For the approved ATMPs, the time required from the submission of the application to the approval is shorter for

the US, requiring a mean of approximately 10 months less in comparison with the EU. In the EU, the median time required for the MAA evaluation under standard or accelerated review exceeds the theoretical standard timelines by ~7 and ~5 months respectively. In the US, the median time for the priority review exceeds the theoretical timelines by only 0.56 months. It should be noted that all the products with PRIME and Breakthrough designation obtained the AA and priority review for the MAA, respectively.

The duration of the first clock stop of the EU MAA has usually an average of 3 to 6 months, and in the case of approved therapies, this tends to be towards the upper limit. Spherox® is considered an outlier since they spent almost 4 years in clock stop highly likely due to the major issues related to quality; a similar case occurred with Holoclar® that had a clock stop of 13 months. The four therapies with PRIME designation had a considerably shorter clock stop compared with other therapies without these designations. Continuous guidance from the Agencies during the development might reduce the number of major objections during the evaluation, as well as help applicants to anticipate the potential questions. In the case of the approved ATMPs there were second rounds of outstanding issues after the second clock stop for half of the approved ATMPs and even third and fourth rounds for some products. This fact might reflect the immaturity of the data initially submitted. With the exception of Zolgensma® that had a second round of outstanding issues, none of the products with a PRIME designation had second rounds of questions after second clock stop.

In the US, those products with a Breakthrough designation had a shorter MAA review time, associated to a priority review. By contrast, the rolling review offers the possibility to submit completed sections of the BLA, rather than waiting until the whole dossier required for the application is available [25]. Yescarta® and Luxturna® agreed on a rolling submission with the FDA, the latter also being eligible for priority review once the BLA was filed. The fact of having submitted this way did not shorten the timelines of the BLA review in comparison with other drugs submitting in a conventional manner.

In exceptional cases, during the EU or US MAA review there is the need for an ad hoc Expert Group consultation in order to clarify issues raised by the reviewers [28][29]. The fact that in both regions approximately half of the assessed products required this additional expert consultation indicates the complexity and specificity of these therapies, including the type of target diseases and the clinical programs with alternatives designs. Interestingly, while the main

development milestones are similar between regions, the issues raised to these external committees during the MAA for the approved ATMP differ between both agencies.

Regarding the milestone of obtaining an expedited MAA assessment in the EU, an AA allows to reduce the timeframe for the MAA if the product is of major interest for public health and therapeutic innovation. Under this procedure, a first 30-day clock stop is expected (compared to a standard 3-6 months clock stop), and a second clock-stop should not occur [10]. Although four out of five products with a granted AA had the shortest review time compared to other approved ATMPs, with the exception of Zynteglo®, the timelines for approval did not meet the expectations of an AA and there was a shift to the standard timelines. For Yescarta® and Kymriah®, the AA was no longer compatible due to major objections in the first and second clock-stop, while Zolgensma® presented deficiencies in many quality and clinical aspects of the dossier. Therefore, it would be advisable for the developers to present a mature dossier when requesting an AA and to anticipate potential questions that may raise during the clarification phase to shorten it as much as possible, otherwise, the AA loses its purpose.

The equivalent program in the US would be the priority review designation. While the expedited review designations do not guarantee a priority review, most Breakthrough therapy designations products are assigned priority status. The priority review implied a shorter time of review in comparison with other approved therapies without this designation, except for Laviv® (i.e., Imlygic®, MACI® and Gintuit®). For those products with an expedited MAA review, the time required from the submission of the application to the approval is shorter for the US, requiring a mean of 4.4 months less in comparison with the EU, although this difference is not statistically significant.

Finally, and with regards to a MA via the centralized procedure for an ATMP in the EU may be granted in three ways: standard, conditional or marketing authorization under exceptional circumstances [31][32]. In the US there are two types of MAA, the standard and the accelerated approval [33] (Table S2). For most of the therapies approved in both regions the type of MA granted was the equivalent. Half of products not commercialised in the US but in the EU obtained a non-standard EU approval. In consequence, all of them required post-authorisation studies to provide comprehensive and conclusive clinical data that sometimes may also result in a negative benefit-risk balance. This was the case of Zalmoxis® that failed to show benefit on the primary endpoint and the application had to be withdrawn [34][11].

The limitations of this study include a small sample size, above all for those ATMPs approved both in the EU and the US, and further analysis is required to conclude differences between regions. In addition, this study is limited to the approved ATMPs and not including the ones under current development. The public information available is not the same for both regions, which hamper the analysis. Nevertheless, this is an exhaustive study that evaluates and compares, when possible, the regulatory steps taken for the approved ATMPs so far and no similar analysis were found in the literature by the authors.

Conclusions

The first ATMPs have been launched in the last decade mainly targeting orphan diseases. From a regulatory standpoint, there are multiple procedures available to facilitate and foster the development of these therapies allowing an earlier MA. Although the EMA and the FDA have their own regulatory recommendations with regards to the preclinical and clinical development, we have demonstrated that the main regulatory milestones obtained for the approved ATMPs are similar. Nevertheless, the number of authorised products, and the time for MAA evaluation differs among regions. Increased regulatory convergence among the main regulatory agencies is a current topic of debate and might imply one of the key factors to simplify and expedite the approval of ATMPs.

Tables

Table 1. Overview of the approved advanced therapy medicinal products in the EU and the US (until May 2020)

Product	Product description	EU Indication[1] and approval	US Indication[1] and approval
Axicabtagene ciloleucel (Yescarta®)	Cell-based GTMP. Autologous T cells transduced gamma retroviral vector	• Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) • Treatment of primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy	• Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
		Submitted: 29 Jul 2017 Status: Authorised CHMP PO: 28 Jun 2018	Submitted: 31 Mar 2017 Status: Authorised Approved: 18 Oct 2017
Tisagenlecleucel (Kymriah®)	Cell-based GTMP. Autologous T cells transduced with lentiviral vector	• Treatment of paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse • Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.	• (1) Treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse • (2) Treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
		Submitted: 02 Nov 2017 Status: Authorised CHMP PO: 28 Jun 2018	(1) Submitted: 27 Oct 2017 (2) Submitted: 02 Feb 2017 Approved: 01 May 2018 Approved: 30 Aug 2017 Status: Authorised
Voritegene meparvovec (Luxturna®)	Non cell- based GTMP. AAV-2	• Treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells	• Treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells
		Submitted: 29 July 2017 Status: Authorised CHMP PO: 20 Sep 2018	Submitted: 16 May 2017 Status: Authorised Approved: 19 Dec 2017

Product	Product description	EU Indication[1] and approval	US Indication[1] and approval
Spheroids of human autologous matrix-associated chondrocytes (Spherox®)	TEP. Spheroids of human autologous matrix associated chondrocytes	• Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2 in adults Submitted 03 Dec 2012 Status: Authorised CHMP PO: 18 May 2017	*Not approved in the US*
Darvadstrocel (Alofisel®)	SCTP. Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue	• Treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy Submitted: 02 Mar 2016 Status: Authorised CHMP PO: 14 Dec 2017	*Not approved in the US*
Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) (Zalmoxis®)	Cell-based GTMP. Allogeneic T cells genetically modified with a retroviral vector	• Adjunctive treatment in hematopoietic cell transplantation Submitted: 05 Mar 2014 Status: Withdrawn CHMP PO: 23 Jun 2016	*Not approved in the US*

Product	Product description	EU Indication[1] and approval	US Indication[1] and approval
An autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells (Strimvelis®)	Cell-based GTMP. Autologous CD34+ cells transduced with retroviral vector	• Treatment of severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency Submitted: 01 May 2015 Status: Authorised CHMP PO: 01 Abr 2016	*Not approved in the US*
Talimogene laherparepvec (Imlygic®)	Non cell-based GTMP. rHSV-1	• Treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease Submitted: 28 Aug 2014 Status: Authorised CHMP PO: 22 Oct 2015	• Indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery Submitted: 28 Jul 2014 Status: Authorised Approved: 27 Oct 2015
Ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar®)	TEP. Ex vivo expanded autologous human corneal epithelial cells containing stem cells	• Treatment of adult patients with moderate to severe limbal stem cell deficiency, unilateral or bilateral, due to physical or chemical ocular burns Submitted: 06 Mar 2013 Status: Authorised CHMP PO: 18 Dec 2014	*Not approved in the US*
Sipuleucel-T (Provenge®)	SCTP. Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor	• Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated Submitted: 30 Dec 2011 Status: Withdrawn CHMP PO: 27 Jun 2013	• Treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer Submitted: 30 Oct 2009 Status: Authorised Approved: 29 Apr 2010

Product	Product description	EU Indication[1] and approval	US Indication[1] and approval
Autologous cultured chondrocytes on porcine collagen membrane (MACI®)	TEP. Autologous chondrocytes expanded ex vivo expressing chondrocyte-specific marker genes, seeded onto a CE marked porcine derived Type I/III collagen membrane	• Repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20 cm^2 in skeletally mature adult patients Submitted: 01 Sep 2011 Status: Withdrawn CHMP PO: 25 April 2013	• Repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults Submitted: 04 Jan 2016 Status: Authorised Approved: 13 Dec 2016
Alipogene tiparvovec (Glybera®)	Non cell-based GTMP. AAV-1/2	• Indicated for adult patients diagnosed with familial lipoprotein lipase deficiency and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The indication is restricted to patients with detectable levels of LPL protein Submitted: 23 Dec 2009 Status: Withdrawn CHMP PO: 23 Jun 2011	Not approved in *the* US
Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins (ChondroCelect®)	TEP. Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	• Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present Submitted: 01 Jun 2007 Status: Withdrawn CHMP PO: 25 June 2009	*Not approved in US*
Betibeglogen autotemcel (Zynteglo®)	Cell based GTMP. Genetically modified autologous CD34+ cell enriched population that contains haematopoietic stem	• Treatment of patients 12 years and older with transfusion-dependent β-thalassaemia who do not have a β0/β0 genotype, for whom haematopoietic stem cell transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available	*Not approved in the US*

Product	Product description	EU Indication[1] and approval	US Indication[1] and approval
	cells transduced with lentiviral vector	Submitted: 21 Aug 2018 Status: Authorised CHMP PO: 26 Apr 2019	
Azficel-T (Laviv®)	Autologous cellular product	*Not approved in the EU*	• Indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults Submitted: 22 Dec 2010 Status: Authorised Approved: 21 June 2011
Onasemnogene abeparvovec-xioi (Zolgensma®)	Non cell-based GTMP. AAV-9	• Treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the survival motor neuron 1 (SMN1) gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene Submitted: 09 Oct 2018 Status: Authorised CHMP PO: 26 Mar 2020	• Treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene Submitted: 01 Oct 2018 Status: Authorised Approved: 24 May 2019
Allogenic cultured keratinocytes and fibroblast in bovine collagen (Gintuit®)	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	*Not approved in the EU*	• Indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults Submitted: 13 Mar 2011 Status: Authorised Approved: 09 Mar 2002

*Indications according to labelling of each region. Date of EU marketing authorisation application submission corresponds to the date where the application was received by the EMA. AAV: Adeno Associated Viral Vector; CHMP PO: The Committee for Medicinal Products for Human Use Positive Opinion; EU: European Union; GTMP: Gene Therapy Medicinal Product; SCTP: Somatic Cell Therapy Medicinal Product; TEP: Tissue Engineered Product

Table 2. Summary of ODD granted in the EU and the US to the approved advanced therapies

Product	Orphan indication		ODD at MA		EU prevalence of disease to support the ODD	Data available to support the ODD*	Significant benefit criterion in the European Union	
	EU	US	EU	US			No satisfactory treatment approved	Significant benefit justification
Yescarta®	Treatment of diffuse large B cell lymphoma	Treatment of diffuse large B cell lymphoma	Yes. COMP adopted a LoQ and required an OE	Yes	2.4 in 10,000	Preliminary clinical data showing a favourable response in patients with progressive disease who are refractory to previous treatments.	NA	Yes
	Treatment of primary mediastinal large B-cell lymphoma	Treatment of primary mediastinal large B-cell lymphoma	Yes. COMP adopted a LoQ and required an OE		0.3 in 10,000	Preliminary clinical data in patients affected by the condition who responded to treatment with the product as assessed by imaging	NA	Yes
	NA	Treatment of follicular lymphoma	NA		NA	NA	NA	NA
Kymriah®	Treatment of diffuse large B-cell lymphoma	Treatment of diffuse large B-cell lymphoma	Yes	Yes	4.5 in 10,000	Preclinical data and preliminary clinical data showing antitumor activity of the proposed product	NA	Yes
	Treatment of B-lymphoblastic leukaemia/lymphoma	Treatment of acute lymphoblastic leukaemia	Yes	Yes	1 in 10,000	Preliminary clinical data in patients	NA	Yes
Luxturna®	Treatment of Leber's congenital amaurosis	Treatment of inherited retinal dystrophy due to biallelic RPE65 gene mutations	Yes. COMP adopted a LoQ and required an OE	Yes	1 in 10,000	Preclinical data supporting improvements in visual function	Yes	NA
	Treatment of retinitis pigmentosa			Yes	3.7 in 10,000			
Alofisel®	Treatment of anal fistula	NA	Positive COMP opinion after appealing a negative opinion	NA	2.3 in 10,000	Not known	Yes	NA

Product	Orphan indication		ODD at MA		EU prevalence of disease to support the ODD	Data available to support the ODD*	Significant benefit criterion in the European Union	
	EU	US	EU	US			**No satisfactory treatment** approved	**Significant benefit** justification
Zalmoxis®	Adjunctive treatment in hematopoietic cell transplantation	NA	Yes	NA	0.32 in 10,000	Clinical trials in patients were ongoing	NA	Yes
Strimvelis®	Treatment of severe combined immunodeficiency due to adenosine deaminase deficiency	NA	Yes	NA	0.02 in 10,000	Clinical trials in patients were ongoing	Yes	NA
Imlygic®	Not orphan drug in the EU	Treatment of stage IIb-stage IV melanoma	NA	Yes	NA	NA	NA	NA
Holoclar®	Treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns	NA	Yes	NA	0.3 in 10,000	Clinical trials in patients were ongoing	NA	Yes
Glybera®	Treatment of lipoprotein lipase deficiency	NA	Yes	NA	0.02 in 10,000	The evaluation of the effects of adeno-associated viral vector expressing LPL in experimental models was on-going. At the time of submission of the application for orphan designation, no clinical trials in patients with LPL deficiency were initiated.	Yes	NA
Zynteglo®	Treatment of ß-thalassaemia intermedia and major	NA	Yes	NA	1 in 10,000	Preclinical results in a model of betathalassaemia intermedia	NA	Yes
Zolgensma®	Treatment of spinal muscular atrophy	Treatment of spinal muscular atrophy	Yes	Yes	0.4 in 10,000	Clinical trials with the medicine in patients with spinal muscular atrophy were ongoing	Yes	NA

COMP: Committee for Orphan Medicinal Products; EU: European Union; LoQ: list of questions; LPL: lipoprotein lipase deficiency; NA: not applicable; OE: oral explanation; US: United States of America

Table 3. Comparison of the issues discussed in the Scientific Advisory Groups meetings during the Marketing Authorisation procedure for the approved advanced therapies in the EU and the US

	Kymriah®		Luxturna®		Imlygic®		Provenge®	
	EU	**US**	**EU**	**US**	**EU**	**US**	**EU**	**US**
Product potency								①
Pharmacology (including dosing and route of administration)						①		①
Pharmacokinetics (biodistribution)			①					
Target population and indication	②		③		②	①	①	
Choice of endpoints				①	①			
Sufficient clinical package to support the MA						①		
Clinical efficacy results	④				①		①	①
Clinical benefit	①		②					
Clinical safety							①	
Safety with regards to product administration		①		①				
Limited S&E follow-up, RM, and post-marketing	①			①			①	

	Kymriah®		Luxturna®		Imlygic®		Provenge®	
	EU	**US**	**EU**	**US**	**EU**	**US**	**EU**	**US**
Risk benefit assessment		①		①		①		
Regulatory pathway for approval						①		
Total	⑧	②	⑥	④	④	⑤	④	③

Categorisation approach were sourced and adapted from Barkholt et al. [1]. EU: European Union; MA: marketing authorisation; RM: risk management; S&E: safety and efficacy; US: United States of America. Laviv® and Gintuit® were only approved in the US. Issues discussed in the Scientific Advisory Groups (SAG) meeting during the MA procedure for Laviv® were pharmacology (1), clinical safety (5), limited S&E follow-up and RM and post marketing (1); and for Gintuit® were validation process and assays (1), impurities, microbiological contamination (2), and comparability and consistency issues (1). Glybera® was only approved in the EU. Issues discussed in the SAG meeting during the MA procedure for Glybera® were: choice of endpoints (1), pharmacodynamics and drug interactions (1), target population and indication (1). Zolgensma® required a SAG meeting in the EU. The issues discussed included: pharmacology (including dosing and route of administration) (1), target population and indication (1) and clinical benefit (1). For Zolgensma® no advisory committee meeting was held in the US because initial review of information submitted did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

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Supplementary Materials

Table S1: Expedited development and accelerate assessment programs in the EU and the US

Expedited development programs

	FDA	EMA
Program	***Fast Track Designation***	***(No equivalent)***
Qualifying criteria	• A drug that is intended to treat a serious condition AND • Nonclinical or clinical data demonstrate the potential to address unmet medical need	NA
Features	• Actions to expedite development and review (e.g. the product could be eligible for priority review if supported by clinical data at the time of marketing application submission) • Rolling review	NA
Program	***Breakthrough Therapy Designation***	***Priority Medicines (PRIME) designation***
Qualifying criteria	• A drug that is intended to treat a serious condition AND • Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	• Target conditions where there is an unmet medical need • Available data should support the claim that the product has the potential to bring a major therapeutic advantage to patients without treatment options (exploratory clinical trial phase)
Features	• Intensive guidance on efficient drug development (i.e. interactive communications to help the sponsor design and conduct efficient clinical trials that may require less time to complete facilitating coordinated internal interactions and communications with a sponsor) • Organizational commitment (i.e. assignment of cross-disciplinary project lead that will lease between members of the review team) All fast track designation features: • Rolling review • Other actions to expedite review	• Potential eligibility for accelerated assessment • Early appointment of a rapporteur from EMA's CHMP to facilitate continuity in support and building of knowledge in view of the submission of a marketing authorisation application • Kick-off meeting with a multidisciplinary group of experts from relevant EMA scientific committees and working parties to give preliminary guidance on the overall development plan and recommended regulatory pathway • Scientific advice at key development milestones with potential involvement of multiple stakeholders (e.g. health technology assessment bodies and patients), when relevant • Dedicated EMA contact point
Program	***Regenerative medicine advanced therapy (RMAT) designation***	***(No equivalent)***
Qualifying criteria	• A drug is a regenerative medicine therapy (a cell therapy, therapeutic tissue-engineering product, human cell and tissue product, or any combination product using such therapies or products*); AND	NA

	• it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; AND • if the preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition	
Features	• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints • Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements	NA

Accelerate assessment and approval

	FDA	**EMA**
Program	***Priority Review Designation***	***Accelerated Assessment Designation***
Qualifying criteria	• An application for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR • Any supplement that proposes a labelling change pursuant to a report on a paediatric study under 505A	• An application where the product is of major interest for public health and therapeutic innovation (usually the product addresses to an unmet medical by introducing new methods of therapy or improving the existing ones) • Applications under centralised procedure
Features	• Shorter clock for review of MAA (from 10 to 6 months)	• Shorter clock for review of MAA (from 210 to 150 days)

*Except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations. CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; FDA: Food and Drug Administration; MAA: marketing authorisation application; NA: not applicable.

Table S2: Types and comparison of marketing authorisations in the EU and the US

	FDA	EMA
Program	***Standard marketing authorisation***	***Standard marketing authorisation***
Features	● Comprehensive clinical data at the time of the MAA ● Positive benefit-risk balance ● Significant demonstration of safety and efficacy based on a therapeutically ● Relevant endpoint or when extensive clinical experience has been gained in the target patient population (including orphan drugs)	● Comprehensive clinical data at the time of the MAA ● Positive benefit-risk balance ● Significant demonstration of safety and efficacy based on a therapeutically ● Relevant endpoint or when extensive clinical experience has been gained in the target patient population (including orphan drugs) ● MAA valid for 5 years from the date of the EC decision, after which it may be renewed on application. Once renewed, the MA is valid for an unlimited period
Approved ATMPs	MACI®, Provenge®, Imlygic®, Luxturna®, Kymriah®, Yescarta®, Zolgensma® Laviv® and Gintuit®	Chondrocelect®, MACI®, Provenge®, Imlygic®, Strimvelis®, Alofisel®, Spherox®, Luxturna®, Kymriah® and Yescarta®
Program	***Accelerate approval program***	***Conditional marketing authorisation***
Features	● Comprehensive clinical data may not readily be obtained ● Benefit-risk balance of the product must be considered positive pending confirmation from the comprehensive post-authorisation clinical data (phase 4 confirmatory trials) ● Serious conditions and unmet medical need based on a surrogate endpoint or intermediate clinical endpoints ● If the confirmatory trial shows that the drug actually provides a clinical benefit, then the FDA grants traditional approval for the drug.	● Comprehensive clinical data may not readily be obtained ● Anticipated positive benefit-risk balance of the product and requires confirmation from the comprehensive post-authorisation clinical data, which the applicant is expected to provide within a certain time frame. ● It may be possible to submit the application upon completion of Phase II studies or when initial efficacy, with a positive benefit-risk balance, is demonstrated through a surrogate clinical endpoint, such as a biomarker, rather than a direct therapeutic measure. ● MAA initially valid for 1 year, and may be renewed annually.
Approved ATMPs	-	Zalmoxis®, Holoclar®, Zynteglo® and Zolgensma®
Program	***(No equivalent)***	***Marketing authorization under exceptional circumstances***
Features	NA	● Extreme situations where comprehensive safety and efficacy data required are never expected to be obtained ● Specific obligations to monitor the ongoing safety of the product ● Accumulated clinical data are reviewed in an annual re-assessment procedure to continuously evaluate the benefit-risk balance

	FDA	EMA
		● MAA valid for 5 years, and continuation of the MA shall be linked to the annual re-assessment.
Approved ATMPs	NA	Glybera®

ATMPs: Advanced Therapy Medicinal Products; EMA: European Medicines Agency; FDA: US Food and Drug Administration; MAA: Marketing authorisation application; NA: Not applicable

Annex 2.2-1: Regulatory update of approved ATMP (as of 31st December 2021)

Table S1. US regulatory procedures followed by approved ATMPs

Product	Year of approval	ODD	Fast track	Breakthrough	RMAT	Priority review	Rolling review	BLA review time (months)	Type of MAA
ABECMA®	2021	X		X		X		7	Standard
STRATAGRAF®	2021	X			X	X		12	Standard
RETHYMIC®	2021	X		X	X	X		30	Standard
BREYANZI®	2021	X		X	X	X	X	8	Standard
TECARTUS®	2021	X		X		X		7	Accelerated
ZOLGENSMA®	2019	X	X	X		X		8	Standard
KYMRIAH® (DBCL)	2018	X		X		X		5	Standard
KYMRIAH® (ALL)	2017	X		X		X		7	Standard
YESCARTA®	2017	X		X		X	X	6.6	Standard
LUXTURNA®	2017	X		X		X	X	7	Standard
MACI®	2016							11	Standard
IMLYGIC®	2015	X	X					15	Standard
GINTUIT®	2012							10	Standard
LAVIV®	2011							6	Standard
PROVENGE®	2010		X					6	Standard

Table S2. EU regulatory procedures followed by approved ATMPs

Product	Year of approval	ODD	PRIME	Accelerated assessment	MAA review time (months)	Type of MAA
ABECMA®	2021	X	X	X	13	Conditional
SKYSONA®	2021	X	X	X	8	Standard
TECARTUS®	2020	X	X	X	10	Conditional
LIBMELDY®	2020	X	X	X	11	Standard
ZOLGENSMA®	2020	X	X	X	17,55	Conditional
ZYNTEGLO®	2019	X	X	X	8	Conditional
LUXTURNA®	2018	X			13	Standard
KYMRIAH® (ALL)	2018	X	X	X	7,82	Standard
KYMRIAH ® (DLBCL)	2018	X	X	X		Standard
YESCARTA®	2018	X	X	X	10,78	Standard
ALOFISEL®	2017	X			21,42	Standard
SPHEROX®	2017				53,49	Standard
ZALMOXIS®	2016	X			27,63	Conditional
STRIMVELIS®	2016	X		X	11	Standard
IMLYGIC®	2015	X			13,8	Standard
HOLOCLAR®	2014	X			21,42	Conditional
PROVENGE®	2013				18	Standard
MACI®	2013				19,78	Standard
GLYBERA®	2011	X			18	Exceptional circumstances

Product	Year of approval	ODD	PRIME	Accelerated assessment	MAA review time (months)	Type of MAA
CHONDROCELECT®	2009				24,8	Standard

2.3: Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States

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Abstract

An environmental risk assessment (ERA) consists of an analysis of the risks to human health and the environment that a medicinal product may cause due to its release during clinical development or after entering the market. Regulators in the EU and the US require that ATMPs that are also genetically modified organisms (GMOs) undergo an ERA to be approved for MA. This work aims to review the regulatory issues that need to be taken into consideration for carrying out an ERA, comparing EU and US. The European regulatory framework for environmental procedures and the dissimilarities in its implementation across the Member States and its implications at a logistical level are analysed in detail. In addition, this review provides a brief insight into the non-clinical and clinical assessments that should be carried out during the development of the product to conduct a successful ERA, and thus, facilitate its MA and post-marketing monitoring. Finally, the need for a European harmonization regarding environmental procedures for ATMPs is discussed.

Introduction

ATMPs such as GTMPs are at the cutting edge of innovation and hold promise to cure or improve the quality of life for a variety of diseases for which there are no satisfactory therapies. In the case of medicinal products consisting or containing GMOs, the requirement for conducting an ERA is regulated by the environmental and human drugs legislation. The clinical use of these therapies might bear a risk of inadvertent exposure of their constituents and/or derivatives into the environment with a potential impact on humans other than patients, causing potentially harmful effects on the ecosystem as well as on human health. GMOs contained in medicinal products may enter the environment by unintended dispersal of the product during administration, by accidental dissemination during product handling, by inappropriate disposal of waste or unused product, or via excretion by the patient. If the GMO is transmitted to other persons, such as medical staff or family members, or the environment at large, the GMO could potentially spread further, undergo genetic or phenotypic changes, infect, reproduce, remain latent, compete with existing species or transfer its genetic material to other species, altering human health and the environment. Therefore, the potential risks associated with such scenarios must be evaluated through an ERA. Both in the EU and the US, specific regulations were introduced around the end of the 1980s and early 1990s to guarantee the safe use of medicinal products containing a GMO [1][2][3].

This review briefly outlines the current regulatory framework in EU and US for the ERA procedures, and discusses the current divergences, hurdles and considerations for ATMPs clinical development relating to GMO applications in EU, bringing up the need for a harmonisation. A brief outline on all reviewed legal acts is presented in Table 1.

Definition of genetically modified organisms and purpose of environmental risk assessment

In the EU and the US both GMO definitions are more focused on genetically modified plants and agricultural products rather in pharmaceutical products. According to Article 2 of the European Directive 2001/18/EC, a GMO is defined as “an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination”, and in accordance with the same Directive,

an “organism” is defined as “any biological entity capable of replication or of transferring genetic material”. In the US, for the first time since 1986, are debating a possible change of the definition of a GMO due to the arrival of new techniques of genetic modification to ensure efficiently assessment of the risks of the future products of biotechnology [4]. According to the US Department of Agriculture (USDA), GMOs are organisms obtained through genetic engineering, defined as “the genetic modification of organisms by recombinant DNA techniques”. The new definition proposed by USDA, genetic engineering would be a family of “techniques that use recombinant or synthetic nucleic acids with the intent to create or alter a genome” [5]. Therefore, many GTMPs such as recombinant oncolytic viruses, replication-incompetent viral vectors, and ex vivo genetically modified cells and other recombinant microorganisms fall within GMO definition. Not all ATMP are by definition a GMO, for example peripheral blood mononuclear cells activated *ex vivo* with recombinant fusion protein (Sipuleucel-T) were excluded from this definition since the genetic material had not been altered [6].

On the other hand, an ERA consists of an evaluation and estimation of the risks to human health and the environment that a medicinal product can pose due to its release during clinical development, or subsequently, once it is placed into the market. In this sense, the ERA identifies and evaluates the potential adverse effects of the medicinal product, either direct and indirect, immediate or delayed, and is a planning and decision-making tool in order to minimize or avoid these effects before they occur [7]. In the EU, an ERA consists of a six-step process while in the US is reduced to four-step, although the analysis is essentially the same (Table 2). Steps two and three of the European ERA are usually assessed simultaneously, and it is considered one single step in the US. When an ERA is performed, it is important not to discount any potential adverse effect on the basis that it is unlikely to occur. Another consideration is that although the ERA should be based on quantifiable outcomes, it is likely that many of the results of the ERA will have to be qualitative [7][8].

Procedures for environmental risk assessment in the EU

Overview of the legislation and regulatory framework

During the lifecycle of a pharmaceutical product, an ERA is a mandatory procedure required by the regulatory authorities to further develop the products containing a GMO. This procedure

is submitted prior to first-in-human clinical trial, during the subsequent clinical development and for the MAA. The documents to be submitted at these stages, and the regulatory authorities that will assess the procedure are different; during clinical development, the ERA, is conducted according to the requirements of the EU member state in which the trial will be performed, whereas for MAA it is centralised and reviewed by the CAT, along with the CHMP, at the EMA.

The European legislative framework contemplates two possible ways in which a GMO can come into contact with the environment: a “contained use” and a “deliberate release". Contained use refers to any activity in which microorganisms are genetically modified or in which such genetically modified micro-organisms (GMMs) are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment, for instance the use of GMOs in confined laboratories [10]. By contrast, deliberate release refers to any intentional introduction into the environment of a GMO for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment, i.e. in the context of research purposes when a product that consists/contains a GMO is tested in clinical trials, or when this product is placed to the market. Although the term GMM is used within the legal framework of contained use, and in the case of deliberate release, the term is GMO, the definitions of these two terms are virtually the same [11]. In both cases, before any GMO can be used in any of these contexts, the ERA should have been submitted and an authorisation must have been granted. The requirements and the procedures for performing an ERA in each case are laid down in Directive 2009/41/EC and in Commission Decision 2000/608/EC10 for contained use of GMOs, and in Directive 2001/18/EC and in Commission Decision 2002/623/EC11 for deliberate release. On one hand, the focus of Directive 2009/41/EC is on the assessment of the biosafety level classification of the GMO and the implementation of physical, chemical and biological barriers in order to limit the contact of the GMO with the environment. The risk classification has consequences for the procedure and review period of the application, and usually requires clinical site-specific notifications. On the other hand, Directive 2001/18/EC seeks to conduct an ERA that considers the effects on human health and the environment prompted by an intentional introduction of a GMO into the environment aiming to provide the safety measures necessary to minimise the potential risks. This Directive was primarily addressed for genetically

modified plants and agricultural products, raising difficulties on preparing the ERA since the application forms are generally not designed for medicinal products [12].

In terms of clinical development, two types of authorizations should be obtained to conduct a clinical trial with a GMO-containing medicinal product: one for the clinical trial application (CTA) reviewed by the ethics committees and competent national health authorities, and another one for the GMO application in order to "release" or to administer the GMO-containing medicinal product in that trial. The competent authorities (CAs) of each Member State in charge of GMO evaluations are the Ministries or agencies responsible for the environment in each country, along with a scientific advisory committee, which usually provides a recommendation to the CA on the ERA assessment (Table 3). The GMO application is usually submitted in parallel with the CTA, yet in some Member States such as Bulgaria, Poland, Romania, Slovenia and Slovakia, sponsors are required to obtain the GMO authorisation before the CTA can be submitted. The information to be submitted comprises the comparison of the characteristics of the parental and the modified organisms, details on the genetic modifications, effects of inserted or deleted sequences, details on the release and the receiving environment, possible interactions between the GMO and the environment, and information on the monitoring, control, waste treatment and emergency response plans. The GMO framework does not apply in those cases where the product has been granted a marketing authorisation and the use of the GMO in an intended clinical trial is in accordance with the summary of product characteristics, which aims to administer the product for the same indication, route of administration and pharmaceutical form. Otherwise, an evaluation would be required in terms of new potential risks that are not covered by the ERA performed for the MAA. In these cases, a special submission form should be provided [13].

Regarding MA, the MAA submitted to the EMA has to include an ERA, which corresponds to Section 1.6.2 of the MAA dossier included in Module 1, in accordance with the principles of deliberate release and assessed as part of the centralised procedure. This ERA, in accordance with Annex II of the Directive 2001/18/EC, should follow the following general principles: the GMO should be compared to the non-modified organism from which it is derived, the ERA should rely on data derived from specific testing of the GMO during the development and performed on a case-by-case basis, and the ERA needs to be re-evaluated if new information on the GMO or its effects on human health or the environment becomes available. The

information to be submitted is outlined in the Annex IIIA, which applies to releases of all types of GMOs other than higher plants, and Annex IV of Directive 2001/18/EC. The EMA has developed two guidelines to provide guidance on the preparation of the ERA for MAA (Table 1) [14][15]. At the EMA, committee members from various states meet to make decisions about marketing approval, and the designated GMO competent authorities of all Member States are also consulted for review of the ERA [1]. Due to the procedural and scientific complexities associated with the ERA evaluation, the EMA recommends requesting pre-submission meetings one year in advance of submission of the MAA (EMEA/CHMP/BWP/135148/2004, 2005). Finally, after marketing authorisation GMO-containing medicinal product is subject to traceability and a monitoring plan is to be performed (Table 4). This monitoring plan should include systemic distribution and shedding in some cases, surveillance of long-term side effects, information about adverse or unexpected effects, monitoring effects in individuals other than the patient, if applicable, and information about off-label use [14][16].

Divergences across EU countries during clinical development

Although the mentioned European Directives define the legal framework and objectives to be met by the Member States regarding ERAs, these Directives have been implemented differently across European countries leading to different GMOs procedures and requirements. This lack of harmonisation entails an impact on the logistics of product development that might affect times, costs and managerial burden. In a recent study conducted among commercial ATMP developers, where challenges experienced during various development phases were shared, the most often mentioned challenges were related to country-specific requirements, mainly driven by issues with the GMO legislation raised by GTMP developers. Developers experienced the GMO procedure as a confusing and resource intensive process, leading to duplicate applications or additional inspections that result in time delays and consumption of extra resources [17].

Different applicability of GMO definition

The applicability of the GMO definition has not been so trivial for some investigational products, such as naked nucleic acid or engineered cell therapies. For instance, so far, the European Member States have held diverging views on the inclusion of plasmids as GMO, and for a multinational clinical trial with the same investigational product there were contradictions regarding the need to submit an ERA procedure. Recently, 23 out of 28 countries of the European Economic Area (EEA) in 2018 along with the CAT, have agreed a common

interpretation for GMO classification, although it has not been adopted yet by the European Commission [13]. The most recent consensus establishes that a medicinal product for human use that consists of one (or more) plasmid(s) does not fall under the scope of the GMO framework, unless it might represent a potential risk; for example, a delivered plasmid encoding for an anti-HER2 antibody for the treatment of HER2-positive breast cancer [18] does not require an ERA procedure, while a plasmid-based therapeutic vaccine for HIV is subject to an evaluation since it contains a viral sequence that might have an impact if released to the environment [19]. Similarly, cell therapies need to be analysed case by case, but those consisting of human cells that have been genetically modified with plasmids will generally not be considered as a GMO, provided that the plasmids are not integrative and non-replicative nor contain a viral sequence [13]. On the other hand, investigational human cells genetically modified with viral vectors are regulated as GMOs, and the differences arise when some countries consider that both the viral vector (a starting material in *ex vivo* transductions) and the genetically modified cells (the drug product) are GMOs, whereas other countries consider that only the viral vector is a GMO [20]. In addition, for modified cells expressing a therapeutic transgene, there might be slight differences when the organism(s) from which this insertion is derived (also called "donor organisms") needs to be defined, creating inconsistencies and confusion in the application process. For instance, it is common for CAR T-cells to be transduced with a replication-deficient viral vector carrying a CAR gene insert. The CAR receptor is usually derived from the murine monoclonal antibody fused to a human hinge region of an antibody and to human intracellular regions. Some countries consider that the donor organism is the viral vector, while in others the donor organism might be the viral vector and/or the Homo sapiens and Mus musculus species due to the genetic origin of CAR receptor [21]. The percentage of trials using genetically modified cells, such as CAR-T, is dramatically increasing [2][22], most of these cells being genetically modified *ex vivo* using retroviral or lentiviral vectors [23]. For this reason, at the end of 2018, these 23 countries of the EEA endorsed a specific ERA with a common application form for clinical research with human cells genetically modified by means of retro/lentiviral vectors, reducing the administrative burden of the process and unifying the requirements for environmental risk assessment. This common procedure is addressed to those cases in which it can be justified that there is no risk of formation of replication competent viruses, and the finished product is free of infectious viral vector particles that can potentially be released in the environment [24].

Finally, cells that have been modified with CRISPR/Cas9 technology should be considered a GMO by definition since the genetic material of the cells has been altered, even if no vector has been used. Some controversy has been generated regarding this issue and it is still under discussion. According to the publicly available information, two recent clinical trials that tested autologous CRISPR/Cas9-modified CD34+ human hematopoietic stem and progenitor cells were authorised after undergoing a GMO procedure [21][25]. In these cases there is no donor organism since the genetic modification creates an insertion–deletion mutation by endogenous non-homologous end-joining following Cas9. As mentioned, the Directive 2001/18/EC on the deliberate release is focused on genetically modified plants and agricultural products, and contains what is known as a "mutagenesis exemption", which exempts organisms obtained by mutagenesis from the obligations imposed by the directive on GMOs. On 25 July 2018, the Court of Justice of the European Union ruled that the GMOs created using gene-editing technologies such as CRISPR/Cas9 are subject hereinafter to GMO regulations, although it does not specify if it is addressed to gene-edited crops and/or pharmaceutical products [26][27]. More clarifications regarding this issue are expected from the European Commission throughout the coming years.

Different legal framework across EU countries

Another hurdle for applicants in the authorization of multinational clinical trials are the dissimilarities in the implementation of legislation among the Member States. The release of a GMO within the context of a clinical trial can be included within 'contained use' or 'deliberate release' regulations depending on the country (Table 3), resulting in wide variability on how the risk is assessed, the requirements and the documents to be submitted, as well as the procedure to be followed. Some Member States decide based on several factors of a clinical trial, whether a notification for deliberate or contained use is needed. Some of the factors are related with the features of the GMO (e.g. replication-deficient), probability of shedding (i.e. when the GMO is released into the environment via the patients' excreta), if proper management procedures and/or working practices are taken to prevent any possible release of the GMO, or if patients are hospitalised in a room that fulfils the contained use criteria or treated on an out-patient basis. For other Member States, a clinical trial where GMO-containing medicinal products will be administered falls under the deliberate release legislation, regardless of the specific circumstances of the clinical trial. A European repository of national

requirements has been created to disseminate the national GMO regulatory requirements and facilitate the development of these medicinal products [28].

For some countries, the sponsor must decide into which category the GMO falls based on a preliminary risk assessment and considering the interpretation of national legislation for each procedure. In these cases, it is highly recommended to determine with the competent body which are the GMO classification and/or the procedure to follow before proceeding with the GMO evaluation. Since the CTA and the GMO procedures are reviewed by separate national agencies, some countries offer the possibility of coordinating a scientific advisory panel between both competent bodies, such as the case of Belgium [29]. Other countries like the Netherlands offer an informal preliminary consultation of the draft GMO application in order to discuss whether sufficient information for a full risk assessment has been included, avoiding time delays after its submission [30].

Considerations at logistical level

multiple parallel clinical trials, each clinical trial usually requires a separate GMO evaluation and authorisation. The possibility of integrating one GMO assessment for a whole clinical development may be considered, but needs to be assessed by a CA on a case-by-case basis [13]. This option might be feasible in cases where there are no contemplated changes throughout the clinical development plan that may alter the overall risk assessment. Changes during the clinical development plan may include variations in the indication or target population, manufacturing or formulation aspects that may alter the characteristics of the product or when the overall dose and exposure to the GMO per subject is likely to change. Obtaining this single authorisation might also be easier in cases where the full clinical development is intended to be conducted in a single clinical site, and the analytical procedures to detect and identify the GMO are also carried out at the same site. By doing so, the technical aspects regarding the GMO manipulation by the hospital staff and the methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release will be the same or highly similar throughout the development. On the other hand, it should be considered that planning a full development program in advance is not common or trivial, since at early stage there is uncertainty as to the performance of the investigational medicinal product, and for some countries, final clinical protocols might be required. In addition, the measures to minimise risks when the product is administered/released should be established in advance, being more complicated for

multicentre clinical trials where the hospital activities, including transport, storage, preparation, administration, disposal of the product (including patient samples) and the analytical procedures, should be defined.

From a scientific standpoint, the principles to be addressed for the overall GMO risk assessment are common among all EU member states since they are under the European legal framework. However, the documentation and requirements to be submitted, as well as the administrative fees and timelines differ for each country, adding complexity in the case of multinational clinical trials where several interactions with different regional stakeholders are needed; interactions with CA bodies, the investigators, biological safety officers, hospital pharmacy services of the clinical sites, etc. The duration of the procedure to obtain authorization may also depend on several regional factors and may differ across countries: the quality of the initial assessment provided by the sponsor in accordance with the requirements of each country, the timing of each CA body to perform the evaluation, or the time that it might take the sponsor to clarify the deficiencies dictated during the assessment. The latter point might require additional time-consuming studies, such as method validation or shedding studies. In addition, certain information related to the clinical trial and the GMO to be released is subject to 30 days of public evaluation through EU register, although this is usually done in parallel to the evaluation of each Ministry and competent committees. Finally, another point to consider is the coordination and the fees of all the necessary translations into the national languages of the documents.

Additionally, there are other specific considerations depending on the member state where the clinical trial will take place. For instance, in Germany the long-term storage of the GMO-containing product or contaminated materials at the study site are not covered by the release authorisation, and interaction with the local GMO authorities are required [1][31]. In Belgium, the sponsor has to deliver to the Service Biosafety and Biotechnology (SBB) a control sample of the GMO along with related scientific documentation, at the latest 15 days after the start of the trial, with the aim of detecting and identifying the recombinant virus or micro-organism in case of inspection or accidental release. The detailed protocol for the method of conservation and analysis of the control sample should be provided to a specific laboratory that will evaluate the data [32].

In conclusion, multinational clinical trials involving a GMO should be carefully planned, not only taking into account the studies that may be required for the environmental risk evaluation, but also in terms of the specific documentation and requirements by each country and the estimated duration of each national procedure, in order to coordinate the intended start date of the trial and the overall costs, which include both the regulatory fees and translations.

The need for harmonisation

The new Clinical Trials Regulation facilitates to conduct clinical trials in the EU, above all those that are multinational. Under this regulation, the requirements for clinical trials are harmonised across the EU and CTAs are submitted, centralised and assessed by a single authorisation procedure [33]. However, this new regulation does not consider the requirements of the GMO legislation and several initiatives have started to encourage the need for GMO harmonisation, which is a current topic of debate. A multi-stakeholder meeting at EMA took place in 2016, where the divergences in the implementation of GMO procedures in Member States were discussed, as well as the need for changes to the GMO directive itself [34]. In 2017, the European Biopharmaceutical Enterprises (EBE), the Alliance for Regenerative Medicine (ARM), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the European Association for Bioindustries (EuropaBio) published a position paper proposing possible solutions to improve the European regulatory procedures for clinical trials with ATMPs consisting of or containing GMOs, bringing this topic into focus [20]. In 2018, the European Commission along with the EMA initiated a dialogue with national competent authorities to address the discrepancies across the EU regarding the application of GMO Directives, with the aim to create coherent approaches without changing the basic legislation [35][36]. So far, as previously discussed, a common position document has been launched in order to unify the interpretation of the GMO framework and the applicability of the GMO definition (European Commission, 2018), and a common application form has been endorsed by the most competent authorities for human genetically modified cells [24].

Procedures for environmental risk assessment in the US

In the US, environmental impacts from pharmaceuticals are assessed under the National Environmental Policy Act (NEPA) and NEPA regulations by the Food and Drug Administration (FDA; the federal regulatory medicines agency in the US). FDA’s NEPA

policies and procedures can be found under the CFR (21CFR Part 25) (Table 1). According to FDA, those products that consist of gene therapies, vectored vaccines, and related recombinant viral or microbial products should be evaluated for the need of an ERA. FDA regulations specify that an ERA must be submitted as part of IND applications (the equivalent of a CTA in Europe), and for the MAA of a biologic product (named BLA in the US; Biologics License Application), unless it qualifies for an ERA exemption, also called categorical exclusion [37][38]. IND applications for the development of an ATMP are ordinarily categorically excluded from the requirement to submit an ERA, unless extraordinary circumstances indicate that the specific action may significantly affect the quality of the environment. Possible exceptions may usually occur for use of virulent organisms or organisms that are ecologically more fit than their wild-type counterparts. The reason to consider a clinical development a categorical exclusion is that a clinical study involves small quantities of a medicinal product and a limited number of patients, not having a significant cumulative effect into the environment. Therefore, the regulatory process is very short, since the trials are usually exempt from an ERA [39][37].

The ERA exemption may also be applicable for the MAA in cases where the gene therapies "occur naturally in the environment", meaning that the product includes functional protein-coding sequences from one or more species within a single genus. This definition also includes products that differ from a wild-type substance only in attenuating point mutations or deletions, or that have been killed or inactivated by undergoing a specific manufacturing step designed to eliminate their ability to replicate. Thus, most MAA for GTMP will require an ERA, since they usually include functional protein-coding sequences from a different genus. However, unlike in EU, genetically-modified human cells are considered substances that "occur naturally in the environment", since these cells are not viable in the environment and are degraded into naturally occurring substances [37]. In fact, the two approved CAR-T therapies in the US were granted with a categorical exclusion [40][41]. In those cases where the ERA is required, the necessary information is usually collected while conducting trials and not at an earlier stage of development.

Environmental studies during development of ATMPs

The ERA in the EU and the US is based on nonclinical and/or clinical data, which mainly includes: description of the biological properties of the product that may pose a hazard, pathogenicity, its genetic stability, replication competence, host range, tissue tropism, the ability of the virus vector to survive after being shed, or the clearance, persistence and latency, shedding and biodistribution [1]. Therefore, during the development of the product it is necessary to generate enough information to address all these issues and conduct a proper ERA (Table 1).

One of the most important factors to analyse consists in the shedding assessment, which is the dissemination of the virus/vector through secretions and/or excreta of the patient, i.e. saliva, sweat, urine, faeces, nasopharyngeal fluids, blood, exudates from skin lesions, breast milk and semen. Shedding studies constitute the fundamental studies for an ERA, since they are used to understand the potential risk associated with transmission to third parties and the potential risk to the environment. These studies are usually carried out for oncolytic and virus-based gene therapy products, and not for genetically modified mammalian cells and other products [42]. When evaluating shedding, biological properties of the product such as replication competence, the status of the host including immunocompetence, dose and route of administration, sampling frequency and duration of sampling, and method analysis, are all important considerations for data interpretation [43]. The biological properties of the wild-type strain can provide guidance in shedding evaluations, as well as inventories of shedding data from publications on clinical gene therapy trials [18]. The nonclinical shedding assessments can be integrated into the design of other nonclinical studies such as preliminary and pivotal nonclinical studies. Clinical shedding assessments are also non-standalone studies and are integrated into the clinical trial designs. The nonclinical data allows the choice of clinical samples that need to be collected from subjects in a trial (e.g., faeces, urine, nasal swabs), the frequency of sample collection and duration of the monitoring period. There are two main guidelines that extensively explain how the design of the shedding studies and its analysis should be conducted; the EMA Guideline on general principles to address virus and vector shedding (ICH considerations) and the FDA Guideline on design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic products. The use of a quantitative polymerase chain reaction PCR (qPCR)-based

assay and/or infectivity assays to detect viral/vector genetic material are the usual methods to assess the shedding, having into consideration that these methods should be qualified [44].

Biodistribution assessments are also another key point for the ERA, as they provide information about the dissemination of the recombinant vector from the site of administration. This fact may influence the routes of shedding of the virus from the recipient, and therefore, the likelihood of transmission to third parties, including vertical transmission. Similarly to shedding assessments, biodistribution is usually part of the pivotal study and there is a minimum panel of tissues to be analysed, apart from the ones considered necessary depending on the product and route of administration, i.e. blood, injection site(s), gonads, brain, liver, kidneys, lung, heart, and spleen [45]. If vector is detected in gonads, germline transmission studies should be performed [46].

Depending on the features of the product and the results of the nonclinical and clinical development, it should be noted that the proposed Summary of Product Characteristics (SmPC) will communicate the risks of shedding and transmission to the prescribing physicians, as well as handling of the product should also adequately described. Some additional environmental considerations for approved ATMPs are summarised in Table 4.

General discussion and conclusions

In the EU, clinical trials with medicinal products that contain or consist of GMOs are subject to both clinical trials and environmental legislations under national competences, where an ERA needs to be submitted at each step of clinical development. In the US, an ERA is necessary for clinical trials only in specific cases, and it is required when the product nears commercialization. In this sense, compared to the European situation, GTMP developers do not need to produce as much information to conduct the ERA at an early stage of development or deal with the administrative burden that it entails. In addition, the lack of harmonisation of the GMO requirements across the European Member States implies a challenge to integrate the GMO assessment in the clinical trial process, above all for multinational trials. Both in the EU and the US, there are harmonised and detailed guidelines on the ERA requirements for a MAA, where the assessment is evaluated under a centralised procedure by the EMA committees in the case of EU, and by the FDA in the case of US. While in US there is the option of categorical exclusion for certain GTMPs, for the same product in EU a full ERA should be submitted in accordance with Annex II to Directive 2001/18/EC on the deliberate release, subject to a

monitoring plan after its authorisation. It is recommended to include shedding and biodistribution assessments at an early stage of development along with a full characterisation of the product, as it will allow a proper ERA and will guide in the design of clinical studies, as well as facilitate the marketing authorisation and post-marketing monitoring requirements. Although EU and US Agencies are actively supporting common scientific approaches on the regulation of ATMPs to facilitate their development, this is not the case with regard to environmental legislation [47][48].

One of the current topics of debate in relation to environmental regulation is the need for a European harmonization that rationalises regulatory processes and where the same scientific approaches are adopted. The rise of advanced therapies and their clinical use in a context of development or commercialization has highlighted these European differences, which is leading to great efforts for harmonization in a short time. Although there is currently a European repository that gathers the required requirements to carry out clinical trials with ATMPs, a centralised process is needed, such the one that will be implemented with the new regulation for clinical trials, consisting of a single "on-line" node for the presentation and consultation of applications throughout the union, where the evaluation and supervision is coordinated by the member states with defined and established timeframes. This would allow the presentation of common documents in a single international language (i.e., English), reduce the times of applications and approvals, especially in multicentre trials, as well as reduce the translation burden to the official languages of each member state. This "single portal" would not have to circumvent certain specific national requirements, such as those mentioned for Germany or Belgium, and would still speed up the process. These specific requirements could be described in this portal in this single language, thus facilitating the procedures. On the other hand, it should be noted that in order to be able to present these common documents, first, an harmonization of which products are defined as GMO, which is considered "donor organism", a common terminology, or a homogeneous classification of "deliberate use" or "contained use" is essential. Although consensus documents are being launched for the EEA countries, a single, consensual European document is needed to address all these points of divergence. The coordination of a parallel review between the health authorities in charge of the CTA and the regulatory authorities for the GMOs is not so trivial, since they are different regulatory bodies evaluating different processes although within the same context, i.e. the clinical trial. This

coordination could be handled by the Sponsor in order to minimize the time between both authorizations.

One of the proposed solutions that would further optimize these procedures is to adapt the future European portal for clinical trials to integrate the GMOs procedures. During the process a single coordinator and contact is proposed between the Sponsor and the authority responsible for CTA review and the regulatory organism responsible for the GMO. Finally, even more optimized would be the implementation of a specific centralized process for clinical trials with ATMPs consisting of or containing GMOs.

Tables

Table 1. Legislative and regulatory framework for environmental risk assessment for advanced therapies in the European Union and the United States

Regulatory Guidelines and Legislation	
European Union	
Directive 2009/120/EC and Regulation (EC) No 1394/2007	Advanced therapy medicinal products regulation
Directive 2001/83/EC and Regulation 726/2004/EC	Procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a EMA
Directive 2009/41/EC	Contained use of genetically modified micro-organisms
Directive 2001/18/EC	Deliberate release into the environment of genetically modified organisms Regulation
EMA (EMEA/CHMP/ICH/449035/2009)	General Principles to Address Virus and Vector Shedding
EMA (EMEA/CHMP/GTWP/125491/2006)	Guideline on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal products
EMA (CHMP/GTWP/60436/07)	Guideline on Follow-up of patients administered with gene therapy medicinal products
EMA (EMEA/CHMP/GTWP/125459/06)	Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products
EMA (CHMP/ICH/469991/2006)	General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors
EMA (EMEA/CHMP/BWP/135148/2004)	Environmental risk assessment for medicinal products containing, or consisting of, genetically modified organisms (Module 1.6.2)
EMA (EMEA/CHMP/BWP/473191/2006-Corr)	Guideline on environmental risk assessment for medicinal products containing, or consisting of, genetically modified organisms
United States	
U.S. Food and Drug Administration (1998)	Environmental Assessment of Human Drug and Biologics Applications

	Regulatory Guidelines and Legislation
U.S. Food and Drug Administration (2015)	Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products
U.S. Food and Drug Administration (2015)	Guidance document for industry on Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products
U.S. Food and Drug Administration (MAPP 5015.7 Rev. 1) (2017)	Manual of policies and procedures. Environmental Assessments and Claims of Categorical Exclusion
U.S. Food and Drug Administration (2015)	Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products
U.S. Food and Drug Administration (2018)	Long Term Follow-Up After Administration of Human Gene Therapy Products. *This guideline provides considerations for preclinical study design to assess biodistribution*
U.S. Food and Drug Administration (2008)	Content and Review of Chemistry, Manufacturing, and Control Information for Human Somatic Cell Therapy Investigational New Drug Applications. *A particular section of this guideline addresses how to the environmental impact should be addressed*
U.S. Food and Drug Administration (2018)	Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up. *This guideline provides recommendations regarding the testing for replication competent retrovirus during the manufacture and follow-up monitoring of patients: key factors to be considered in an ERA*
U.S. Food and Drug Administration (2016)	Recommendations for Microbial Vectors used for Gene Therapy. *This guideline considers biodistribution studies at preclinical level and shedding assessments as a part of clinical monitoring*
International guidelines	
ICH (2009)	General Principles to Address Virus and Vector Shedding
ICH (2006)	General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors
ICH (2009)	Oncolytic Viruses. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

EMA: European Medicines Agency; ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; FDA: U.S. Food and Drug Administration.

Table 2. Environmental risk assessment step procedure in EU and US

Region	ERA step process	Environmental analysis	Examples and/or Comments	Comparison
EU	1. Identification of characteristics which may cause adverse effects	• Characteristics of the GMOs linked to the genetic modification that may result in adverse effects on human health or the environment. • Comparison of the characteristics of the GMO(s) with those of the non-modified organism under corresponding conditions of the release or use will assist in identifying the particular potential adverse effects arising from the genetic modification.	• Location of the construction in the genome of the GMO where the transgenes were inserted • Potential interaction of the different transgenes • Phenotypic and genetic instability • Spread of the GMO(s) in the environment (e.g., pathways of dispersal, biological fitness, etc.) • Interactions with other organisms	Equivalent to steps 1 and 2 of the ERA in US
	2. Evaluation of the potential consequences of each adverse effect, if it occurs	• For each adverse effect identified, the consequences for other organisms, populations, species or ecosystems exposed to the GMO have to be evaluated. • In quantitative terms the magnitude should be expressed as 'high', 'moderate', 'low' or 'negligible'.	• One single hazard could have more than one adverse effect, and the magnitudes of the individual adverse effects could be different.	Equivalent to step 2 of the ERA in US
	3. Evaluation of the likelihood of the occurrence of each identified potential adverse effect	• Estimate how likely it is that adverse effects will actually occur. In some cases both the likelihood and the frequency should be addressed • The likelihood of the occurrence of an effect will depend on the specific risk management measures that may prevent that risk from occurring	• The relative likelihood of the consequence can probably not be assessed quantitatively, but it can be expressed in terms of 'high', 'moderate', 'low' or 'negligible'	Equivalent to step 2 of the ERA in US
	4. Estimation of the risk posed by each identified characteristic of the GMO(s)	• Estimation of the risk to human health or the environment posed by each identified adverse effects, given the state of the art, by combining the likelihood of the adverse effect occurring and the magnitude of the consequences, if it occurs.	• To include assumptions and extrapolations made at various levels in the ERA, different scientific assessments and viewpoints, uncertainties, the known limits of mitigation measures	Equivalent to step 2 of the ERA in US

Region	ERA step process	Environmental analysis	Examples and/or Comments	Comparison
		• The overall uncertainty for each identified risk has to be described.		
	5. Application of management strategies for risks from the deliberate release or marketing of GMO	• The ERA may identify risks that require measures to manage them, and a risk management strategy should be defined.	-	Equivalent to steps 3 and 4 of the ERA in US
	6. Determination of the overall risk of the GMO	• An evaluation of the overall risk of the GMO(s) should be made taking into account any risk management strategies which are proposed.	-	Equivalent to step 3 of the ERA in US
US	1. Identification of substances subject to proposed action, which includes a description of the drug product and its potential metabolites, degradants, or by-products released into the environment	-	• Identify degradation products to be released Identify known and potential variants of the GMO released into the environment (e.g. replication competent product may be present as an impurity) • Data to demonstrate the release of vector DNA into the environment (detectable by PCR at the injection site and/or in excreta)	Equivalent to step 1 of the European ERA
	2. Identification and assessment of potential environmental effects	• Assessment of the magnitude and likelihood of each environmental effect should be presented, and a conclusion should be given regarding the overall risk to the environment. • To be based both on events known to occur and those that may be reasonably foreseeable. • The likelihood of environmental effects may be assessed experimentally: amount of GMO and their metabolites released from patients into the environment,	• Identification of characteristics which may cause adverse effects: phenotypic attributes of the parental strain and/or vector, environment into which the GMO may be introduced, attributes of the genetic alteration • Assessment of the magnitude of each environmental effect is combined with the likelihood of the effect occurring.	Equivalent to steps 2, 3, and 4 of the European ERA

Region	ERA step process	Environmental analysis	Examples and/or Comments	Comparison
		environmental decay and half-life measurements, frequency of uptake by susceptible species and estimates of infectious dose.	• The risk may be described in qualitative terms ranging from high, moderate, and low to negligible.	
	3. Mitigation measures	• This section should describe any measures taken to avoid or mitigate the overall environmental risk and may include procedures to inactivate, contain, limit exposure, or monitor release of a product.	-	Equivalent to step 5 of the European ERA
	4. Alternatives to the proposed action, which discusses alternatives that offer less environmental risk if potentially adverse environmental impacts are identified	• Measures may be proposed to mitigate individual effects and depending on the adequacy of these measures, they may lower the overall risk level	-	Equivalent to step 5 of the European ERA

Table 3. ERA framework for GMOs in some European Unino Member States

Member State	Competent authority	Scientific advisory committee	ERA Framework for clinical trials with GMOs
Netherlands	The Ministry of Infrastructure and Water Management (IenW) and the Office for Genetically Modified Organisms (GMO Office).	Netherlands Commission on Genetic Modification (COGEM)	Deliberate release
Germany	The Federal Office of Consumers Protection and Food Safety (BVL)	Central Commission on Biological Safety (ZKBS) and Paul-Ehrlich-Institute, residing with the Ministry of Health	Deliberate release
Spain	Ministry of Environment	The Spanish Biosafety Commission (CNB) and the Interministerial Advisory Committee (CIOMG)	Deliberate release
Italy	Italian Medicines Agency (AIFA), Ministry of Health (Competent Authority for the contained use), Ministry for Environment, Land and Sea Protection (Competent Authority for the deliberate release)	-	Depending on the potential for releasing the GMO in the environment and its capacity replicate, transmit and disseminate into the environment, clinical trials are handled as contained use or deliberate release activities.
Belgium	Regional authorities from the Flemish, Walloon and Brussels-Capital Region are responsible for the contained use. The Federal Agency for Medicines and Health Products (FAMHP; Competent Authority for the deliberate release)	Biosafety and Biotechnology Unit (SBB; responsible of the scientific evaluation of clinical trials regulated under the 'contained use' framework) Belgian Biosafety advisory Council (advisory body for deliberate release),	For clinical trials in all cases an authorisation must be obtained according to the contained use legislation. However, if there is a probability of possible release that may confer a risk to human health or the environment which cannot be avoided by proper management procedures or working practices, a notification under 'deliberate release' is also required.
France	Ministries of Environment, Agriculture, Research, Health and Consumer Affairs	Haut conseil des biotechnologies	Depending on the potential for releasing the GMO in the environment, clinical trials are handled as contained use or deliberate release activities.
Denmark	Working Environment Authority (WEA), Ministry of Employment, is responsible for the safety regarding contained use.	-	Contained use

Member State	Competent authority	Scientific advisory committee	ERA Framework for clinical trials with GMOs
	Environmental Protection Agency (EPA), Ministry of Environment and Food of Denmark		
Finland	Board for Gene Technology	-	Depending on the potential for releasing the GMO in the environment and its capacity replicate, transmit and disseminate into the environment, clinical trials are handled as contained use or deliberate release activities.
Poland	Ministry of the Environment	-	Contained use
Portugal	Portuguese Environment Agency (APA)	-	Depending on the potential for releasing the GMO in the environment and its capacity replicate, transmit and disseminate into the environment, clinical trials are handled as contained use or deliberate release activities.

Table 4. Considerations of environmental risk assessment for the approved advanced therapy medicinal products in the EU and the US

Product Name	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
		MAA	Post-marketing considerations/surveillance	MAA
Glybera	Non-cell-based GTMP: AAV-1 capsid with AAV-2 backbone expressing the S447X variant of the human lipoprotein lipase (LPL) gene. The virus is replication deficient and non-integrating.	• Discussion of the effects of over-expression of LPL in an otherwise healthy human, including an estimation of the exposure that an accidental self-inoculation would result in. • Discussion of the risk of integration and potential insertional mutagenesis. • Describe the origins of each of the vector genome sequences and provide details of these small intervening DNA sequences. • Clarify if WPRE expressing X protein may be associated with oncogenesis. • Since WHV is endemic to marmot species found in the EU were concerns whether the WPRE might be a novel sequence for this environment. • Submission of batch release tests to preclude the presence of replication competent vector. • Justification of pathogenicity of baculoviruses in humans since vector particles may contain fragments of baculovirus DNA which could encode for ORFs expressed late in baculovirus replication*. • Justify the recombination events that might occur between baculovirus vectors during manufacture of Glybera and their potential to result in the formation of replication-competent AAV*. • To justify the frequency of homologous recombination with sequences in the	• Long term monitoring was conducted on the health of patients and any healthcare workers accidentally exposed to the product.	Not approved in U.S.

Product Name	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
		MAA	Post-marketing considerations/surveillance	MAA
		environment (horizontal gene transfer) and the possibility of uptake of vector DNA by microorganisms. • Shedding and biodistribution studies were submitted. • Discussion of possible gem line transmission. • Discussion of potential dissemination of infectious disease or the creation new reservoirs or vectors. • Justification for not conducting a post-marketing monitoring plan.		
Imlygic	Non-cell-based GTMP: Disabled recombinant HSV-1 encoding for human granulocyte macrophage colony-stimulating factor (hGM-CSF) gene	• Describe the tropism, pathogenicity and infection capability of talimogene laherparepvec in comparison to the wild type HSV1. • Discuss the potential recombination of talimogene laherparepvec with wild-type HSV-1 virus. Clinical data investigated whether talimogene laherparepvec after being injected intratumorally could also distribute to the site of natural HSV-1 infection and establish infection, latency and reactivation. • Discussion of the potential transmission of talimogene laherparepvec to an unintended human recipient and establishment of latency/ re-activation. • Discussion of the risks from inadvertent transmission, the likelihood of transmission to occur at the site of talimogene	• Evaluate the disseminated herpetic infection in immunocompromised patients • Monitor the potential transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Monitor symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients • Assessment of accidental exposure of HCP to talimogene laherparepvec • Additional clinical biodistribution and shedding data in melanoma	• An ERA was prepared pursuant to 21 CFR part 25. The ERA provided a quantitative assessment of Imlygic environmental exposure and environmental stability. • Evaluation of the biodistribution and shedding was subject of a postmarketing requirement (PMR) • Imlygic-associated herpetic infection in non-tumour tissue of treated patients (primary infection or reactivation/latency) and contacts (transmission/accidental

Product Name	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
		MAA	Post-marketing considerations/surveillance	MAA
		laherparepvec administration and the potential for exposure from the environment. • Discussion of the magnitude of consequences of talimogene laherparepvec transmission to immune-compromised and pregnant individuals. • The clinical pharmacology program was focused on the assessment of the viral clearance of talimogene laherparepvec by analysing the biodistribution in the blood and urine, and viral shedding of the infectious virus (from the surface of injected tumour(s) and the exterior occlusive dressing).		exposure) was a PMR requirement.
Strimvelis	Cell-based GTMP The viral vector is a replication deficient gamma-retroviral vector based on MoMLV	• Long-term monitoring of potential RCR in clinical trials. Discussion of homology with human endogenous retroviral sequences (HERV). • Two biodistribution studies were submitted • Discussion related to risk of germline transmission • Justification for not conducting shedding studies. • Discussion of the probability of introducing surface-bound retroviral particles • Product-related manufacturing materials are tested for recombinant virus formation in line with good manufacturing practice	• Pharmacovigilance plan: development of RCR	Not approved in U.S.
Zalmoxis	Cell-based GTMP The γ retroviral vector used for *ex vivo*	• Analysis of the characteristics of Zalmoxis and its components and their possible interaction with the environment, in	• Pharmacovigilance plan: development of RCR.	Not approved in U.S.

Product Name	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
		MAA	Post-marketing considerations/surveillance	MAA
	transduction is an integrative, replication defective vector	particular any potential adverse effects due to survival, multiplication or dispersal. • No specific studies on viral shedding were performed since no direct *in vivo* administration of the retroviral vector was foreseen • Discussion of possible gem line transmission of vector related sequence to the progeny and justification for not conducting studies • Discussion of the possibility to release free retroviral vectors or RCR and infection of non-target human and animal species.		
Kymriah	Cell-based GTMP	• Assessment of the likelihood of presence of RCLs in the final product and subsequent transmission of RCRs to thirds • Assessment of the likelihood of formation of RCL in patients • Assessment of the likelihood of transmission of replication-incompetent vectors. • Assessment of the likelihood of transmission of genetically modified T-cells by accidental administration to thirds or after bleeding	• Monitoring of RCR • Long-term safety	Categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c)
Yescarta	Cell-based GTMP			Categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c)
Luxturna	Non-cell-based GTMP	• Justification for not performing sequencing of each batch, testing product identity on import into the EU, and testing for gene product expression and potency. • Justification of the p5 promoter position and potential for minimising homologous recombination between vector plasmid and packaging plasmid	• Long-term safety (> 9 years) • Third party transmission	• The ERA provided a quantitative assessment of the product environmental exposure based on data from biodistribution and shedding studies, lot release testing and related nonclinical studies, and a worst case assumption in each case.

Product Name	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
		MAA	Post-marketing considerations/surveillance	MAA
		• Proof of absence of an ability to transform bacteria and possibly confer resistance to bacteria in the environment • Clinical shedding studies were performed analysing samples of tears and serum in Phase III trials. • Biodistribution justification after sub-retinal injection of the product. The assays used to detect virus and immune response to the capsid and the transgene were not validated to an acceptable standard, and these data were not considered to be definitive.		(Studies were developed in parallel with EU).
Zolgensma	Non-cell-based GTMP	Not approved yet in EU	No data available	• The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The Agency determined that approval of the drug product will not result in any significant environmental impact. • Vector shedding after infusion with the drug product was investigated at multiple time points during the clinical study. Samples of saliva, urine and stool were collected the day after infusion. • Biodistribution was evaluated in nonclinical

Product Name	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
		MAA	Post-marketing considerations/surveillance	MAA
				studies and in two patients who died

AAV1: Adeno-associated virus serotype 1; AAV2: Adeno-associated virus serotype 2; ERA: environmental risk assessment; HSV-1: herpes simplex virus serotype 1; MAA: Marketing Authorisation Application; MoMLV: Moloney murine leukaemia virus; ORF: open reading frame; RCR: replication competent retrovirus; RCL: Replication Competent Lentivirus; WPRE: Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element; WHV: Woodchuck Hepatitis Virus. * The GMO is manufactured using a system of 3 recombinant baculoviruses in an insect cell line.

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Chapter 3: Clinical development of advanced therapy medicinal products in the European Union and Japan

3.1: Methodological characteristics of clinical trials supporting the Marketing Authorisation of advanced therapies medicinal products in the European Union

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Abstract

Several ATMPs have been approved in the EU. The aim of this study is to analyse the methodological characteristics of the clinical trials (CT) that supported the MA of the approved ATMPs in the EU. A systematic review of the characteristics of pivotal CT of ATMPs approved in the EU until January 31st, 2021 was carried out. A total of 17 ATMPs were approved and 23 CT were conducted to support the MA (median, 1, range, 1 to 3). Of those studies, 8 (34.78%) were non-controlled and 7 (30.43%) used historical controls. Only 7 (30.4%) were placebo or active-controlled studies. Among all CT, 21 (91.3%) were open-label and 13 (56.52%) had a single-arm design. To evaluate the primary endpoint, 18 (78.26%) studies used an intermediate and single variable. The median (IQR) number of patients enrolled in the studies was 75 (22-118). To date, ATMPs' approval in the EU is mainly supported by uncontrolled, single-arm pivotal CTs. Although there is a trend toward an adaptive or a life cycle approach, a switch to more robust clinical trial designs is expected, to better define the benefit and the therapeutic added value of ATMPs.

Introduction

ATMPs are a medicinal class that includes gene, cell and tissue therapies. The success of ATMP development and the approval of these therapies in the EU has been crucial to the growth of clinical research during the last few years in this field, particularly for gene therapy.

Multiple indications are being targeted, most of them being refractory and recurrent stages of a disease that lacks effective therapeutic alternatives, and a significant proportion of them affecting the paediatric population [1]. With the introduction of ATMPs that can cover unmet needs and have the potential to cure life-threatening diseases, biological therapies initiated a shift from traditional clinical development pathway to an accelerated and highly product-specific one. The adaptive pathway concept and PRIME were launched in the EU specifically to speed the access of products targeting a significant unmet medical need. Several approved ATMPs were granted a PRIME designation and accelerated MAA assessment during their development, allowing early access to these medicines [2].

Due to the type of target diseases, the inherent complexity of these products, and their accelerated developments, less comprehensive clinical data might be generated. These characteristics may lead to uncertainties in the benefit/risk profile for the product at the time of MA. The aim of this study is to further analyse the clinical development of the current approved ATMPs. Here, we describe the methodological features of the clinical trials that have driven ATMPs to their European approval and we compare the gene therapy trials versus the cell and tissue engineered trials.

Methodology

A systematic review of the pivotal trials' features that supported the MA of the ATMPs approved in the EU was carried out using the following approach:

***Search strategy*:** Data collection was primarily extracted from European Public Assessment Reports on the EMA website (www.ema.europa.eu). The search was carried out until January 31st, 2021. In addition, a search for the main clinical trials of the approved ATMPs was conducted using ClinicalTrials.gov database and the related publications.

Eligibility criteria: Only products classified as ATMPs according to the EMA criteria [3][4] and authorised under centralised procedure in the EU have been considered. Combined ATMPs class, i.e., ATMP combined with a medical device, have been grouped according to the main ATMP category: gene therapy medicinal product, somatic cell therapy medicinal products or tissue engineered products. Only those trials identified or referenced as pivotal, and therefore, decisive for the MAA were analysed.

Data extraction and collected variables: The authors designed specific data extraction forms using Excel 2019 (Microsoft Corporation, Redmond, WA, USA) to collect information. For each ATMP the following variables were collected: type of ATMP, pharmacotherapeutic group, ATC code, therapeutic area (according to MeSH terms), diseases and other circumstances for its use (according to chapter's title from the international version of the ICD-10), number of assessed clinical indications and pivotal clinical trials conducted. For each pivotal clinical trial, the following variables were selected: phase, design, type of randomization, type of control, type of study blinding, number of arms, participating centres, type of hypothesis and primary endpoint, presence and type of health-related quality of life (HRQoL) endpoints, presence of pre-specified analysis, duration of the main phase of the study, pivotal trial ongoing at the time of MAA, overall number of patients that participated in the study (enrolled, on intervention arm or control arm and safety set), age and sex of population, existence or absence of previous treatments, and geographic location of the pivotal trial. To determine if the study was ongoing at the time of the submission, the MAA submission date and the final data collection date for the primary outcome measure of the pivotal clinical trial were reviewed. Standard definitions of analysis set were used to classify among intended to treat (ITT), modified ITT (mITT) and per protocol set (PP) following ICH (E9) and EMA guidelines [5][6]. To assign the type of hypothesis in the case of two variables being used to evaluate the primary endpoint, the most robust variable was selected, i.e., final versus surrogate variables.

Statistical analysis: Statistical analysis for categorical and continuous variables was made using means of proportions, mean, standard deviation (SD), median, quartiles 25 and 75 (Q25, Q75), and range (minimum and maximum). The statistical analysis was performed using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 17 ATMPs have been approved in the EU (Table 1) and 23 main trials were conducted to support the MA for these products (median, 1, range, 1 to 3). The ATMPs trials by disease area, according to ICD-10 classification, included: neoplasms (7), endocrine, nutritional and metabolic diseases (2), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (2), diseases of the eye and adnexa (2), diseases of the nervous system (1), diseases of the musculoskeletal system and connective tissue (3), diseases of the digestive system (1). In addition, there were 6 ATMPs for rare inherited disorders and 6 for neoplasms in which 4 were indicated for haematological malignancies and 2 for solid tumours. The detailed results of this study are presented in Table 2 by type of ATMP, in Table 3 for gene therapy studies and in Table 4 for cell and tissue therapy studies.

Regarding the design of the studies, 13 (56.52%) were Phase 2/3 and Phase 3 trials, 9 (39.13%) were Phase 1/2 or Phase 2 trials, and 1 (4.35%) was a retrospective study. For all types of therapies, 8 (34.78%) trials were non-controlled, 7 (30.44%) where active- or placebo-controlled, and 7 (30.43%) used an historical control as a comparator. Differences were observed between gene and non-gene therapies (Table S1 in Supplementary material). Six (42.87%) gene therapy studies were non-controlled and 6 (42.87%) used a historical control, whilst cell and tissue therapies studies were mainly controlled (n=6; 66.66%). A total of 14 (60.87%) studies were not randomized. Similarly, differences in the existence of randomization between gene and non-gene therapies studies were also observed. Most of the studies for gene products lacked randomisation (85.71%), whereas this was present in 75% of the cell therapies studies and 80% of the tissue therapies studies. A total of 21 (91.30%) were open-label studies; all gene and tissue therapy studies were open-label, and this was also the approach for 50% of cell products trials. However, there is a difference in the blinding evaluation of the relevant endpoints between gene and non-gene therapy studies, as such evaluation is mostly absent in the case of gene therapies (85.71%) but is present in the case of cell and tissue engineered therapies (50% for cell therapy studies and 100% tissue engineered therapy studies). A total of 13 (56.52%) studies were single-arm trials and 10 (43.48%) had two or more arms. A difference in the number of arms between gene and non-gene therapy studies was also observed, where single-arm studies comprised 78.57% of total trials for gene therapy products versus the two- or three-arm designs present in 75% of cell therapy studies and 80% of tissue therapy studies. Accordingly, there are some differences in the design between gene and non-gene therapies

studies, mainly in the parallel designs for cell and tissue engineered therapy studies versus single-arm designs for gene therapy studies. Of all studies analysed, 19 (82.60%) were multicentric.

Regarding the methodology used in these pivotal studies, 16 (69.56%) of the studies did not use a superiority or non-inferiority hypothesis but an alternative premise, e.g., comparison with historical controls. There is a difference between gene and non-gene therapies studies, where this type of alternative premises was mainly used for gene therapies trials (92.85%), while standard superiority or non-inferiority tests were used more frequently for cell and tissue engineered therapies trials (75% and 60%, respectively). To evaluate the primary objective, 18 (78.26%) of the trials used an intermediate and single main variable, which was mainly qualitative (73.91%). Final and quantitative variables were used in 5 (21.74%) and 7 (30.43%), respectively, which represents a smaller proportion (Table 5). Of these confirmatory studies, 18 (78.26%) used the ITT principle in assessing the primary efficacy, 2 (14,28%) gene therapy trials used mITT and 2 (14,28%) used per protocol set (PP). A total of 16 (69.56%) analysed studies included HRQoL questionnaires, 9 (39.13%) of those being disease-specific. No differences were observed in the type of HRQoL questionnaires between gene and non-gene products studies, i.e., generic versus disease-specific variables.

The mean (SD) time for the main phase of the trial was 35.33 (31.08) months, approximately one year for the gene therapies and more than two years for cell and tissue engineered therapies. A total of 12 (57.14%) studies were ongoing at the time of submission, meaning that the final data collection for primary outcome measuring was not completed. Globally, 17 (73.91%) of the studies had a prespecified interim analysis, with similar proportion among the three types of ATMPs (75-78.57 %).

Regarding the overall population size and location of these studies, the median (IQR 25-75) number of patients enrolled in the analysed ATMPs pivotal clinical trials was 75 (22-118). The mean ± SD age of the adult population included in these confirmatory trials was 48 ± 18.45 years old. There is no sufficient data to establish a mean ± SD age for paediatric populations. The sex distribution is higher for males (62.47%) than for women (37.53%). The analysed clinical trials were equally performed in both women and men, but the sex distribution was higher for males due to Provenge®´s indication, i.e., treatment of metastatic castration-resistant prostate cancer. The median (IQR 25-75) sample size in the intervention arm was 41 (16-94) patients and 63 (20-118) for the safety set. More than half of participants in these clinical trials

had received previous treatments (65.22%). From the 23 pivotal studies analysed, 18 included sites located in the EU (78.26%), and 10 (43.48%) in the United States of America (US) or in other regions, such as Israel, Japan or Australia.

Discussion

Clinical research on ATMPs has increased during the last few years [7]. The introduction of ATMPs and the long-term expectancy of their benefit adds a new challenge for the regulatory agencies. In the present study, we aimed to describe the most relevant methodological features of the clinical trials that have driven ATMPs to their EU approval. The major findings reveal that the pivotal studies of currently approved advanced therapies typically share the following characteristics: i) they are small, open-label, non-randomised, single-arm studies without control or using historical ones, and ii) intermediate and single variables are used to evaluate the primary efficacy outcome. In addition, this type of designs is more common for gene therapies than for cell and tissue therapies.

Hanna *et al.*, previously reported the methodological characteristics of clinical trials assessing ATMPs in an early development phase based on clinical trials registries [8]. The results showed very similar characteristics to those found in this study such as small sample size, non-randomised trials, single-arm trials, surrogate endpoints, and adaptive designs. Coppens *et al.*, also reported that the level of scientific evidence required for the approval might differ among different regulatory agencies [9]. Elsallab *et al.*, showed that clinical trials of ATMPs did not meet the same strict standards for clinical evidence that were applied to other biologicals submissions [10]. This previously reported data, together with the results of the present study, highlight the limited clinical evidence upon which the authorisation of most ATMPs is based. Of these approved ATMPs, it was considered that eleven (64.70%) had sufficient data for a full MA, while for the remaining six products, five (29.41%) obtained a conditional approval and one (5.88%) was granted with a MA under exceptional circumstances.

The low disease prevalence, the disease severity and burden, the lack or scarce availability of disease-modifying treatments, the patient population's heterogeneity and the strong presence of paediatric patient populations comprise some of the factors that could contribute to this type of designs.

The type of target diseases has been one of the key factors that might have given more flexibility in terms of level of evidence required for the MA. Our analysis shows that these designs are

more commonly used for the development of gene therapy products, which target orphan diseases such as hematologic cancers or rare inherited monogenic disorders (40% and 60% of approved gene therapies, respectively), usually with unmet medical needs. Gene therapies were mainly authorised after conducting a single open-label study, usually non-randomised and non-controlled or using historical controls, and only few of them being Phase III studies. By contrast, tissue therapies trials consisted of Phase III studies controlled with the standard of care, and two out of three cell therapy trials conducted placebo-controlled studies. The approved tissue therapies primarily cover products for articular cartilage damage or prostate cancer, which are relatively common among the overall population and with several treatments available. Moreover, the target population might have also contributed to these alternative designs for gene therapies products, given that 60% of approved gene therapies target paediatric population, while all the tissue and cell therapies target adults. The targeted paediatric diseases are life-threatening or with a huge impact on patients' and caregivers' quality-of-life, and randomised, controlled trials could have posed ethical concerns, as well as recruitment issues.

It is noteworthy to mention that different types of historical controls were used to compare the efficacy of the intervention: historical references from retrospective studies and retrospective databases, prospective natural history cohorts' studies, untreated sibling data and within-subject comparison between pre- and post-treatment assessments [11][12][13][14]. The current EMA guideline states that orphan products are assessed according to the same standards as those for other products but considering their limitations due to low patient recruitment [15]. While the same guideline states that most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials and deviation from such standards is uncommon, in the case of the current approved ATMPs, alternative approaches as historical controls were frequently used, i.e., Strimvelis®, Kymriah®, Luxturna®, Zolgensma® and Libmeldy®.

On the other hand, the line of treatment is another factor that might have justified these types of designs so far. As an example of the approved ATMPs, CAR-T therapies are indicated at least as a third-line therapy for relapsed or refractory cancer patients. The four pivotal studies conducted for these products were non-controlled, open-label, Phase II studies where the intervention arm was compared to a historical control. After the approval of the aforementioned therapies, the EMA has published recommendations on clinical considerations on CAR-T-cell product development [16], where it is stated that randomized controlled trial design should be

followed even for those cases of late-stage refractory disease. It will be interesting to see how these recommendations are implemented in the near future.

Another important factor observed in the studied designs is the use of surrogate variables instead of a clinically relevant final endpoint. Intermediate endpoints can be used as a primary endpoint for MA, especially when there is a high unmet need, when clinical events are rare/delayed in slowly progressive diseases and a very long follow-up is needed for their assessment, and for rare and/or life-threatening diseases with no therapeutic alternative available [17][18]. In the case of all approved gene therapies that target cancer diseases, the proportion of patients with objective overall response rate (ORR) was used as the intermediate primary variable, unlike cell therapy trials that used overall survival (OS) as a final endpoint. OS analysis usually requires a large sample size, a long follow-up and should be evaluated in a randomised, control trial to avoid cofounding factors due to the switch-over of control to intervention or subsequent therapies [19][20]. However, ORR has been the most commonly used surrogate endpoint in support of accelerated/conditional approvals, but also of standard approvals, since it is directly attributable to a drug's effect, providing an accurate assessment in single-arm trials conducted in patients with refractory tumours [21]. On the other hand, for gene therapies targeting inherited monogenic diseases, biomarkers were commonly used to predict changes in the desired clinical endpoints, and at least one of the pivotal studies included HRQoL outcomes. Exceptionally for other products, a novel clinical meaningful endpoint, i.e. Luxturna® [22], or survival as a final primary outcome were used, i.e. Zolgensma® [23][24].

These types of non-robust designs for new drugs in areas of high unmet medical need are mainly justified on the basis of ethical reasons, based on the potential life-saving opportunities or quality of life improvement for patients who may not survive or will progress rapidly until robust clinical data is available. On the other hand, the difficulties of conducting standard clinical developments with orphan drugs are well-recognised, and single small trials using alternative approaches have been the basis for numerous MAA in the recent years [25][26], [27][28]. This regulatory flexibility sometimes comes at the cost of having a less comprehensive clinical data, and in consequence, greater uncertainty about the product's benefit-risk balance at the time of MA [29]. In addition, since the introduction of the adaptive pathway concept, the shift towards accelerated clinical developments has also been associated with an intrinsic uncertainty on effectiveness and safety, which can result in promising Phase II results but an unsuccessful Phase III or post-marketing studies [30][31]. This highlights the possibility for a patient to receive an early-authorised treatment without meaningful clinical benefits and with

exposure to its adverse effects, missing clinical opportunities, and wasting healthcare system resources [32].

The speeding up access to new drugs is achieved by putting aside traditional Phase III clinical trials in favour of post-marketing evidence generation. This fact is translated into the need to perform long and extensive post-marketing studies, where the costs of evidence generation as well as the costs of therapy are likely to be transferred from the MA holder to healthcare systems [32][33]. It is known, that this post-authorisation commitments can be challenging due to the long-term follow-up, which may lead to delays to complete the studies, and given that patients are more reluctant to participate in a post-marketing trial with all its constraints, if the medicine is already available, above all in those cases where the trial includes randomization [34].

Costly treatments with high uncertainties regarding its benefits, translates to a complex evaluation by the Health Technology Assessment bodies (HTAb), as well as there is industry pressure for corporate pharma and its investors to ensure sustainability in drug development.

Several detailed methodological recommendations for clinical trial designs have been launched to address the shortcomings of carrying out studies in small population [35][36][37][38] and examples of effective use of a historical control have also been reported [39]. Multi-arm designs and platform designs sharing where a common control is shared have been raised as a potential solution [40][41]. Comparator data can also be taken from pragmatic trials, observational studies or registries, but ensuring its quality [42]. In addition, real world data plays a key role to provide sufficient therapeutic evidence for this type of therapies and efforts are being made for a better use of registries [43].

Methodological and clinical guidelines for a specific medical condition is an effective manner of obtaining regulatory guidance and providing a predictable decision-making regulatory framework. Given that ATMPs are innovative and more complex than traditional pharmaceuticals or other biological drugs, some specific requirements related to the study design and methodology, study population, safety, dose selection, as well as preclinical and product controls need to be considered for the development of these therapies. The FDA has launched several guidelines for the development of ATMPs aimed at certain types of conditions based on the acquired experience of the current approved advanced therapies. These guidelines address the point of uncontrolled designs and the need of more robust study designs to provide proper evidence of efficacy [44][45][46]. Although still limited, with the current experience of the approved ATMPs in the EU, EMA has started to launch new recommendations on the types

of study designs and methodologies that can support the MA more robustly [16]. This fact might lead to a switch on the current trend used in clinical designs based on uncontrolled pivotal studies or with historical control comparisons to randomised-controlled trials.

The limitations of this study are the small sample size and the fact that further analysis, once more therapies are approved, is required to determine with greater accuracy the most common clinical design and methodology for ATMPs, as well as to elucidate the potential differences between gene therapy trials versus cell and tissue therapy trials. Another limitation is that approved ATMPs have not been compared to other approved medicines. Nevertheless, this is an exhaustive study that evaluates the pivotal trials for approved ATMPs.

Conclusion

The results of our study show that most authorised ATMPs are based on small, open-label, uncontrolled and single-arm pivotal trials using single and intermediate variables to evaluate outcomes. ATMPs are innovative therapies that mainly target orphan diseases and high unmet medical needs. This fact has led to methodological weaknesses in their pivotal clinical trials, which in turn has resulted in limited data to robustly assess the benefit/risk of the product. A gradual shift towards the production of more methodologically sound randomized-controlled trials is expected to better define the benefit and the therapeutic added value of ATMPs.

Tables

Table 1. Approved ATMPs in the European Union and therapeutic indication

Trade Name	International non-proprietary name (INN) or common name	Pharmacotherapeutic group/ ATC code	Therapeutic Area (MeSH)	Chapter's title from the international version of the ICD-10
Gene therapy* medicinal *products				
Kymriah®	Tisagenlecleucel	Antineoplastic agents/ L01XX71	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	Neoplasms
Kymriah®	Tisagenlecleucel	Antineoplastic agents/ L01XX71	Lymphoma, Large-B-cell, Diffuse	Neoplasms
Yescarta®	Axicabtagene ciloleucel	Antineoplastic agents/ L01XX70	Lymphoma, Large-B-cell, Diffuse	Neoplasms
Tecartus®	Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured	Antineoplastic agents/ L01X	Lymphoma, Mantle-Cell	Neoplasms
Imlygic®	Talimogene laherparepvec	Antineoplastic agents/ L01XX51	Melanoma	Neoplasms
Glybera®	Alipogene tiparvovec	Lipid modifying agents/ C10AX10	Hyperlipo-proteinemia type I	Endocrine, nutritional and metabolic diseases
Strimvelis®	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with	Immunostimulants/ L03	Severe combined immunodeficiency	Diseases of the blood and blood-forming organs and certain

Trade Name	International non-proprietary name (INN) or common name	Pharmacotherapeutic group/ ATC code	Therapeutic Area (MeSH)	Chapter's title from the international version of the ICD-10
	retroviral vector that encodes for the human ADA cDNA sequence			disorders involving the immune mechanism
Luxturna®	Voretigene neparvovec	Ophthalmologicals, other ophthalmologicals/ S01XA27	Leber congenital amaurosis Retinitis Pigmentosa	Diseases of the eye and adnexa
Zynteglo®	Betibeglogene autotemcel	Other haematological agents/ B06AX02	Beta-Thalassemia	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
Zolgensma®	Onasemnogene abeparvovec	Other drugs for disorders of the musculoskeletal system/ M09AX09	Muscular Atrophy Spinal	Diseases of the nervous system
Libmeldy®	Atidarsagene autotemcel	Other nervous system drugs/ N07	Leukodystrophy, Metachromatic	Endocrine, nutritional and metabolic diseases
Somatic-cell therapy medicinal products				
Provenge®	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (Sipuleucel-T)	Other immunostimulants/ L03AX17	Prostatic Neoplasms	Neoplasms
Zalmoxis®	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	Antineoplastic agents/ L01	Hematopoietic Stem Cell Transplantation Graft vs Host Disease	Neoplasms Factors influencing health status and contact with health services
Alofisel®	Darvadstrocel	Immunosuppressants/ L04	Rectal Fistula	Diseases of the digestive system

Trade Name	International non-proprietary name (INN) or common name	Pharmacotherapeutic group/ ATC code	Therapeutic Area (MeSH)	Chapter's title from the international version of the ICD-10
Tissue-engineered medicinal products				
Chondrocelect®	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins/	Other drugs for disorders of the musculoskeletal system/ M09AX02	Cartilage Diseases	Diseases of the musculoskeletal system and connective tissue
MACI®	Matrix-applied characterised autologous cultured chondrocytes	Other drugs for disorders of the musculoskeletal system/ M09AX02	Fractures, Cartilage	Diseases of the musculoskeletal system and connective tissue
Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Other drugs for disorders of the musculoskeletal system/ M09AX02	Cartilage Diseases	Diseases of the musculoskeletal system and connective tissue
Holoclar®	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Ophthalmologicals/ S01XA19	Stem Cell Corneal Diseases	Diseases of the eye and adnexa

Table 2. Design features of pivotal clinical trials for the approved advanced therapy medicinal products in the EU

ATMP Clinical development		Gene Therapy medicinal products	Somatic Cell Therapy medicinal products	Tissue engineered therapies	All types of therapies
Number of products	N	10	3	4	17
Number of indications per product	Mean (SD)	1.10 (0.32)	1 (0)	1 (0)	1.06 (0.24)
Total number of pivotal trials and studies	N	14	4	5	23
	Mean (SD)	1.27 (0.65)	1.33 (0.58)	1.25 (0.5)	1.28 (0.57)
	(min, Max)	(1, 3)	(1, 2)	(1, 2)	(1, 3)
Clinical trials					
Phase 1	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Phase 1/2	N (%)	4 (28.57%)	1 (25%)	0 (0%)	5 (21.74%)
Phase 2	N (%)	3 (21.43%)	0 (0%)	1 (20%)	4 (17.39%)
Phase 2/3	N (%)	3 (21.43%)	0 (0%)	0 (0%)	3 (13.04%)
Phase 3	N (%)	4 (28.57%)	3 (75%)	3 (60%)	10 (43.48%)
Observational retrospective studies	N (%)	0 (0%)	0 (0%)	1 (20%)	1 (4.35%)
Randomization					
No	N (%)	12 (85.71%)	1 (25%)	1 (20%)	14 (60.87%)
Yes 1:1	N (%)	0 (0%)	1 (25%)	4 (80%)	5 (21,74%)
Yes ≥2:1	N (%)	2 (14.29%)	2 (50%)	0 (0%)	4 (17.39%)
Control					
Not controlled	N (%)	6 (42.87%)	0 (0%)	2 (40%)	8 (34.78%)
Placebo controlled	N (%)	0 (0%)	2 (50%)	0 (0%)	2 (8.70%)
Active controlled	N (%)	1 (7.14%)	1 (25%)	3 (60%)	5 (21.74%)
Historical control	N (%)	6 (42.87%)	1 (25%)	0 (0%)	7 (30.43%)
Other	N (%)	1 (7.14%)	0 (0%)	0 (0%)	1 (4.35%)
Blinding					
Open label	N (%)	14 (100%)	2 (50%)	5 (100%)	21 (91.30%)
Single blind	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

ATMP Clinical development		Gene Therapy medicinal products	Somatic Cell Therapy medicinal products	Tissue engineered therapies	All types of therapies
Double blind	N (%)	0 (0%)	2 (50%)	0 (0%)	2 (8.70%)
Blinding evaluation					
Yes	N (%)	2 (14.28%)	2 (50%)	5 (100%)	19 (82.61%)
No	N (%)	12 (85.71%)	2 (50%)	0 (0%)	4 (17.39%)
Multicentric					
No	N (%)	4 (28.57%)	0 (0%)	0 (0%)	4 (17.39%)
Yes	N (%)	10 (71.43%)	4 (100%)	5 (100%)	19 (82.60%)
Number of arms					
1 arm	N (%)	11 (78.57%)	1 (25%)	1 (20%)	13 (56.52%)
2 arms	N (%)	2 (14.29%)	3 (75%)	3 (60%)	8 (34.78%)
3 arms	N (%)	1 (7.14%)	0 (0%)	1 (20%)	2 (8.70%)
Design					
Parallel groups	N (%)	2 (14.29%)	3 (75%)	3 (60%)	8 (34.78%)
Single arm	N (%)	11 (78.57%)	1 (25%)	1 (20%)	13 (56.52%)
Other	N (%)	1 (7.14%)	0 (0%)	1 (20%)	2 (8.70%)
Main Outcomes					
Final variable	N (%)	2 (14.28%)	2 (50%)	1 (20%)	5 (21.74%)
Intermediate variable	N (%)	12 (85.71%)	2 (50%)	4 (80%)	18 (78.26%)
Co-primary	N (%)	2 (14.28%)	1 (25%)	1 (20%)	4 (17.39%)
Composite variable	N (%)	1 (7.14%)	0 (0%)	0 (0%)	1 (4.35%)
Single variable	N (%)	11 (78.57%)	3 (75%)	4 (80%)	18 (78.26%)
Type of variable for main outcome					
Qualitative	N (%)	13 (92.85%)	3 (75%)	1 (20%)	17 (73.91%)
Quantitative (discrete and continuous)	N (%)	2 (14.28%)	1 (25%)	4 (80%)	7 (30.43%)
Health related quality of life:					

ATMP Clinical development		Gene Therapy medicinal products	Somatic Cell Therapy medicinal products	Tissue engineered therapies	All types of therapies
No	N (%)	7 (50%)	2 (50%)	1 (20%)	10 (43.48%)
General questionnaires	N (%)	5 (35.71%)	1 (25%)	1 (20%)	7 (30.43%)
Specific questionnaires	N (%)	4 (28.57%)	1 (25%)	4 (80%)	9 (39.13%)
Prespecified previous analysis:					
Interim analysis	N (%)	11 (78.57%)	3 (75%)	3 (75%)	17 (73.91%)
Final analysis type (primary analysis):					
ITT	N (%)	10 (71.43%)	3 (75%)	5 (100%)	18 (78.26%)
mITT	N (%)	2 (14.28%)	0 (0%)	0 (0%)	2 (8.69%)
PP	N (%)	2 (14.28%)	0 (0%)	0 (0%)	2 (8.69%)
Hypothesis:					
Superiority	N (%)	1 (7.14%)	3 (75%)	1 (20%)	5 (21.74%)
Non-inferiority	N (%)	0 (0%)	0 (0%)	2 (40%)	2 (8.7%)
Other	N (%)	13 (92.85%)	1 (25%)	2 (40%)	16 (69.56%)
Mean time for the main phase (months)	Mean (SD)	11.5 (9.30)	70.50 (91.22)	24 (9.80)	35.33 (31.08)
Ongoing at the time of the MAA submission (final data for primary outcome measure)					
Yes	N (%)	8 (57.14%)	3 (75%)	1 (25%)	12 (57.14%)
No	N (%)	6 (42.86%)	1 (25%)	3 (75%)	10 (47.62%)
Population					
Population randomized/enrolled	N	1065	798	543	2406
	Median (Q25 - Q75)	22 (18.75 - 106.5)	134.5 (27 - 437)	104 (88.50 - 131)	75 (22 - 118)
	(min, Max)	(5, 437)	(17, 512)	(75, 144)	(5, 512)
Population on intervention arm	N	797	495	254	1546
	Median (Q25 - Q75)	21.5 (11.5 - 93.75)	68.5 (20.25 - 282.5)	64.5 (53.25 - 72.75)	41 (16.25 - 93.75)
	(min, Max)	(5, 296)	(17, 341)	(52, 73)	(5, 341)

ATMP Clinical development		Gene Therapy medicinal products	Somatic Cell Therapy medicinal products	Tissue engineered therapies	All types of therapies
Population on control arm	N	151	416	183	750
	Median (Q25, Q75)	75.5 (NA)	140 (105 - 171)	61 (50 - 72)	88.50 (27.5 - 140.5)
	(min, Max)	(10, 141)	(105, 171)	(50 - 72)	(10, 171)
Population on safety set	N	933	780	439	2152
	Median (Q25 -Q75)	22.5 (13.5, 93,75)	128.5 (25.75 - 430.75)	110 (81.75 - 137.5)	63.5 (20 - 118)
	(min, Max)	(5, 419)	(17, 506)	(75, 144)	(5, 419)
Age of adult population (years)	Mean (SD)	54.29 (9.24)	52.77 (16.67)	37.14 (5.56)	47.84 (18.45)
Age of paediatric population (years)	Mean (SD)	6.15 (8.26)	NA	NA	6.15 (8.26)
Sex					
Female	N (%)	443 (47%)	191 (30.31%)	231 (42.54%)	865 (37.53%)
Male	N (%)	498 (53%)	630 (76.73%)	312 (57.45%)	1440 (62.47%)
Location of the pivotal clinical trial					
United States	Mean (SD)	9 (64.28%)	1 (25%)	0 (0%)	10 (43.48%)
Europe	Mean (SD)	10 (71.42%)	3 (75%)	5 (100%)	18 (78.26%)
Canada	Mean (SD)	5 (35.71%)	1 (25%)	0 (0%)	6 (26.09%)
Others	Mean (SD)	7 (50%)	3 (75%)	0 (0%)	10 (43.48%)
Previous treatments:					
Yes & No	N (%)	1 (7.14%)	0 (0%)	0 (0%)	1 (4.35%)
No	N (%)	3 (21.74%)	0 (0%)	2 (40%)	5 (21.74%)
Yes	N (%)	10 (65.21%)	2 (50%)	3 (60%)	15 (65.22%)

ITT: intended to treat; mITT: modified intended to treat; NA: not applicable; PP: per protocol set; Zynteglo pooled analysis (Studies HGB-204, HGB-205 and LFT-303) was counted as one pivotal study; Holoclar retrospective study was counted as a pivotal study, since it was considered the main study which lead to the Marketing Authorisation of the product; The final analysis type (primary analysis) for TK0008 study of Zalmoxis was not available; The mean time for the main phase excludes Provenge (defined as ¨until disease progression or death¨) and TK0008 study for Zalmoxis; Age of adult population: data not available for TK0008 study for Zalmoxis; Age of paediatric population: data only available for Tecartus, Libmeldy, Kymriah and Strimvelis; Previous treatments: not applicable for Zalmoxis. For the Health related quality of life outcomes, the percentages can exceed 100% given that there might be multiple questioners for the same product (i.e., generic and disease-specific).

Table 3. Design features of pivotal clinical trials for the approved gene therapy medicinal products in the EU

Gene Therapies	Glybera®			Imlygic®	Strimvelis®	Yescarta®	Kymriah®		Luxturna®	Zynteglo®		Zolgensma®	Tecartus®	Libmeldy®
CHMP Positive Opinion date	23-jun-11			22-oct-15	01-abr-16	28-jun-18	29-jun-18		20-set-18	26-apr-19		26-mar-20	15-oct-20	15-oct-20
Authorisation status/type	Withdrawn			Authorised	Authorised	Authorised	Authorised		Authorised	Authorised		Authorised	Authorised	Authorised
Type of authorisation	Under exceptional circumstances			Standard	Standard	Standard	Standard		Standard	Conditional		Conditional	Conditional	Standard
Clinical trial Acronym	CT-AMT-011-01	CT-AMT-011-02	CT-AMT-010-01	Study 005/05	Study AD1115611/Gene-ADA	ZUMA-1	Study B2202	Study C2201	AAV2-hRPE65v2-301 / 302	Studies HGB-204, HGB-205 and LFT-303	Studies HGB-207, HGB-212	Study CL-303 (STR1VE)	ZUMA-2	Study 201222
Phase	II/III	II/III	II/III	III	I/II	I/II	II	II	III	I/II	III	III	II	I/II
Randomization	No	No	No	2:1	No	No	No	No	2:1	No	No	No	No	No
Control	Non-controlled	Non-controlled	Non-controlled	Active control	Historical control	Historical control	Historical control	Historical control	Delayed-intervention control group	Non-controlled	Non-controlled	Historical control	Non-controlled	Historical control
Blinding design	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label
Blinding evaluation	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No
Multicentric	Single-centre	Dual-centre	Single-centre	Multicentric	Single-centre	Multicentric	Multicentric	Multicentric	Dual-centre	Multicentre	Multicentre	Multicentre	Multicentre	Single-centre
Number of arms	Three	One	One	Two	One	One	One	One	Two	One	One	Two	One	One
Design	Parallel arms (dose range)	Single arm	Single arm	Parallel arms	Single arm	Single arm	Single arm	Single arm	Parallel arms	Single arm	Single arm	Single arm	Single arm	Single arm
Main Outcomes	Intermediate and single variable	Intermediate and single variable	Intermediate and composite variable	Intermediate and single variable	Final and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Final and co-primary variable	Intermediate and single variable	Intermediate and co-primary variable
Type of variable for main outcome	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Quantitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative and Quantitative

Gene Therapies	Glybera®			Imlygic®	Strimvelis®	Yescarta®	Kymriah®		Luxturna®	Zynteglo®		Zolgensma®	Tecartus®	Libmeldy®
Health related quality of life	No	General Q	No	Specific Q	No[a]	No	General Q	General and specific Q	No	No	General and specific Q	No	General Q	Specific Q
Prespecified previous analysis	Interim analysis	Interim analysis	N/A	Interim analysis	None	Interim analysis	Interim analysis	Interim analysis	None	Interim analysis	Interim analysis	Interim analysis	Interim analysis	Interim analysis
Final analysis type (primary efficacy analysis)	ITT	ITT	ITT	ITT	ITT	mITT	PP	PP	ITT	ITT	ITT	ITT	mITT	ITT
Hypothesis	Description of efficacy of intv	Description of efficacy of intv	Description of efficacy of intv	Superiority over an active control	Superiority over historical control group	Intv compared to historical control	Description of efficacy of intv	Intv compared to historical control	Intv compared non-intervention (natural history)	Description of efficacy of intv	Description of efficacy of intv	Superiority versus natural observation study	Description of efficacy of intv	Superiority versus natural history cohort (or untreated sibling when available)
Mean time for the main phase (months)	3	3	3	12	36	12	3	12	12	12	12	14	3	24
Ongoing at the time of the MAA submission (final data for primary outcome measure)	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Two studies ongoing	Yes	Yes	No	No
Population														
Population randomised /enrolled	22	5	18	437	12	111	92	147	31	22	19	22	105	22
Population on intervention arm	14	5	8	296	12	101	75	99	21	22	10	22	92	20
Population on control arm	NA	NA	NA	141	NA	NA	NA	NA	10	NA	NA	NA	NA	NA

Gene Therapies	Glybera®			Imlygic®	Strimvelis®	Yescarta®	Kymriah®		Luxturna®	Zynteglo®		Zolgensma®	Tecartus®	Libmeldy®
Population on safety set	14	5	8	419	12	101	75	99	29	23	14	22	92	20
Age of population (years)														
Mean	45,6	41,8	N/A	63,07	1.7	56,3	12	54	N/A	N/A	N/A	0,31	65	3.6
Sex:														
Female	9	1	N/A	250	5	33	32	36	18	15	6	12	15	11
Male	5	4	N/A	187	7	68	43	63	13	7	5	10	77	9
Geographic region:														
North America	X	X		X		X	X	X	X	X	X	X	X	
Europe			X	X	X	X	X	X		X	X		X	X
Others				X	X	X	X	X		X	X			
Previous treatments:	Yes	Yes	Yes	Yes/No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No

ITT: intended to treat; intv: intervention; mITT: modified intended to treat; NA: not applicable; N/A: not available; PP: per protocol set; Q: Questionnare; [a]Not at the time of the submission. The HRQoL objective applied to the long-term follow-up (4 to 8 years after gene therapy) only.

Table 4. Design features of pivotal clinical trials for the approved cell and tissue engineered therapy medicinal products in the EU

	Cell Therapies				Tissue therapies			
	Provenge®	**Zalmoxis®**	**Alofisel®**	**ChondroCelect®**	**Holoclar®**	**MACI®**	**Spherox®**	
CHMP Positive Opinion date	27-jun-13	23-jun-16	14-dec-17	25-jun-09	06-mar-13	25-apr-13	18-may-17	
Authorisation status	Withdrawn	Withdrawn	Authorised	Withdrawn	Authorised	Withdrawn	Authorised	
Type of authorisation	Standard	Conditional marketing authorisation	Standard	Standard	Conditional	Standard	Standard	
Clinical trial Acronym	9902B (IMPACT)	TK007	TK008	ADMIRE-CD	TIG/ACT/01&EXT'	HLSTM01	SUMMIT	Cod 16 HS 14	Cod 16 HS 13
Phase	III	I/II	III	III	III	Observational retrospective study	III	II	III
Randomization	2:1	No	3:1	1:1	1:1	No	1:1	1:1:1	1:1
Control	Placebo	Historical control[a]	Active treatment	Placebo	Active treatment	Non-controlled	Active treatment	Non-controlled	Active treatment
Blinding	Double-blind	Open-label	Open-label	Double-blind	Open-label	Open-label	Open-label	Open-label	Open-label
Blinding evaluation	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Multicentric	Multicentric	Multicentric	Multicentric	Multicentric	Multicentric	Dual-centre	Multicentric	Multicentric	Multicentric
Number of arms	Two	One	Two	Two	Two	One	Two	Three	Two
Design	Parallel groups	Single arm	Parallel groups	Parallel groups	Parallel groups	Retrospective case-series	Parallel groups	Single arm (three doses)	Parallel groups
Main Outcomes	Final and single variable	Intermediate and single variable	Intermediate and single variable	Final and co-primary variable	Intermediate and co-primary variable	Final and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable
Type of variable for main outcome	Qualitative	Qualitative	Quantitative	Qualitative	Quantitative	Qualitative	Quantitative	Quantitative	Quantitative
Health related quality of life	No	No	General questionnaire	Specific questionnaire	Specific questionnaire	No	General and Specific questionnaire	Specific questionnaire	Specific questionnaire

	Cell Therapies					Tissue therapies			
	Provenge®	**Zalmoxis®**		**Alofisel®**	**ChondroCelect®**	**Holoclar®**	**MACI®**	**Spherox®**	
Prespecified previous analysis	Interim analysis	None	Interim analysis	Interim analysis	None	NA	Interim analysis	Interim analysis	Interim analysis
Final analysis type (primary efficacy analysis)	ITT	ITT	NA	ITT	ITT	ITT	ITT	ITT	ITT
Hypothesis	Superiority over placebo	Description of efficacy of intervention	NA	Superiority over placebo	Non-inferiority vs SOC	Exploratory	Superiority over SOC	Superiority over baseline for the three dose groups	Comparison with baseline and non-inferiority/superiority with SOC
Duration of the main phase (months)	Until disease progression or death	135	NA	6	36	NA	24	12	24
Ongoing at the time of the MAA submission (primary completion)	No	No	Yes	No	No	NA	Yes	Yes	Yes
Population									
Population enrolled	512	57	17	212	118	NA	144	75	102
Population on intervention arm	341	30	17	107	57	104	72	73	52
Population on control arm	171	140	Not known	105	61	NA	72	NA	50
Population on Safety set	506	52	17	205	118	NA	144	75	102
Age of population:									
Mean	71	49	N/A	38.3	33.9	46.8	34	34	37
Sex:									
Female	NA	30	N/A	161	42	24	51	53	61
Male	512	22	N/A	96	76	80	93	22	41
Geographic region:									
North America	X								

	Cell Therapies					Tissue therapies			
	Provenge®	Zalmoxis®		Alofisel®	ChondroCelect®	Holoclar®	MACI®	Spherox®	
Europe		X	X	X	X	X	X	X	X
Others		X	X	X					
Previous treatments:	Yes	NA	NA	Yes	Yes	Yes	No	No	No

ITT: intended to treat; mITT: modified intended to treat; NA: not applicable; N/A: not available; PP: per protocol set; SOC: standard of care; [a]Upon assessment of the TK007 data and as only limited data from the TK008 study were available, the applicant was asked to perform a comparison of the MM-TK treated patients (TK007 and TK008 combined) with results from suitable historical controls.

Table 5. Primary clinical variables of pivotal clinical trials for the approved ATMPs in the EU

Type of product	Product	Type of target disease	Intermediate (I) o Final (F) variable	Primary variable description
GTMP	Kymriah (ALL)	Haematological malignancies	I	Overall remission rate, which included CR and CR with incomplete blood count recovery
	Kymriah (DLBCL)		I	Overall response rate defined as the proportion of patients with a BOR of CR or PR, where the BOR was defined as the best disease response recorded from tisagenlecleucel until progression disease or start of new anticancer therapy.
	Yescarta		I	Objective response rate, defined as a CR or PR per the revised International Working Group Response Criteria for Malignant Lymphoma as determined by study investigators
	Tecartus		I	Objective response rate, defined as CR or PR using central assessment per Lugano Classification
	Imlygic	Solid tumour	I	Durable response rate was defined as the percentage of participants with a CR or PR maintained continuously for at least 6 months from the time the objective response was first observed and initiating within 12 months of starting therapy as assessed by the Endpoint Assessment Committee
SCTMP	Provenge		F	Overall survival defined as time from randomization to death due to any cause was analysed for the ITT population
GTMP	Glybera	Inherited monogenic diseases	I	Reduction in fasting plasma triglycerides (median of baseline vs median of week 3-12 post AMT-011) ≥ 40%
				Achievement of 40 % reduction of median fasting triglycerides concentrations 12 weeks after treatment with AMT-011
				Reduction in individual median fasting plasma triglyceride levels of ≤10 mmol/L concurrent with a low-fat diet, or 40% reduction, concurrent with a low-fat diet
	Strimvelis		F	Survival at 3 years post-gene therapy
	Luxturna		I	Subject's bilateral performance (no eye patching) on the mobility test, as measured by a change score, one year following vector administration as compared to a subject's Baseline bilateral mobility test performance
	Zynteglo		I	The proportion of subjects who meet the definition of transfusion independence (TI). TI is defined as a weighted average Hb ≥9 g/dL without any packed red blood cells transfusions for a continuous period of ≥12 months at any time during the study after drug product infusion
	Zolgensma		F/Co-primary	Proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3), confirmed by video recording, as a patient who sits up straight with head erect for at least 30 seconds

Type of product	Product	Type of target disease	Intermediate (I) o Final (F) variable	Primary variable description
				Survival at 14 months of age
	Libmeldy		I/Co-primary	Total Gross Motor Function Measure score two years after treatment was the primary endpoint
				The co-primary endpoint was the ARSA activity
TEP	Chondrocelect	Condrophaties	I/Co-primary	Histomorphometry on end point biopsies at 12 months post-surgery and overall Histology Assessment on First Subscale of ICRS II Score
				Change from Baseline in Overall Knee Injury and Osteoarthritis Outcome Score at 12-18 Months
	MACI		I	Change from Baseline to Week 104 for the Participant's Knee Injury and Osteoarthritis Outcome Score Pain and Function (Sports and Recreational Activities) Scores
	Spherox		I	Change of overall Knee Injury and Osteoarthritis Outcome Score from baseline to final assessment determined for each dosage group and between the dosage groups
				Change of overall Knee Injury and Osteoarthritis Outcome Score from baseline to final assessment compared between intervention arm and comparator
SCTMP	Zalmoxis	Adjunctive treatment in haploidentical haematopoietic stem cell transplantation	I	Proportion of patients who achieved immune reconstitution, empirically defined a priori as an absolute CD3+ cell count of 100/µL or more for two consecutive observations (and/or CD4+ cells ≥ 50/µL and/or CD8+ cells ≥ 50/µL)
				Disease-free survival measured from the date of randomization until the date of relapse (or progression), or death from any cause, whichever occurs first.
	Alofisel	Complex perianal fistula(s) - Crohn's disease	F/Co-primary	Combined remission of perianal fistulising Crohn´s disease and absence of collections > 2 cm of the treated fistula confirmed by MRI images, at week 24. Remission was defined as clinical closure of external openings that were draining at baseline despite gentle finger compression

Type of product	Product	Type of target disease	Intermediate (I) o Final (F) variable	Primary variable description
TEP	Holoclar	Limbal stem cell deficiency	F	Composite endpoint of the rate of patients with a successful transplantation at 12 months post-intervention, based on the co-presence of clinical signs

Intermediate variable: a clinical endpoint such as measure of a function or of a symptom (disease-free survival, angina frequency, exercise tolerance) but is not the ultimate endpoint of the disease, such as survival or the rate of irreversible morbid events (stroke, myocardial infarction).
Final variable: describes a valid measure of clinical benefit due to treatment: the impact of treatment on how a patient feels, functions and survives. It is clinically relevant, sensitive (responsive to change) and is both accepted and used by physicians and patients. Clinical endpoints may be a clinical event (e.g. mortality) a composite of several events, a measure of clinical status, or health related quality of life (HRQoL) [*Ref: EUnetHTA (2015). Guideline on Endpoints used for Relative Effectiveness Assessment of pharmaceuticals: Clinical endpoints. https://www.eunethta.eu/wp-content/uploads/2018/01/Clinical-endpoints.pdf*]
ARSA: arysulfatase A enzyme; ALL: Acute lymphocytic leukaemia; CR: complete response; DLBCL: Relapsed or refractory diffuse large B-cell lymphoma; GTMP: gene therapy medicinal product; ITT: intended to treat; PR: partial response; SCTMP: somatic cell therapy medicinal product; TEP: tissue engineered medicinal product.

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Supplementary Materials

Table S1. Differences by type of advanced therapy (gene therapies versus cell and tissue therapies)

Design and methodology of the pivotal trial	Gene Therapies	Non-Gene Therapies
Mean (SD) number of pivotal clinical trials	1,27 (0,65)	1,14 (0,38)
Phase of the trials		
Phase 1, Phase 1/2, Phase 2 and retrospective trials	7	3
Phase 2/3 and Phase 3[1]	7	6
Type of control		
Non-controlled[2]	13	3
Placebo or active controlled	1	6
Randomisation		
Yes	2	6
No	12	3
Blinding design		
Open	14	7
Single or double	0	2
Blinding evaluation		
Yes	2	7
No	12	2
Multicentre		
Yes	11	9
No	3	0
Number of arms		
1 arm	11	2
≥ 2 arms	3	7
Design		
Parallel	2	6
Other[3]	12	3
Type of objective		
Superiority and non-inferiority	1	6
Other	13	3
Main outcome		
Final variable	2	3
Intermediate variable	12	6
Type of primary variable		

Design and methodology of the pivotal trial	Gene Therapies	Non-Gene Therapies
Number of quantitative variables	13	4
Number of qualitative variables	2	5
Health-related quality of life variables		
Yes	9	7
No	7	3

Sample size (n=17): Gene therapies (n= 10), non-gene therapies (n=7). Non-gene therapies comprise both cell and tissue engineered medicinal products. [1] Including 1 retrospective study; [2] Including historical controls and ¨other¨ studies; [3] Including single, crossover and ¨other¨ studies. SD: standard deviation.

3.2: Current landscape of clinical development and approval of advanced therapies medicinal products

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Abstract

ATMPs are innovative therapies that mainly target orphan diseases and high unmet medical needs. The uncertainty about the product's benefit-risk balance at the time of approval, the limitations of nonclinical development and the complex quality aspects of those highly individualized advanced therapies are playing a key role in the clinical development, approval and post-marketing setting for these therapies. This article reviews the current landscape of clinical development of advanced therapies, its challenges and some of the efforts several stakeholders are conducting to move forward within this field. Progressive iteration of the science, methodologically sound clinical developments, establishing new standards for ATMPs development with the aim to ensure consistency in clinical development and the reproducibility of knowledge is required, not only to increase the evidence generation for approval but to set principles to achieve translational success in this field.

Introduction

ATMPs are a medicinal class that includes gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered therapies [1][2]. The MA of these therapies in the last years has been crucial to the growth of clinical research in this field [3]. However, due to the current type of target diseases, i.e., orphan and unmet needs, and the inherent complexity of these products, less comprehensive clinical data has justified their approval. Here, we review and discuss the current landscape and challenges for clinical development and approval of advanced therapies, as well as the current efforts and potential future approaches to overcome these obstacles.

Level of clinical evidence at the time of marketing authorisation

Until September 31st, 2021 19 advanced therapies were approved in the EU [4]. The key therapeutic areas mainly include haematological malignancies, monogenic diseases and cartilage diseases (Table 1). The clinical development of these approved ATMPs for the authorised clinical indications was based on 25 pivotal trials. Most of these trials consisted of small, open-label, non-randomised, single-arm studies, comparing the efficacy with historical controls, and using intermediate variables to evaluate the primary efficacy outcome (Table 2). Other studies that analysed ATMP clinical trials in an early development phase reported similar results [5]. The type of current target diseases including orphan indications [6], unmet needs [7], and the presence of paediatric patient populations has justified more flexible clinical designs and methodologies using adaptive pathways and balancing the need for timely patient access through staggered approval (Table 2) [8].

Although controlled randomized clinical trials are the standard for evidence generation in terms of efficacy and safety for regulatory decision making, the treatment comparison with the SoC or placebo might have not been considered feasible and/or ethical in these cases. This is translated into less comprehensive clinical data at the time of MA, and therefore, greater uncertainty about the product's benefit-risk balance [9]. For instance, Zalmoxis® authorisation was mainly based on promising results of an open-label, non-randomized Phase I-II study, supported by the preliminary efficacy and safety data from the first seventeen patients of an ongoing Phase III controlled study. The final results from this controlled study failed to confirm any benefit at post-marketing level and the drug had to be withdrawn [10]. Another recent case is Kymriah®, approved based on a Phase II open-label and single arm study and where the

randomized post-marketing Phase III trial that analysed the drug against SOC failed to meet the primary efficacy endpoint, i.e., event-free survival [11] [12]. Nevertheless, the patient profile for this last study may differ from that included in the pivotal trial that led to its MA. It should be mentioned that although most of the products were approved based on single arm designs, some of their competitors conducted controlled studies to support the MA for the same indication, e.g., Spinraza® [13], or planned controlled post-marketing trials, e.g., Kymriah® or Yescarta® [9]. By contrary for cell therapies, it should be noted that even though Zalmoxis® and Alofisel® were granted with an orphan designation, Phase III studies were conducted including a comparator arm [14][15].

With these types of flexible and expedited developments with the ATMPs, the current landscape of biological therapies has initiated a shift from traditional clinical developments to a highly product-specific one. Elsallab *et al*., conducted a matched comparison of the regulatory submissions between ATMPs (n=17) and other biologicals (n=17). The results showed that clinical studies for ATMPs did not meet the same strict standards for clinical evidence that were applied to other biological products. The evidence on the design, conduct, and outcome of ATMP clinical studies suffered from more objections when compared to other biologicals. Despite matching for the disease area and orphan status, ATMPs had more non-randomized, non-blinded trials and included significantly lower numbers of patients, raising doubts about the trial outcomes [16]. How this non robust data can affect the approval of advanced therapies has also been reviewed. Bravery *et al*., tried to answer the question whether ATMPs are more or less likely to be approved than other medicines. The results showed that for all medicine applications combined, there is a 76% success rate (n=632) compared to 59% for ATMPs (n=22), but for non-orphan ATMPs the chance of success seems to be lower, at only 50% (n=10) [17]. Other studies also analysed the evidence submitted to support the ATMPs MA by quantifying the objections raised by regulatory authorities during the assessment. The two more common issues included suitable quality and clinical data demonstrating the efficacy and safety [18][19]. Barkholt *et al.,* identified the 'hot spots' in ATMP development analysing the MAAs (n=20) and all scientific advice given for ATMPs by the EMA (from 2009 to 2018). The clinical data package, the clinical results, the target indication, limited safety information and limited safety and efficacy follow up and risk management were the most common development issues and objections raised during the MAA procedure [19]. Similar results were obtained by Bravery et al., where 74% of applications (n=19 ATMP submissions) raised major objections to the clinical data package. This category covers issues such as lack of randomisation, issues with

the design, conduct of the clinical study, and/or choice of control group. It was found that failed products have more issues in this category (83% of applications; n=6). The authors found that evidence submitted with the ATMP dossiers are in need of improvement [17]. This point is also highlighted by the fact that those applications that have been granted with an accelerate assessment revert to standard timelines during the MA procedure due to the immaturity of the data and the major issues raised (n=6 out 7 EU approved ATMP granted with AA; as of September 31st, 2021) [1]. Carvalho et al., analysed and compared the major objections reported in the MAA assessment for approved ATMPs (n=3) and non-approved ATMPs (n=4) [20]. The most frequent objections for gene therapy medicinal products in terms of clinical efficacy were the lack or insufficient efficacy demonstration, the change or use of novel and non-validated primary endpoints, and efficacy claims based on non-prespecified post-hoc analysis. Regarding safety, the most common objections were the limited safety database and the risks associated with immunogenicity. Most deficiencies were addressed through the submission of additional data either during the MAA review or post marketing setting [20].

Efforts to overcome the clinical challenges faced by advanced therapies medicinal products

All these reported data support the fact that there is room for improvement in terms of clinical evidence generated to support the drug approval (Figure 1). A more efficient, consistent and robust clinical development not only may give more chances to achieve MA and led to less objections by the agencies allowing for a quicker product launch, but it also may prevent from post-marketing withdrawal anticipating the negative benefit/risk balance. It is recognised that clinical development for diseases that have a high unmet need and/or are orphan can be complex and can leverage the opportunities that regulatory bodies offer to speed up access and get an accelerated approval. However, given all the implications that expedited clinical developments might have - not only to the patients and payers but to the pharmaceutical companies - whenever feasible, the gold standard pivotal randomised clinical trials, clinically relevant endpoints and longer follow-up should be performed.

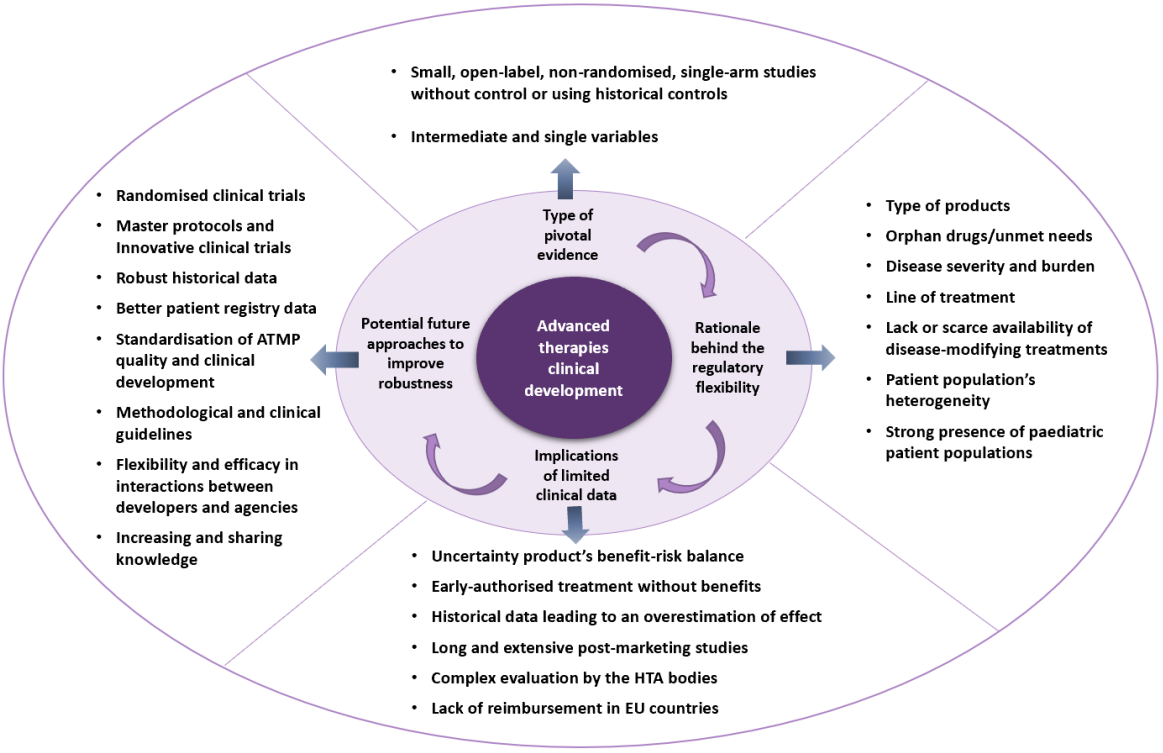

Figure 1. Current landscape of ATMPs clinical development

When randomised control designs are not feasible, alternative design options should be considered aimed to provide robust evidence. Many efforts have been carried out to launch methodological recommendations to address the shortcomings of conducting studies in small populations. The Small Population Clinical Trials Task Force within The International Rare Diseases Research Consortium (IRDiRC) investigated the use of non-conventional statistical methods on small population trials with the input of regulatory agencies [21]. Three relevant European Commission funded projects (i.e., ASTERIX, IDeAl and InSPiRe) are promoting the development of new or improved statistical methodology for clinical trials for small population groups, as well as defining adequate randomization procedures, investigating adaptive designs, extrapolating dose-response information, among others [22][23][24].

On the other hand, several innovative trial designs under the concept of master protocol are starting to change the landscape of clinical research [25][26][27]. This approach uses a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple sub-studies, allowing for efficient and accelerated drug development. A master protocol provides an opportunity to increase data quality through shared standardised trial procedures and the use of centralized data capture systems [28]. Within this concept there are different innovative typologies, i.e., basket, umbrella and platform designs,

which have been raised as a potential solution to improve clinical evidence robustness. Platform trials allows multiple interventions being evaluated simultaneously against a common control group within a single master protocol. The treatments are tested for similar indications and with test products entering and leaving the study based on results. The control arm usually consisting of the SoC may change over time if newer drugs replace the SoC [29]. Comparisons between each of the intervention arms and the control arm can be done to determine which is the best intervention option for a given disease. Yescarta® and Kymriah® are CAR T-cell therapies approved for patients with DLBCL based on ZUMA-1 and JULIET trials, respectively [30][31]. In the absence of head-to-head trials, an indirect treatment comparison between both products was carried out. It was concluded that this comparative analysis is not feasible due to the substantial differences between the trials, e.g., timing of leukapheresis and enrolment, use of bridging chemotherapy (90% in JULIET vs. 0% in ZUMA-1), different lymphodepleting regimens, different outcome definitions, etc. [32]. In addition, as previously mentioned, the comparison of Kymriah® against SoC failed to meet the primary efficacy endpoint [33]. To explore the option of a platform trial for these therapies would have allowed the comparisons between each of the intervention arms and the SoC, as well as efficiently sharing the same control group given that is an orphan disease. The same point can be raised in the case of spinal muscular atrophy (SMA), a rare disease. The SoC for SMA has improved over the last decade due to changes in care, as well as new promising drugs are becoming available such as Zolgensma®, Spinraza® or Evrysdi®. The IQWiG, Germany's health technology appraisal institute, has carried out separate benefit assessments comparing these three new drugs, finding that Zolgensma® offers no additional benefit compared with Spinraza® for treating SMA. IQWiG pointed that the differences between populations across different studies made indirect comparisons challenging and makes it difficult to understand which of the three products might be suitable in different situations [34]. This type of innovative trials would allow a stratification into multiple subgroups depending on the SMA type and SMN2 gene copy number, with eligibility for each intervention arm defined by the intervention's mechanism of action. In addition, another advantage of conducting platform trials is the investigation of treatment combinations. For instance, during clinical development of Zolgensma®, Spinraza® treatment was started on parental request to determine if there was additional benefit from this combination therapy [35]. Finally, it should be noted that master protocols for CAR-T therapies have already been initiated in the field of ATMP, e.g., Phase 1 proof-of-concept study in relapsed and refractory multiple myeloma and a Phase 2 for patients with metastatic or unresectable synovial sarcoma or myxoid/round cell liposarcoma [36][37]. Although platform

trials are usually focused to oncology, they also have been conducted in other disease settings such as Alzheimer's disease [38].

Even though still limited, with the current experience of the approved ATMPs, the regulatory agencies are launching recommendations on the types of study designs and methodologies that can support the MA more robustly. This fact might lead to the shift on the current trend clinical designs based on uncontrolled pivotal studies or with historical control comparisons to randomised-controlled trials. After the approval of the CAR-T-cell products, the EMA has published guidance on clinical development for CAR-T-cell products [39]. The recommendations include the performance of confirmatory trials with a randomized controlled design allowing the comparison with a reference product, e.g. high dose chemotherapy followed by autologous stem cell transplantation. In the guideline, it is recognised that refractory settings are clinically very different from early settings, which in some cases may justify different requirements in terms of level of evidence for MAA. However, it is emphasised that even for those cases where late-stage refractory disease is targeted or where reference therapies are not available, a randomized controlled trial design should be followed, and an uncontrolled single arm one would be exceptionally accepted [40]. In parallel, the FDA has also launched several guidelines for the development of ATMPs aimed at certain types of conditions. For instance, to support the standard approval of a gene therapy for haemophilia, the FDA recommends a non-inferiority clinical trial design, to compare the primary efficacy endpoint to that of current prophylaxis therapies, using within-subject comparison trial [41]. In the case of gene therapies aimed to retinal disorders, inclusion of a randomized, concurrent parallel control group (placebo or active) is recommended whenever possible. Given that for these study designs, the intravitreal injection of the vehicle alone could be feasible but not ethical, other possibilities suggested including alternative dosing regimens or dose levels [42]. The new guidance on gene therapy for neurodegenerative diseases comprises different study design alternatives depending on the indication, study population, or where the disease course is well-characterized. For studies involving placebo, FDA recommends add-on designs or randomized, concurrent-controlled, double-blind crossover trials when possible [43]. On the other hand, it is recognized that the typical paradigm of clinical development, i.e., Phase I, II, and III, is shifting for advanced therapies and adaptive designs are becoming common. Regulatory agencies are also in consequence releasing new recommendations on innovative designs as well as advice programs to ensure that these adaptive approaches are as solid as possible [44][45][46]. Finally,

analytical tools, such as matching-adjusted indirect comparisons and network meta-analyses, have also been introduced for regulatory submissions and HTAs allowing comparisons [47].

Use of historical controls

When a randomized clinical trial is not possible, the historical controls can be used to supplement a control arm. Different sources of external control can be used: retrospective data, prospective natural history, external data from completed trials, data from pragmatic trials, observational studies or registries [48]. The use of historical controls to compare the treatment effect have been highly used so far for the EU approved ATMPs (8 out of 19 approved therapies, as of September 31st, 2021), above all in the case of gene therapies (7 out of 12 approved products) (Table 1).

Strimvelis®, Kymriah®, Luxturna®, Zolgensma®, Libmeldy® and Skysona® target orphan diseases for paediatric population and all of them contextualised the results of the pivotal study with different types of historical controls. For Strimvelis® and Libmeldy®, the hypothesis of the study was based on demonstrating superiority over a historical control group, which was considered acceptable given the rarity of the disease. For Strimvelis®, while the primary endpoint based on survival was compared to this historical reference, other efficacy endpoints were considered as within-subject, between pre- and post-treatment assessments. The historical control used was based on the outcomes obtained in a multicentre retrospective study (between August 1981 and March 2009) including 106 patients with adenosine deaminase-deficient severe combined immunodeficiency from 16 international centres [49]. The main study for Libmeldy® was conducted in a single centre, as well as the concurrent natural history cohort. Both natural history cohort (n=31) or untreated sibling data (n=11), were used as controls to compare the treatment effect for the co-primary endpoint. It was considered by the assessors that a comparison with matched sibling appears to have the least variability and the comparison between pre-symptomatic subjects versus their affected siblings is considered the most informative [50]. In the case of Kymriah® for relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL), the single-arm design was planned to test for an improvement in overall remission rate relative to historical control rates from two previous studies performed for the same indication with other products (clofarabine and blinatumomab approved in 2007 and 2015 by the EMA, respectively) [51]. Luxturna®´s trial randomised patients to a control or to intervention arm, given that for most inherited retinal dystrophies, natural history data was limited. The control group became eligible to receive the product one year after their baseline

evaluations. Nevertheless, a natural history study that consisted of a retrospective medical chart review (from July 2014 to February 2016) was also submitted as a supportive by the applicant to further support the MAA (n=70) [52]. For Zolgensma®, two natural history studies were used for comparison; one retrospective and prospective study using data from The Paediatric Neuromuscular Clinical Research (PNCR) database (inclusion of the patients ranged from May 2005 to April 2009), and another prospective, multi-centre natural history study (from November 2012 to September 2014) that enrolled 26 SMA infants [35][53]. Similarly, in the case of Skysona®, both data from a retrospective natural history study (data collected between 2011 and 2012; n=137) and a retrospective and prospective data collection study (from 2015 to December 2019; n= 59) were used [54].

Yescarta®, Zalmoxis®, Kymriah® and Abecma® target adult orphan indications and also used historical controls to compare product´s efficacy. For Yescarta®, a retrospective, patient-level, pooled analysis from two randomized phase 3 clinical and retrospective databases was conducted to support the results from the pivotal study (SCHOLAR-1) [55], and for Kymriah®, the pivotal efficacy results were compared with three historical data sets (SCHOLAR-1, the pooled CORAL extensions and the open-label, randomised PIX301 trial). For Zalmoxis®, at the time of approval, there were neither approved therapy nor widely accepted standard of care. Therefore, the treatment effect could only be compared versus historical control data from either a large retrospective survey (between January 1995 and December 2004) or single-centre experiences [14][56]. For additional comparisons with historical control data from patients, the European Blood and Marrow Transplant (EBMT) society patient database was used to better define the product´s clinical benefit [14]. For Abecma®, the results were compared with a matched real-world historical control that consisted of a non-interventional, retrospective study (n=190) as well as reported literature [57].

The relevance of historical data is sometimes questioned and could led to an overestimation of effect. The limitations of historical controls are well known; comparability of the population, potential changes in standard of care, lack of standardized diagnostic criteria or equivalent outcome measures, and variability in follow-up procedures [58][59][60]. The standardisation and quality of the data collection, the selection of an applicable approach to account for biases, to plan for extensive sensitivity analyses to demonstrate the robustness of the results, or the use quantifiable and objective outcomes are some of the measures that would improve the quality of the historical controls [61]. Abecma® case is an example of the historical control limitations. The real-world evidence study was found to be inconclusive by the FDA to provide context or

comparison for the outcome of the pivotal study. The missing data, differences in follow-up and response assessment, population heterogeneity, and bias in endpoint assessment, hampered the comparison [62][63]. When similarity can be proven between arms, the use of a historical control replacing the concurrent control arm can be the alternative source of data in a context of life-threatening disease with no treatment available. In other scenarios, a clear justification for a non-randomised trial is needed and an early dialogue with regulatory agencies at the design stage is highly encouraged to avoid potential problems during the clinical development plan and final authorization. According to recent FDA recommendations, the use of historical controls is discouraged but it might be considered appropriate only under very exceptional circumstances where: the product targets a rare and serious neurodegenerative disease for which there is an unmet medical need, the disease course is well-documented, highly predictable and can be objectively measured and verified, the study population and the historical controls are suitably comparable, and the expected treatment effect is large and self-evident [43].

It is known that registries provide an important source of information on diseases, patients, standards of care or outcomes of treatments, in particular for rare diseases or patients treated with ATMPs. In this sense, there have been some proposals to overcome the current challenges in using registries data such as interoperability and patient privacy improvement, data and terminology standardisation, better reporting clinical trial outcomes, and other measures to maximize registry use in drug and therapeutic development to support evidence-based clinical decision-making [64]. EMA's initiative for patient registries, launched in September 2015, is focused on supporting a systematic and standardized approach to their use for regulatory purposes [65]. The need of individual patient data is a key factor to conduct better historical comparison. For instance, for Kymriah® in refractory ALL indication, external control was used for comparison to data pooled from the three main Kymriah® trials, despite confounding patient populations and matching on few variables [31][66]. For Kymriah® and Yescarta® in DLBCL indication, the treatment effect was compared with SCHOLAR-1 sponsored by Kite Pharma (MA holder of Yescarta®) [55]. The acceptance of comparison between Yescarta® pivotal results and SCHOLAR-1 study was attributed to the availability of individual patient data, enabling the company to match patients in both trials [66][67]. However, for Kymriah® given that only published data of SCHOLAR-1 was available for comparisons, the data from the pooled CORAL extensions study was accepted by the agency as a more suitable comparator than SCHOLAR-1 due to similarities in the populations enrolled and the objective response rate results obtained [31][66][55].

Use of surrogate endpoints

Another important factor observed in the pivotal studies of the approved ATMPs is the use of surrogate variables instead of a clinically relevant final endpoint. Results from surrogate end points are common in accelerated approvals and allow for clinical trials with shorter follow-up periods and smaller sample sizes [68][69]. It has been reported that the pivotal trial evidence supporting MA for products granted conditional marketing authorization or accelerated assessment was based dominantly on non-validated surrogate endpoints [70]. This point can be translated into lower likelihood identifying safety issues (especially if they are rare) and long-term observations of safety adverse events. It has been reviewed that surrogate endpoints might lead to erroneous, or even harmful conclusions, since they might fail to fully capture the complete risk-benefit profile [71]. On the other hand, this type of endpoints is ethically preferable especially when clinical events are rare/delayed in slowly progressive diseases or when there is a high unmet need, as well as practically preferable since the short-term assessment helps to avoid non-compliance and missing data, increasing effectiveness and reliability of the study [71][72][73]. The acceptability of the surrogate endpoints needs to be based on their biological plausibility and empirical evidence, and should be validated with evidence that goes beyond showing a statistical association between the surrogate and clinical endpoints [71][72][74].

In the case of all approved gene therapies that target cancer diseases, the proportion of patients with ORR was used as the intermediate primary variable. In these cases, ORR was an acceptable endpoint given that the studies that support the MA consist of Phase II exploratory trials and given that an accelerated approval was granted. According to the most recent version of the EMA guideline on anticancer drugs, for confirmatory trials the overall survival, progression/event/disease-free survival would be considered as adequate primary endpoints. However, selected patient-reported outcomes (PROs), such as symptom control, could also constitute clinically relevant and valid primary endpoints, provided high data quality is ensured [75]. In addition, and if available, the use of validated biomarkers should be considered to allow a clinical trial to identify and differentiate between drug responders and non-responders.

Although surrogate variables are not always ideal, it is not trivial to select either a final and/or surrogate primary efficacy endpoint for an ATMP, which can accurately predict or correlate with clinical benefit in the studied indication. For instance, in the case of Luxturna®, the applicant had to develop a novel clinical meaningful endpoint to assess the drug effect through

a mobility test [52]. For Zolgensma®, although the survival endpoint was used as a final co-primary outcome, survival with no motor milestone achievement would have not probably been considered as clinically meaningful outcome in the treatment of SMA. Moreover, performance and socialisation at school age around 5-6 years was suggested by the experts as long-term data to be captured relating to efficacy [35][76]. For those patients with lipoprotein lipase (LPL) deficiency, the most severe associated complication is pancreatitis. The hypothesis that Glybera® could improve chylomicron particle metabolism and then reduce the pancreatitis in these patients could not be substantiated by clinical data at the time of MA [77].

With increasing pressure for an early access to therapies, the use of surrogates is likely to increase. The key guidelines of the European network for Health Technology Assessment (EUnetHTA), which have been adopted by many European HTA agencies, state a preference for using final patient-relevant outcomes, but it also is recognised the need of surrogate endpoints [46, 79]. It is therefore recommended the use of surrogate variables only to those that have been validated appropriately, in order to avoid uncertainty on coverage decisions on health technologies, as well as to ensure less objections during the MAA assessment [79]. It has been analysed that only few HTAs have provided specific methodological guidance on the statistical methods that should be used for the validation and assessment of acceptability of surrogate endpoints, and there is still lack of methodological consensus around the level of evidence necessary for the validation of these endpoints. In consequence, efforts on better harmonisation are currently being conducted to minimise different access for patients across different jurisdictions [78], [80]. On the other hand, to guide the developers, the FDA has recently published a list of accepted surrogate endpoints that were the basis of approval of a medicinal or biological products under both the accelerated and standard pathways [81]. Finally, the validation of a surrogate endpoint is not a straightforward process, given that the association between surrogate and final outcome usually is demonstrated by randomized controlled trials, or epidemiological/observational studies. Therefore, as discussed by Ciani et al., extension of follow up studies, as well as the natural history studies combined with analyses on baseline data, emerging large data networks, or previous conducted trials on the disease might help to identify adequate surrogate variables [79].

Limitations of nonclinical development

Properly designed nonclinical studies can reduce the clinical uncertainty and support a positive risk/benefit ratio. However, the traditional and standardized approaches for nonclinical toxicity

testing are often not appropriate for evaluating the safety of gene and cell therapy products and several challenges are also associated with the nonclinical development of ATMPs [82][83], [84]. General nonclinical studies and toxicity studies may be unable to detect the effects relevant for human efficacy and safety. Some examples include Glybera®, the proof of concept demonstrated reduction in plasma triglycerides related to LPL activity of treated animals, and this was used as the primary pharmacodynamic measure to show activity. However, the applicant failed to adequately demonstrate pharmacokinetic and pharmacodynamic properties of the product in the clinical setting, since LPL plasma activity could not be consistently demonstrated, and no sustained triglycerides decrease could be observed [77]. Associated CAR-T cell toxicities, such as cytokine release syndrome, neurological toxicity, on target/off tumour events were not fully anticipated by nonclinical studies either [84][85]. For Zolgensma®, different cardiovascular safety profile observed in the preclinical and clinical stage was attributed to a difference in transduceability at individual cardiomyocyte level between mice and human [35]. Finally, AAV related toxicities are currently being discussed by the Agencies [86]. Dorsal root ganglion pathology has been observed in nonhuman primates but it is still unclear if it is translated to the clinical setting in human beings [35][87]. Similarly, although AAV integration associated with hepatocellular carcinoma (HCC) was observed in neonatal mice, there has been minimal evidence of HCC occurring in patients receiving gene therapies [87].

An iterative approach was suggested to be informative, for example, when early clinical experience identifies unexpected adverse reactions then additional preclinical studies may provide a mechanistic basis for mitigation measures [84][88]. On the other hand, the need for standards to enable cross-comparisons of, and confidence in, testing results, or ensure techniques that are consistently implemented for the nonclinical studies so that data can be compared, would allow to increase and share knowledge in the field, e.g. biodistribution studies [89]. Finally, a risk-based approach during product development to design a tailor-made ATMP development program is usually recommended to determine the extent of quality, nonclinical and clinical data necessary for a MA and to justify any deviation from the requirements, i.e., as defined in Annex I, part IV of Directive 2001/83/EC [90][91].

Interplay between clinical evidence and product quality

Not only the limited clinical evidence at MAA stage impact the approval decision, but the quality development and lack of quality standards for these products is a key challenge [92].

Several factors limit the achievement of consistent data and adequate interpretation of clinical results across studies: the uniqueness of each product, the heterogeneity of this novel group of products, the variability in the pipeline of clinical development and approaches chosen, the divergent manufacturing strategies, and the different tests/assays applied during clinical development and its validation [73][93].

The quality of manufacturing can affect the clinical outcome, and issues within the quality module of MAA dossier might be directly related with the acceptability of the clinical package. Issues are mostly related to validation of the analytical methods, design and control of the manufacturing process, and comparability [16]. The comparability of manufacturing processes remains one of the major issues and was raised during assessment of the majority of the approved products [94]. When a process change is required, for instance to increase production volume for a phase III trial or commercialization, questions of comparability between processes during the MAA review and how this can affect the clinical safety and efficacy outcomes are common. This point can imply the requirement of generating additional clinical data or impair the validity of previously generated one, as it was the case for Kymriah® or Zolgensma® [35] [94]. Not only the comparability between manufacturing processes, but batch to batch inconsistency, which might contribute to the heterogeneity of clinical response, has been observed for some approved therapies [35]. The inadequate comparability assessments, coupled with the difficulty of potency assays, can also impact key clinical aspects such as the consistency of doses administered during the clinical development [35][95]. For cell therapies, the mechanisms to study cell activity are complex and poorly understood and the cell counts may vary over time, which makes it difficult to establish standard, effective doses and routes of administration in clinical trials. This might lead to inconsistent trial results that are hard to interpret and replicate across studies [89]. For some approved gene therapies, uncertainties with regards to control of the effective dose, without stable reference standard to control the potency of the product have been also observed [35].

Standardization of manufacturing may be difficult given proprietary platforms, but some common processes such as common operational steps, product characterization, design and validation of processes and testing could be achieved to improve some of these issues [96]. Previous experience available in humans with similar products and with similar standards that allows performing comparison with valid pooling data would help to improve the current translations challenges in the ATMP field, e.g., AAV-based gene therapies, CAR-T therapies, autologous cultured chondrocytes, mesenchymal adult stem cells. For instance, it has been

stated that longitudinal investigations of anti-CAR immune responses through the same validated assays would be particularly important in understanding how immunogenicity can lead to treatment failure. For the three approved CAR-T therapies, there were huge differences in the reported percentages of patients with pre-existing antibodies and it was suggested that this fact could reflect the different assays used for detection [97]. Similarly, pre-existing immunity and immunogenicity towards the vector or transgene are the largest challenge for AAV-based gene therapies given that can interfere with therapeutic efficacy if not identified and managed optimally [98]. Common ways to test tissue engineering product integrity, including tensile strength and suture retention, to ensure that these products meet safety thresholds for use in clinical environments has also been raised [89].

The quality requirements are not reduced due to accelerated access routes, and it is under debate that greater standardization and harmonization across regulatory authorities could reduce the burden on companies to ensure compliance at every phase of the development and commercialization process [99][100]. Several organizations are working to assemble and define standards and the convergence of common requirements [99][101][102][103]. Although it should be recognised how challenging standardization is given the diversity in the cell and gene therapy space and it is rapid progress, the standard needs have already been identified [89][96]. Examples from a quality standpoint include: i) management systems for processing and handling cells, establish cell collection requirements that ensure consistency, safety, and comparability in final products, ii) to identifying potential commonalities across manufacturing processes and create broadly applicable guidelines, or iii) establish guidelines to harmonize manufacturers' characterization, design, and validation processes to lower barriers. From nonclinical and clinical standpoint, it has been proposed: i) to establish consensus on which biodistribution approaches are most applicable, ii) implementing a standard approach to pre-existing immunity assay development, selection, and evaluation to enhance patient safety and quality of clinical trial data, or iii) cell counting methods/technologies, optimal timing for dose assessment, qualifying routes of administration and dose preparation methods to select safe and effective doses, among others [89].

Impact at post-marketing setting and market access

Pre-registration randomized clinical trials are not always representative of patient populations in the routine practice due to the strict patient inclusion and exclusion criteria, and the strict intervention protocols [33][104][105][106][107]. Therefore, the evidence generation

throughout the medicine's life cycle is essential to gain more information about its effectiveness and safety in a more diverse clinical setting, to improve healthcare quality and to provide information to either complement initial evidence or to verify whether the MA should be maintained as granted, varied, suspended or revoked. In the case of ATMPs, real world evidence plays even a major role and is essential to confirm the benefit-risk profile given the imprecise clinical data available at the time of MA. This point might be translated into the need to perform long and extensive post-marketing studies [108][109].

It has been reviewed that the post-authorization studies for the approved ATMPs consist both in interventional studies (some of them ongoing at the time of MA) and observational studies. The profile of the planned interventional trials to further assess effectiveness resemble pre-market trials in terms of design, i.e., using single-arm designs, reduced sample sizes and focused on a narrow study population [9]. In some cases post-launch evidence generation can be particularly challenging especially when it requires long-term follow-up, since participants may be lost during the trial due to different causes (i.e., cure of the disease, depression, among others) or may be reluctant to participate when the pharmaceutical is already launched. The latter is more evident when the study is randomized [110]. On the other hand, the burden that the clinical post-marketing requirements imply, along with the extensive manufacturing commitments, could hamper market access. This was the case of Glybera®, where the extremely limited use of the product and the costs of post-marketing requirements including maintaining the commercial manufacturing capabilities, led to its withdrawal after two years on the European market [111][112].

The insufficient evidence available on comparative clinical effectiveness or clinical benefits hinder the determination of appropriate pricing and payment schemes. The decision on price and reimbursement requires an exhaustive study of the evidence generated during the product development, the relative effectiveness and safety, the patient reported outcomes (including quality of life), cost-effectiveness and budget impact to finally assess its place in therapy. At this stage, HTAb have an important role. The scientific evidence of the product and its potential contribution in the therapeutic management of the disease is deeply studied in EU countries but the recommendations from the HTAb may differ among them, above all for orphan drugs [113]. HTAb-specific requirements can be related to the acceptability of the endpoints used, the control arm, the inclusion and exclusion criteria and, at the end, the generalization of the results obtained in their clinical practice [74]. When the product clinical data is limited, to determine all the aforementioned is complex and usually it translates to long negotiations between the

marketing authorization holder and the health authorities. This negotiation may be one of the reasons for the time elapse between MA and final drug prescription and this represents a major concern for healthcare systems, patients and industry. The difficulty of accessing the market once the product is authorised highlights the differences in the answers that a regulatory agency and a healthcare system are seeking in clinical trials [114].

Finally, there is industry pressure for corporate pharma and its investors to ensure the return of drug development investment. With a high expected value but with the immature evidence and highly prices requested, the complexity of negotiations between the industry and payers is becoming common, and sometimes the non-reimbursement has been justified. Managed entry agreements (MEAs) have been a solution to this challenge. Commercial arrangements have been frequently used in European countries either financial (discounts and rebates) or outcome-based to finally release a product into the market. Provenge®, MACI® and ChondroCelect® were withdrawn because of poor commercial performance and lack of reimbursement in EU countries [1][115][93]. The limited use of the product, the costs of post-marketing requirements including clinical trials and maintaining commercial manufacturing capabilities are other factors that contributed to ATMP withdrawal [111][115].

To avoid costly corrections in late clinical development and a weak market access value dossier (document that provides evidence-based messages in communicating product value), a comprehensive risk assessment must be carried out before committing to a particular pivotal trial design. The development strategy for an ATMP should also include parallel EMA-HTAb advice regarding evidence generation optimization in the EU, to discuss different design options during clinical development, their applicability with respect to efficiency and risk of bias and the potential post-launched evidence generation. Same approach is recommended through FDA interactions in the case of United States, such as special protocols assessments [1]. These discussions along with the potential implementation of the advice, could reduce the risk of benefit/risk uncertainty and production of data that would be inadequate to support the company's future reimbursement request [116][117]. In addition, Company´s retrospective analysis from the drug pipeline development and failures during different phases of clinical trials have led them to improve its research and development workflow in terms of learning, strategy, costs and performance [118][119]. For instance, Alofisel® (sponsored by TiGenix) set a model of iterative strategy that enabled MA through improving late clinical development with the lessons learnt from the previous autologous cell therapy, sponsored by Cellerix [120].

Conclusion

ATMPs are innovative therapies that mainly target orphan diseases and high unmet medical needs. The level of generated clinical evidence and the quality aspects of advanced therapies are playing a key role in the development, approval and post-marketing setting for these therapies. This article aimed on describing the current landscape of clinical development of advanced therapies, its challenges and some of the potential solutions that are currently under discussion. Most authorised ATMPs are based on adaptive, small, open-label, uncontrolled and single-arm pivotal trials. Flexibility on conventional regulatory requirements has been widely implemented by regulators, especially for low prevalence, life-threatening or seriously debilitating diseases. Progressive iteration of the science, establishing new standards for ATMPs development with the aim to ensure consistency in clinical development and the reproducibility of knowledge is required not only to increase the evidence generation for approval but to set principles to achieve translational success in this field. Although there is a trend toward an adaptive approach to licensing or a life cycle approach, after the experience with the ATMPs approvals so far, regulators' and global working groups are developing and releasing new recommendations to promote an approach of clinical development that is methodologically sound and thus significantly more relevant. It remains to be seen how ATMP clinical development will evolve, but it is recommended that the industry stakeholders should strive to understand and try to apply the recommendations of relevant parties to better succeed in market access.

Tables

Table 1. Approved ATMPs in the European Union and therapeutic indication

Trade Name	International non-proprietary name (INN) or common name	Pharmacotherapeutic group/ ATC code	Therapeutic Area (MeSH) / Type of authorisation
Gene therapy* medicinal *products			
Kymriah® (Orphan medicine)	Tisagenlecleucel	Antineoplastic agents/ L01XX71	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma Lymphoma, Large-B-cell, Diffuse / Standard approval
Yescarta® (Orphan medicine)	Axicabtagene ciloleucel	Antineoplastic agents/ L01XX70	Lymphoma, Large-B-cell, Diffuse/ Standard approval
Tecartus® (Orphan medicine)	Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured	Antineoplastic agents/ L01X	Lymphoma, Mantle-Cell / Conditional approval
Imlygic®	Talimogene laherparepvec	Antineoplastic agents/ L01XX51	Melanoma / Standard approval
Glybera® (Orphan medicine)	Alipogene tiparvovec	Lipid modifying agents/ C10AX10	Hyperlipo-proteinemia type I / Approval under exceptional circumstances
Strimvelis® (Orphan medicine)	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Immunostimulants/ L03	Severe combined immunodeficiency/ Standard approval
Luxturna® (Orphan medicine)	Voretigene neparvovec	Ophthalmologicals, other ophthalmologicals/ S01XA27	Leber congenital amaurosis Retinitis Pigmentosa / Standard approval
Zynteglo® (Orphan medicine)	Betibeglogene autotemcel	Other haematological agents/ B06AX02	Beta-Thalassemia /Conditional approval

Trade Name	International non-proprietary name (INN) or common name	Pharmacotherapeutic group/ ATC code	Therapeutic Area (MeSH) / Type of authorisation
Zolgensma® (Orphan medicine)	Onasemnogene abeparvovec	Other drugs for disorders of the musculoskeletal system/ M09AX09	Muscular Atrophy Spinal/ Conditional approval
Libmeldy® (Orphan medicine)	Atidarsagene autotemcel	Other nervous system drugs/ N07	Leukodystrophy, Metachromatic / Standard approval
Abecma® (Orphan medicine)	Idecabtagene vicleucel	Antineoplastic agents/ L01	Multiple Myeloma / Conditional approval
Skysona® (Orphan medicine)	Elivaldogene autotemcel	Other nervous system drugs/ N07	Adrenoleukodystrophy / Standard approval
Somatic-cell therapy medicinal products			
Provenge®	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (Sipuleucel-T)	Other immunostimulants/ L03AX17	Prostatic Neoplasms / Standard approval -withdrawn
Zalmoxis® (Orphan medicine)	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	Antineoplastic agents/ L01	Hematopoietic Stem Cell Transplantation Graft vs Host Disease / Conditional approval - withdrawn
Alofisel® (Orphan medicine)	Darvadstrocel	Immunosuppressants/ L04	Rectal Fistula / Standard approval
Tissue-engineered medicinal products			
Chondrocelect®	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins/	Other drugs for disorders of the musculoskeletal system/ M09AX02	Cartilage Diseases / Standard approval - withdrawn
MACI®	Matrix-applied characterised autologous cultured chondrocytes	Other drugs for disorders of the musculoskeletal system/ M09AX02	Fractures, Cartilage/ Standard approval - withdrawn

Trade Name	International non-proprietary name (INN) or common name	Pharmacotherapeutic group/ ATC code	Therapeutic Area (MeSH) / Type of authorisation
Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Other drugs for disorders of the musculoskeletal system/ M09AX02	Cartilage Diseases / Standard approval
Holoclar® (Orphan medicine)	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Ophthalmologicals/ S01XA19	Stem Cell Corneal Diseases / Conditional approval

Table 2. Design features of pivotal clinical trials for the approved advanced therapy medicinal products in the European Union

Trade Name	Pivotal study	Non-Randomised	Non-controlled	Historical control	Intermediate endpoints	Population / Number of patients (enrolled)
Gene therapy* medicinal *products						
Kymriah® (ALL)	Phase II	✓	✓	✓	✓	Children / 92
Kymriah® (DLBCL)	Phase II	✓	✓	✓	✓	Adult / 147
Yescarta®/	Phase I/II	✓	✓	✓	✓	Adult / 111
Tecartus®	Phase II	✓	✓			Adult / 105
Imlygic®	Phase III				✓	Adult/ 437
Glybera®	3 Phase II/III	✓	✓		✓	Adult / 45
Strimvelis®	Phase I/II	✓	✓	✓		Children/ 12
Luxturna®	Phase III				✓	Children and adult/ 31
Zynteglo®	Phase I/II and Phase III	✓	✓		✓	Children and adult /41
Zolgensma®	Phase III	✓	✓	✓		Children/ 22
Libmeldy®	Phase I/II	✓	✓		✓	Children / 22
Skysona®	Phase II/III	✓		✓		Children/ 32*
Abecma®	Phase II	✓	✓	✓	✓	Adult /140
Somatic-cell therapy medicinal products						
Provenge®	Phase III					Adults /512
Zalmoxis®	Phase I/II and Phase III	✓ (Phase I/II)		✓ (Phase I/II)	✓	Adult /71
Alofisel®	Phase III					Adult / 212
Tissue-engineered medicinal products						
Chondrocelect®	Phase III				✓	Adult /138
MACI®	Phase III				✓	Adult / 144
Spherox®	Phase II and Phase III		✓ (Phase II)		✓	Adult / 177
Holoclar®	Observational retrospective	✓	✓			Adult / 104*

ALL: Refractory B-cell acute lymphoblastic leukaemia; DLBCL: Diffuse large B-cell lymphoma; *Number of patients in the intervention arm.

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3.3: Regulatory and clinical development to support the approval of advanced therapy medicinal products in Japan

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Abstract

Introduction: A new category of products, i.e., regenerative medicine products (RPs), has been defined for advanced therapies medicinal products in Japan, as well as a legislative and regulatory framework to promote their clinical development.

Areas covered: This review analyses the most relevant features of the regulatory strategies and clinical development that led RPs to their approval in Japan.

Expert Opinion: As of September 31st 2021, a total of 14 RPs were approved for 16 indications. From regulatory standpoint, the available designations allow attractive benefit packages that promote the development of innovative products in Japan and is one of the key points to consider when the global regulatory strategy for the product is being developed. RPs regulations in Japan allow adaptive licensing and constitute shortcut through the clinical development to the approval. RPs have been mainly approved so far based on small studies with inconclusive and limited evidence of efficacy and safety, prioritising the unmet medical needs of the target diseases, and therefore, the early access for patients. This review also compares the regulatory and clinical development for the current approved RPs in Japan with the development trends in the EU and the US.

Introduction

ATMPs are a group of innovative and complex biological products for human use that comprise gene, cell- and tissue-engineered therapies. The discovery of induced pluripotent stem cells in 2006 and the approval of the two first autologous cell products in Japan, JACE® and JACC®, set a precedent and constituted a major breakthrough in stem cell and ATMP research [1]. With the introduction of this type of therapies, the regulations for the human use of ATMPs were established in several regions and are evolving in accordance with the acquired scientific knowledge and clinical experience. In Japan, a new product category was defined for advanced therapies, i.e., regenerative medicine products (RPs), and new laws were implemented in 2014 to provide a legislative framework for these treatments, promote their timely development and bring these innovative products to patients [2].

The key regulatory procedures and considerations for the development of RPs in Japan are the following:

1) Legal framework and regulatory classification – Since 2014, advanced therapies are regulated as RPs under the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act) when a MA is sought. The Act on the Safety of Regenerative Medicine (RM Act), which falls outside of the scope of this paper, covers clinical research with these products, performed in medical institutions for academic purposes. The Japanese Pharmaceuticals and Devices Agency (PMDA) conducts the scientific reviews of the applications for regenerative medicines, and the Ministry of Health, Labor and Welfare (MHLW) approves the MA or withdraws products in case of safety concerns. Within the PMDA, the Office of Cellular and Tissue-based Products (OCTP) is responsible for regulating regenerative therapies [2].

RPs include two main categories of products: gene products (in vivo and ex vivo), and cellular medicinal products [3]. Gene therapies must be intended for the treatment of disease in humans (or animals) and carry or deliver transgenes to be expressed in human (or animal) cells. This category includes products derived from plasmid vectors, products derived from viral vectors and gene expression treatment products. Vaccines or siRNAs, antisense RNAs oligonucleotides, aptamers, and nucleic acid derivatives that are chemically synthetised will be excluded of this category, although the use of non-viral vectors designed to express the siRNAs or antisense RNAs might be considered a gene therapy [4][5]. On the other hand, the cell therapies are intended for either: the reconstruction, repair, or formation of the structure or function of the human or animal body (i.e., tissue-engineered products),

or the treatment or prevention of human or animal diseases (i.e., cellular therapy products). To be classified as a cellular medicinal product, the cells must be processed and/or intended for non-homologous use. Cell/tissue processing is defined as the propagation of a cell or tissue, any pharmaceutical or chemical treatment to activate the cells or tissue that alters the biological features, the combination with a noncellular component and/or manipulation by genetic engineering. A list of manipulations that are not considered processing is also provided in the PMD Act, e.g., disintegration of tissue or treatment with antibiotics. In addition, the term ¨processing¨ includes cells for non-homologous use. Therefore, the cells or tissues (whether processed or not) that are not used to maintain the original function(s) in the same anatomical or histological environment, are considered regenerative products [5]. Whether the products are processed or not is judged on a case-by-case basis, and consultation with the MHLW/PMDA is recommended in case of uncertainty. Finally, it should be noted that there is a clear differentiation between cell-based products considered as RPs, and cell-based therapies covered by other legal frameworks such as the blood system or transplant laws, e.g. hematopoietic stem cell transplantation [2][4][6].

2) Scientific advice – Apart from a wide range of consultation procedures, the PMDA also offers specific scientific advice procedures for RPs: i) advice on pre-exploratory clinical study, ii) at end of this exploratory clinical study and for clinical study design after the conditional limited-term MA, and iii) advice and certification on the qualification of manufacturing material. Differently to the EMA, the PMDA does not differentiate between consultations for orphan products and regular ones [7].

3) Orphan drug designation – Products with an ODD benefit from a 10-year market exclusivity period and from other financial incentives, but with the particularity that in Japan these products are also automatically granted a Priority Review for the MAA. The eligibility criteria to obtain the orphan status are: i) the target indication must affect less than 50,000 patients in Japan or consist of an intractable disease with unknown mechanisms for which standard therapy has not yet been established, ii) the product must be indicated for the treatment of serious diseases with high medical needs (if there is available treatment, the new product must be expected to achieve substantially higher efficacy or safety), and iii) there is medical plausibility for the use of the product for the target disease and an appropriate development plan [8][9].

4) Environmental risk assessments (ERA) –GMOs, referred to as living modified organisms (LMO) in Japan, are regulated under the Cartagena Act. The ERA needs to be submitted during the clinical development phases in parallel with the clinical trial applications and for the MAA, unless a claim of

categorical exclusion applies. The framework contemplates two possible ways in which a LMO can come into contact with the environment: “Type 1 use”, which refers to any intentional introduction into the environment, and “Type II use”, which entails the use of LMOs under a “closed containment” environment. The ERA for the MAA is submitted to the PMDA and reviewed by the MHLW and the Ministry of Environment. The assessment report can be submitted separately to the MAA dossier, with the content being similar to what is required for an ERA in the EU [10][11].

5) Expedited development programs and fast track approval processes – More focused on product development and similar to the concept of breakthrough and RMAT designations in the US or PRIME designation in the EU, the Sakigake designation was introduced in Japan in 2015 to enhance the early access of innovative medical products. The benefits of the Sakigake include: continuous support and guidance from the agencies during clinical development so as to optimize and speed up the drug development plans and evaluation, de facto review of the application before the submission, rolling submission and a target review application period of 6 months, the extension of the re-examination period once an approval is granted, and potential pricing concessions [12][13]. The key feature of this designation is that to be eligible, the sponsor must develop the product first in Japan with the aim to launch the product in the Japanese market first or at least not later than in other regions. In addition, the product should represent an innovation (e.g., new mechanism of action), be intended to treat a serious disease or a disease with chronic debilitating conditions and target conditions with an unmet medical need, as well as a mechanism of action that demonstrates promising effectiveness during early-phase clinical studies and non-clinical studies [14][12][15].

An option to expedite the MAA assessment includes the Priority Review designation, which grants an accelerated MAA review lasting 9 months instead of the 12 months that the standard procedure requires. Similarly to the US designation, the eligibility criteria for the priority review include: i) that there are no available therapies, or the product shows clinical superiority compared with the existing products (including quality of life of patients), and ii) the product must be indicated for severe diseases or have an orphan designation [12]. Therefore, Priority review status is usually granted to orphan drugs and to Sakigake -designated drugs for therapeutic areas of significant medical need.

6) Type of marketing authorisation – RPs might be authorised through a standard MA, conditional MA or under a conditional and time-limited MA. The latter was instituted in 2017, and is a MA designed exclusively for RPs. With this type of authorisation, the sponsor needs to demonstrate the product´s quality and safety, but the efficacy can be supported with limited data (i.e. from early-phase phase I/II,

with a small patient number, using surrogate endpoints and accepting wider significance levels than those used in conventional trials). This first conditional MA must be followed by a re-application and a second approval procedure within a period of 5 to 7 years from the initial MA, where additional safety and efficacy data from post-marketing clinical studies (PMS) is submitted to confirm the positive benefit-risk profile. This second MAA review can lead to a standard approval if the data confirms the efficacy and safety of the product, or to the product´s withdrawal from the market. It is recommended to obtain the Agency´s advice at an early clinical stage to discuss the design of the trial and the data needed to be considered for obtaining the standard or conditional limited-term approval [14][16][17].

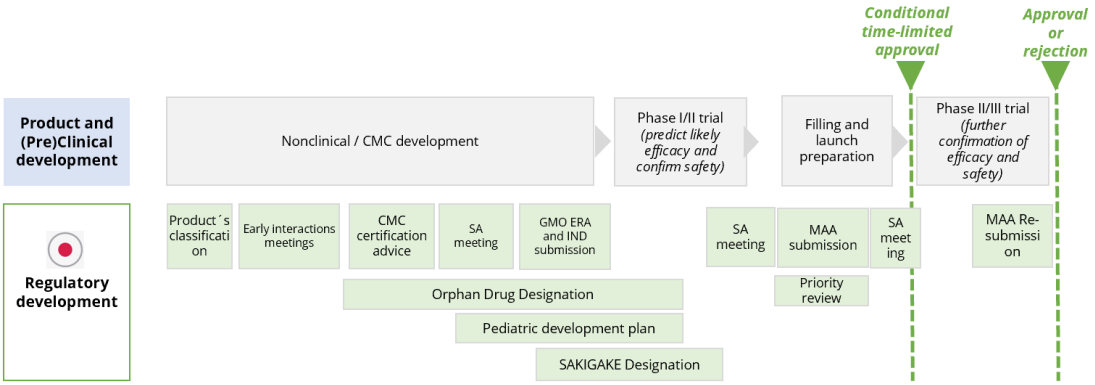

Figure 1. Overview of EU and US regulatory steps for advanced therapies during development.

CMC: Controls Manufacturing Chemical; GMO: genetically modified organism; IND: investigational new drug application; MAA: marketing authorisation application; SA: scientific advice or consultation.

Therefore, considering the particular characteristics of the regulatory framework for the development of RPs in Japan, it is interesting to analyse the clinical development that have supported the current RPs approval in the Japanese market. The aim of this review is to analyse the regulatory and clinical developmental strategies that supported the MA for the current approved RPs in Japan. In addition, this development of ATMPs in Japan is compared with the development trends in the EU and the US.

Methodology

A systematic review of the pivotal trials' features that supported the MA of the RPs approved in Japan was carried out until September 31st, 2021.

***Search strategy*:** Data collection was primarily extracted from the "Review reports for Regenerative Medical Products" on the PMDA website (www.pmda.go.jp) and the related publications. Data was

collected on the features of regulatory and clinical development for the approved RPs, excluding experimental research that falls under the RM Act.

Data extraction and collected variables: For each RP the following variables were collected: type of RP, number of approved clinical indications and their diseases area according to ICD-11 classification, pivotal clinical trials conducted and supportive clinical studies, ODD, expedited program or expedited review designation (Sakigake or Priority review, respectively), timing and type of MA, timing for re-examination period, and post-marketing data required. For each pivotal clinical trial, the following variables were selected: phase, design, type of randomization, type of control, type of study blinding, number of arms, centres participating, type of hypothesis and primary endpoint, duration of the main phase of the study, overall number of patients that participated in the study (enrolled, on intervention arm or control arm and safety set), and age and sex of population.

A specific data extraction form was designed using Excel 2019 (Microsoft Corporation, Redmond, WA, USA) to collect information and to perform the statistical analysis. Data was only collected and analysed for those approved products with an available PMDA report as of September 31st, 2021. For Yescarta®, the PMDA summary report was not publicly available and data collection was done through publications, and thus its analysis excludes some variables. Ocural® was excluded from the clinical analysis since the report was also not publicly available. One indication was counted for Collatagen®, i.e., chronic arterial occlusive disease (which includes arteriosclerosis obliterans and Buerger's disease).

Statistical analysis: Statistical analysis for categorical and continuous variables was made by means of proportions, mean, standard deviation (SD), median, quartiles 25 and 75 (Q25, Q75) and range (min, max).

Results

Regulatory development for approved advanced therapies in Japan

A total of 14 RPs were approved in Japan for 16 indications. Of these products, 9 were developed specifically in Japan and 5 products were developed in the EU and the US and later or simultaneously applied to the Japanese market. Two of those products developed in Japan also submitted foreign data from a global program to support the MA, Collategen® and Temcell®. Overall, a total of 6 (42.85%) products consists of gene therapies and 8 (57.14%) were cell therapies (6 autologous and 2 allogenic).

For the products specifically developed in Japan, 7 (77.78%) were cell therapies. Table 1 summarises the regulatory procedures adopted for the approved RPs that were specifically developed in Japan, and Table 2 summarises the regulatory development for those products with the main development in regions other than Japan, such as EU and/or US.

Ten out of 14 (71.4%) approved therapies were granted an ODD and 3 products (21.4%) obtained the Sakigake designation. Overall, the mean (SD) time required from submission of the MAA to its final approval was 13.38 (10.27) months (median, 9, IQR, 8-14.5, range, 4-36). For those therapies with an ODD (and therefore with a Priority Review designation), the mean (SD) time required from the submission of the MAA to its final approval was 9.57 (3.36) months (median, 9, IQR, 8-11, range, 4-15). For the 3 products with a Sakigake designation, the MAA procedure lasted 4 months, less than 6 months for one of them and 15 months, the latter being substantially delayed due to the applicant's time to provide responses. A total of 12 out of 16 (75%) indications received a standard approval, whereas 4 (25%) received a conditional and time-limited one. For those therapies granted a standard approval, the mean (SD) time required from submission of the MAA to its final approval was 15.77 (11.38) months (median, 11, IQR, 8.25-14, range, 8-36), while for those products granted with a conditional and time-limited approval was 8 (4.55) months (median, 7, IQR, 4.25-12.75, range, 4-14). The timing for re-examination period, was set at 5 years under conditional and time-limited approval and exceptionally extended for Delytact®, Stemirac® and HeartSheet® due to the (potential) recruitment issues in the post-marketing study.

Clinical development that supported the marketing authorisation of regenerative therapies in Japan

RPs by disease area according to ICD-11 classification included: neoplasms (4), diseases of the musculoskeletal system and connective tissue (1), diseases of the eye and adnexa (2), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (1), diseases of the skin (1), diseases of the circulatory system (2), diseases of anal canal (1) and diseases of the nervous system (2). A total of 14 main trials were conducted to support the MA for these therapies specifically developed in Japan (median, 1, range, 1 to 3). The characteristics of clinical trials that support the MA for those products are included in Table 3, except for Ocural®.

Of these studies, a total of 3 (21.42%) were Phase III, 1 (7.14%) was a Phase II/III and 10 (71.42%) were Phase I/II or II. All the RPs, except for Collategen®, were approved based on a small, open-label,

non-randomised, uncontrolled, single-arm clinical trial conducted in Japan, independently of whether they were granted a standard or conditional and term-limited approval. Regarding the methodology used in these pivotal studies, all the studies (except for Collategen®) provided a description of the efficacy and safety of the intervention (92.85%), 3 (21.43%) of the studies also used historical references to provide context for interpreting the results and 2 studies (14.28%) used literature references to set up the efficacy threshold. To evaluate the primary objective, 11 (78.57%) of the trials used intermediate variables, which were mainly qualitative (85.71%). The mean (SD) time for the main phase of the trial (i.e., to evaluate the primary outcome) was 5.32 (4.29) months. The median (IQR 25-75) number of patients enrolled and treated was 15 (5-22) and 13 (6-17), respectively. It is noteworthy to mention that based on the limited number of patients included in these studies (including Phase III trials), the efficacy could not be evaluated or concluded in most cases. Finally, the mean (SD) age of the adult population included in these confirmatory trials was 45.32 (12.78) years old. There was an imbalance in the sex distribution, there being more males (n= 99, 66%) than females (n= 51, 34%), for those analysed trials where the sex of the enrolled participants was reported.

Yescarta®, Kymriah®, Breyanzi®, Alofisel® and Zolgensma® were not specifically developed in Japan but were approved in the three key regions: US and/or EU and Japan. Foreign data was used to support the MA of Kymriah® and Zolgensma®, along with data from the Japanese cohorts in these studies (n=15 for Kymriah and n=3 for Zolgensma®). The approval of Yescarta® was based on data from the global pivotal trial (ZUMA-1) and the results of a phase 2, open-label, single-arm study conducted in Japan to assess efficacy and safety in 16 patients. For Breyanzi®, the safety and efficacy data was based on a US Phase 1 trial and a Japan-included global Phase 2 study. The approval of Alofisel® was supported by data from two clinical trials, a Phase 3, multicentre, open-label, uncontrolled study conducted in Japan that assessed the efficacy for 24 and 52 weeks, and safety for 156 weeks in 22 patients, and a pivotal study conducted in Europe and Israel.

From the 10 indications targeted with the products specifically developed in Japan, 4 (36.36%) of them had to perform use-results surveys (i.e., post-marketing surveillance system unique to Japan to collect information on treatment outcomes in real-world clinical practice) in all treated patients until the end of the re-evaluation period as the only post-marketing requirement. For 2 (18.18%) indications an open-label, uncontrolled study to further assess efficacy and safety had to be conducted, and for the other 4 (36.36%) indications a prospective clinical study to compare the treatment with a control group in order

to evaluate the efficacy and safety was agreed (Table S1). For Zolgensma®, Breyanzi® and Kymriah® only use-results surveys in all Japanese treated patients were required.

Discussion

Clinical research on ATMPs has increased during the last few years and Japan is among the countries investing in this emerging technology [18]. Nagai et al., described and compared the expedited review processes for advanced therapies in the US, the EU, and Japan, emphasising how the regulatory agencies have elaborated regulatory frameworks for innovative products and have influenced each other [8]. Kurauchi et al., compared several aspects of the clinical and non-clinical development of ATMPs between Japan and the EU [19]. In the present study, we provide an overview of the current picture, describing the most relevant features of the regulatory and clinical development that has driven RPs to their approval in Japan. Several RPs have already reached the Japanese market, but the regulatory and clinical development that supported their MA has not been systematically analysed to our knowledge for all of them.

The main characteristics of the RPs approved in Japan and the ATMPs approved in the EU and the US are shown in Table 4 and Table 5. In the EU, the US and Japan, ATMPs are regulated as biological products for human use with a specific framework for advanced therapies. Like in the US, the Japanese classification of RPs comprises two main categories: cell and gene therapy products, and in the three regions, the processing of cells is a mandatory criterion to consider a cell-based product as an advanced therapy [20]. More than half of the approved RPs target orphan indications, in line with our previously reported results for the approved advanced therapies in the EU and the US [21]. For the three regions, in order to obtain the orphan status, the medical plausibility needs to be demonstrated. The defined cut-off for the disease prevalence is different in each region, and the criterion of targeting a serious disease or unmet need and/or the clinical benefit demonstration is applicable to both the EU and Japan.

The Sakigake designation not only speeds up drug development but also the MAA assessment. The attractive benefit package that this designation constitutes, promotes the development of innovative products and is one of the key points to consider when the global strategy for the product launch is being developed. A low percentage of approved products were granted this designation, similarly to the percentage of approved products in the EU that obtained a PRIME designation [21]. However, there are at least 9 RPs with this designation, some of them still in development, and the number of approved products with this designation is expected to increase in the near future [22]. On the other

hand, the three regions have an expedited MAA assessment, called “priority review” in Japan and the US and “accelerated assessment” in the EU. The eligibility criteria for the priority review in Japan are similar to the US, although three additional months are required for the MAA review under this designation. It should be mentioned that another appealing regulatory tactic in Japan is to automatically obtain a Priority Review for having an ODD, where the developers can benefit from both an expedited review and market exclusivity.

The overall MAA review period in Japan for the currently approved products is shorter than in the EU (15.2 ± 6 months) and higher than in the US (10 ± 2.8 months) [21]. Regarding the types of MA, the conditional and term-limited approval system has similarities with the accelerated approval in the US and the conditional approval in the EU. These three types of approvals require that exploratory clinical trials predict a reasonable likelihood of clinical benefit by using a surrogate endpoint, in those cases where comprehensive clinical data may not be readily obtained.

The clinical development that supported the MA for RPs is mainly based on small exploratory Phase I/II, uncontrolled, single-arm trials. Similarly to the adaptive licensing in the EU, the concept behind the conditional and term-limited approval pathway entails that a product can be approved based on the limited available safety, and efficacy data and a low number of treated patients. However, in the case of the analysed RPs, it seems that those products developed in Japan and granted standard approval did not have a substantially more robust clinical development (Table S2). Even though in the EU and the US the type of trial designs to support the MA with advanced therapies has a similar trend (i.e., open-label, non-randomised, single-arm studies without control or using historical ones) [23], it seems that more robust confirmatory evidence support the clinical benefit. In the EU and US, the approval was based on the assessment of more patients and more conclusive efficacy, comparison with different types of historical controls and supportive studies, whereas in Japan the approval is mainly granted with non-confirmatory evidence under the ground of prioritising the unmet medical needs of the target diseases. Similar results have been reported by Coppens et al., where the level of scientific clinical evidence for approval in the US, the EU and Japan was analysed, concluding that in Japan non-significant trends of efficacy and uncertain safety were sufficient for approval [24]. Considering that the methodology used for these studies was mainly descriptive and using surrogate variables, had a low sample size and presented data with a wide variation in cases and responses, it can be inferred that determining the efficacy can be a particularly challenging endeavour. In addition, it also should be noted that the timing assessments did not exceed 52 weeks, averaging approximately 5 months. These

short-term investigations allow the assessment of acute adverse events, long-term safety and effectiveness being evaluated in the post-marketing setting along with the efficacy. Finally, the lower number of subjects could be compensated using the results of clinical studies from other countries with the proper clinical extrapolation [25].

Examples of products that might have had more solid data but were approved based on their potential benefit for diseases with high unmet needs include JACC®, Collategen®, JACE® and Stemirac®. The efficacy of JACC®, a product for cartilage damage, was investigated in a non-controlled trial with 24 evaluable cases and 12 months of clinical data. Given the prevalence of this target indication and the availability of standard treatments, the design of the trial was questioned, as even in a non-blinded manner, a control could have been included. A re-analysis of efficacy had to be performed and the product was approved on the basis that it represented a new treatment option for patients with a rare disease, narrowing the indication to patients who are unlikely to be adequately responsive to conventional therapies and who have a relatively large cartilage defect area. On the other hand, given that the trial did not support cartilage regeneration, the indication consists of "alleviation of clinical symptoms" [26]. For a similar product approved in the EU, ChondroCelect®, a non-inferiority trial with the standard of care as the comparator was conducted with 118 patients (57 treated and 61 in the control arm), with 36 months of follow up data and morphological assessment using tissue sections and biopsies that supported the "repair of cartilage defect" indication.

For the only product investigated on a controlled trial (Collategen®), a conditional time-limited approval was granted, since the efficacy could not be adequately established. A final clinical endpoint (limb salvage) was not used, the thresholds for the chosen primary endpoints did not have an established criterion (ulcer size or improvement in pain at rest), there were differences in efficacy among studies in different regions, and there were also some deficiencies with the blinding that compromised the integrity of the study and the reliability of the results [27].

For JACE®, the submission was based on the results of the percentage of epithelialization 4 weeks after grafting in 2 patients, and the approval was justified on the absence of standard therapy, the seriousness of disease and it is potential contribution to a higher survival rate [28]. Specialists in stem cells and spinal cord injuries flagged the fact that Stemirac®´s approval was based on poorly designed clinical trial that could not reveal efficacy, as well as the potential safety concerns associated with the infusion of stem cells into the blood. Moreover, the mechanism of action of the product was strongly questioned (i.e., mesenchymal stem cell differentiation into neurons) [29][30]. While JACC® and

JACE® obtained a standard approval, the limitations of Collategen®´s and Stemirac®´s development were justified with the type of approval, conditional and time limited.

As discussed in our previous publication [23][31], limited data at the time of approval has consequences and implications for the patient, the healthcare system and for reimbursement, and implies that substantial post-marketing risk management activities need to be conducted. The post-marketing conditions in Japan include follow-up for all patients treated. In addition, under the conditional and time-limited approval scheme, it is required to demonstrate efficacy within the granted time period and the applicant is subject to a PMS as a condition for approval. Four products were granted this type of approval requiring a PMS, where the treatment is compared with a control group, there is a reasonable sample size and the primary and secondary endpoints are focused on efficacy and include final variables. While it could have been questioned why these controlled and more solid studies were not conducted at pre-marketing stage, the Japanese framework for RP allow this staggered approval, which implies uncertain benefit-risk balance at the time of MA.

Finally, the conditional and time-limited approval scheme constitutes a separate drug approval pathway for RPs unique to the Japanese market. Within this scheme, an approval can be granted based on inconclusive efficacy and limited safety, relying on robust Phase III studies conducted in the post-MA setting. This high regulatory flexibility, the extremely abbreviated clinical development required to obtain approval and the benefits of the available designations, can be seen attractive incentives for the future development of RPs. On the other hand, it should be noted that no product has yet been granted a standard authorisation after a re-application under this conditional and time-limited framework. However, while under this framework these products could obtain full approval based on controlled studies and sound data, drugs that were directly granted a standard authorisation obtained their MA through smaller and uncontrolled trials. Therefore, when choosing a regulatory strategy for approval in Japan, the opportunity cost of pursuing the conditional and time limited approval must be considered, as this scheme can provide faster market access but might require more comprehensive and burdensome PMS than a direct standard approval. It should also be noted that Japan's eight-year experience with RPs may not be enough to accurately evaluate whether or not Japan's model is successful and if further monitoring is needed.

Limitations of the current study

The limitations of this study are its small sample size and the fact that further analysis is required, once more therapies are approved, to determine with greater accuracy the most common clinical trial design and methodology for RP approval in Japan. Nevertheless, this is an exhaustive study that evaluates the regulatory development and pivotal clinical trials for the approved RPs in Japan with the available information.

Conclusion

Severely debilitating or life-threatening targeted diseases, most of them with lack of available alternative treatments, or rare diseases have had an impact on the decision-making for the approval of regenerative therapies in Japan so far. RPs regulations, including adaptive licensing, promote early patient access, enabling shortcuts to speed up clinical development and thus shortening the time to approval. Under this scheme, study designs might lead to limitations in the interpretation of efficacy and safety outcomes, but these are accepted based on the severity of targeted diseases and the poor prognosis of patients with no treatment options. When developing the regulatory strategy for Japan, key levers must be considered at the early stages of clinical development: opportunity to pursue ODD, Sakigake designation and the possibility of obtaining a conditional time limited approval instead of a standard authorisation. Given the limited experience with Japan's model, it will be interesting to see its pros and cons in the future.

Expert Opinion

Japan has made considerable efforts to enhance the adoption of RM, particularly since the discovery of induced pluripotent cells. Flexible regulatory framework is promoting the development of innovative products with designations that include attractive benefit packages and marketing authorisation granted based on phase 1 and 2 clinical trials if safety is confirmed, efficacy can be assumed and there is a planned PMS.

So far, the introduction of these therapies is being granted with inconclusive evidence of efficacy and safety, prioritising the unmet medical needs of the target diseases. Although similar approach is being applied in the US and the EU through accelerate and adaptive pathways and in favour of post-marketing evidence generation, more robust developments and higher sample sizes seem to be needed for the approval of the same type of products. Similarly, most of those RPs not specifically developed in Japan, were authorized with a standard approval based on data from Phase 2 international trials that include

Japanese cohorts and small Japanese trials. No Phase 3 clinical trial results were required. These products were previously approved in the EU and US, probably due to a later clinical development and regulatory requirements in Japan (such as GMO procedures).

Currently, RPs are mainly focused on orphan diseases, which have the additional benefits of an orphan regenerative medical product designation, i.e., financially support during drug development, market exclusivity and priority review. However, in the near future, we expect that the RPs will cover higher prevalence indications rather than orphan conditions, which, in turn, will increase the number of RP submissions for approval. Ideally, these changes should evolve in parallel with the regulatory model. While Sakigake is an attractive alternative designation, the regulatory strategy plan for product development should consider the parallel international development in Japan, which so far has not been the case for most of the approved products. When orphan or Sakigake designations are not possible to obtain, the Priority review might be a good option to accelerate market access. However, a comparison with the existing products is required (in case a SoC is available), which might change the type of clinical trial designs.

As outlined in this manuscript, a future re-assessment once more treatments are approved would determine more accurately the most common clinical trial designs and methods for RP approval in Japan. Given the limited experience with this approval model, it remains to be analysed its pros and cons in the future and how many products might withdraw from the market and their reasons. It would be interesting to assess the differences between standard approvals and conditional and time limited ones, given that so far, the former did not seem to have a substantially more robust clinical development than the latter. Timely publication of evaluation reports in English is essential, not only for transparency purposes but also to increase regulatory knowledge in the field and for pharmaceutical companies as a reference for product development.

Tables

Table 1. Product classification and regulatory procedures for the approved regenerative medicine products

Products with specific development in Japan

Product Brand name	**Delytact Injection®**	**Ocural®**	**Nepic®**	**Collategen®**	**Stemirac®**	**Temcell®**	**HeartSheet®**	**JACC®**	**JACE®**		
Type of therapy and Classification	Gene expression therapy products (excluding those listed in the preceding item 2)	Human somatic stem cell-processed products	Human cellular/tissue-based products. Human somatic stem cell-processed products	Gene Therapy Product. Plasmid vector product.	Human cellular/tissue-based products. Human somatic stem cell-processed products	Human cellular/tissue-based products. Human somatic stem cell-processed products	Human cellular/tissue-based products. Human somatic stem cell processed products	Human autologous tissue for transplantation*	Human cellular/tissue-based products. Human somatic stem cell processed products*		
Product´s description	Genetically engineered herpes simplex virus type 1	Human (autologous) oral mucosa-derived epithelial cell sheet	Human (autologous) corneal limbus-derived corneal epithelial cell sheet	Plasmid DNA encoding the gene of human hepatocyte growth factor	Human (autologous) bone marrow-derived mesenchymal stem cell	Human (allogeneic) bone marrow-derived mesenchymal stem cell	Human (autologous) skeletal myoblast-derived cell sheet	Human (autologous) chondrocytes in a three-dimensional environment using atelocollagen gel	Human (autologous) epidermis-derived cell sheet		
Date of MAA application	28 Dec 2020	Not known	20 Mar 2019	22 Jan 2018	29 Jun 2018	26 Sep 2014	30 Nov 2014	24 Aug 2009	20 Mar 2018	29 Jan 2016	06 Nov 2004
Date of Committee positive opinion	24 May 2021	11 Jun 2021	26 Feb 2020	26 Mar 2019	28 Dec 2018	18 Sep 2015	18 Sep 2015	27 Jul 2012	28 Dec 2018	29 Sep 2016	29 Nov 2007
Type of authorisation	Conditional/Time limited approval	Standard approval	Standard approval	Conditional/ Time-limited Approval	Conditional/ Time-limited Approval	Standard approval	Conditional/ Time-limited Approval	Standard approval	Standard approval	Standard approval	Standard approval
Re-examination period	7 years	Not known	10 years	5 years	7-8 years	10 years	5-8 years	7 years	10 years	10 years	10 years
Orphan Drug designation	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No
ODD	10 Jul 2017	Not known	25 Mar 2015	N/A	N/A	12 Dec 2013	N/A	N/A	18 Mar 2011	25 Nov 2014	N/A

Products with specific development in Japan											
Product Brand name	**Delytact Injection®**	**Ocural®**	**Nepic®**	**Collategen®**	**Stemirac®**	**Temcell®**	**HeartSheet®**	**JACC®**	**JACE®**		
SAKIGAKE Designation	Yes	No	No	No	Yes	No	No	No	No	No	No
Priority review	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes

It has been assumed that the products with an ODD were granted with a Priority Review designation. *JACC and JACE were originally approved as medical devices. Under the PMD Act (effective from 2014), these products were transferred from the medical device category to the regenerative medicine product category.

Table 2. Product classification and regulatory procedures for the approved regenerative medicine products with a global development

Product Brand name	Products with global development				
	Alofisel®	**Breyanzi®**	**Yescarta®**	**Zolgensma®**	**Kymriah®**
Type of therapy and Classification	Human somatic stem cell-processed products	Human cellular/tissue-based products. Human somatic cell processed product	Human cellular/tissue-based products. Human somatic cell processed product	Gene therapy products, Viral vector products	Human cellular/tissue-based products. Human somatic cell processed product
Product´s description	Cell suspension of expanded allogenic adipose-derived stem cells	Autologous CAR-T cells	Autologous CAR-T cells	scAAV9 vector containing human survival motor neuron gene (SMN1)	Autologous CAR-T cells
Date of MAA application	Not known	22 June 2020	Not known	01 Nov 2018	23 Apr 2018
Date of Committee positive opinion	27 Sep 2021	05 March 2021	Jan 2021*	06 Feb 2020	20 Feb 2019
Type of authorisation	Standard approval	Standard approval	Standard approval	Standard approval	Standard approval
Re-examination period	Not known	10 years	Not known	10 years	10 years
Orphan Drug designation	Yes	Yes	Yes	Yes	Yes
ODD	Not known	Oct 2018	Oct 2018	Oct 2018	25 May 2016
SAKIGAKE Designation	No	No	No	Yes	No
Priority review	-	Yes	Yes	Yes	Yes

It has been assumed that the products with an ODD were granted with a Priority Review designation. *Date of Japanese Ministry of Health, Labor and Welfare granting the MA approval. CAR-T: chimeric antigen receptor T cell product; scAAV: self-complementary Adeno-Associated Virus.

Table 3. Clinical development of the approved regenerative medicine products developed in Japan

Product	Delytact Injection®	Nepic®		Collategen®		Stemirac®	Temcell®		HeartSheet®	JACC®	JACE®			
Clinical trial Acronym	Study GD01	EYE-01M	ASO phase III	TAO open-label	Advanced medical care B clinical research study	Study STR01-03	JR031-201	JR-031-301	M-51073-21 (pivotal study)	J-TEC002	J-TEC-EB	J-TEC-01-01	3SI-GCMN001	J-TEC003
Indications	Malignant glioblastoma	Limbal stem cell deficiency	Critical limb ischemia of arteriosclerosis obliterans (ASO)	Buerger's disease	ASO and Buerger's disease	Neurological symptoms and functional disorders associated with spinal cord injury	Corticosteroid-refractory acute graft versus host disease (GVHD) following hematopoietic stem cell transplantation		Severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies	Symptoms of traumatic cartilage defect or osteochondritis dissecans (excluding gonarthrosis) of the knee*	Dystrophic Epidermolysis Bullosa and Junctional Epidermolysis Bullosa		Giant Congenital Melanocytic Nevus	Serious and Extensive Burns
Phase	II	III	III	II	II	II	I/II	II/III	I/II	I/II	II	III	I/II	I/II
Randomization	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Control	Uncontrolled	Uncontrolled	Placebo-controlled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled
Blinding	Open-label	Open-label	Double-blind	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label
Number of centres		5 centres	57 centres	8 sites	5 sites	1 centre	12 centres	18 centres	3 centres	5 centres	4 centres	1 centre	4 centres	2 centres
Number of arms	One	One	Two arms	One	One	One	One	One	One	One	One	One	One	One
Design	Single arm	Single arm	Parallel groups	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm
Main Outcomes	Final and single variable	Intermediate and single variable	Intermediate and composite variable	Intermediate and single variable	Intermediate and composite	Final and single variable	Intermediate/final variables and co-primary	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable

Product	Delytact Injection®	Nepic®		Collategen®		Stemirac®	Temcell®		HeartSheet®	JACC®	JACE®			
Type of variable for main outcome	Quantitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Quantitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative
Type of objective	Comparison against a reference threshold of 15%, where a statistical significance with the one-sided significance level of 5% was required to demonstrate the efficacy	Description of efficacy of intervention (efficacy threshold for the primary endpoint set as 15% based on literature)	Intervention compared to placebo	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention. Historical reference used to provide context for interpreting the results	Description of efficacy of intervention	Intervention compared to historical reference	Description of efficacy of intervention. Historical reference used to provide context for interpreting the results	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention
Duration of the main phase (months)	12	13	3	3	3	7	6	1	6,5	12	3	1	3	1
Population														
Population enrolled or randomised	19	12	46	11	6	17	na	25	7	33	4	3	8	2
Population on intervention arm	13	10	29	10	6	13	14	25	7	32	4	3	8	2
Population on control arm	NA	NA	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Population on Safety set	16	10	41	10	6	13	14	25	7	33	4	3	8	2
Age of population														
Mean (SD) or reported age range	53 (na)	51.1 (22.65)	71.9 (7.6)	na	na	47 (14,71)	46,43 (16,35)	5 to 66	56,28 (13,22)	31,75 (9,61)	29,25 (20,37)	44,33 (18,77)	34 (16,97)	33,5 (0,71)
Sex:														
Female	3	3	6	na	na	1	9	10	0	10	2	2	4	1

Product	Delytact Injection®	Nepic®		Collategen®		Stemirac®	Temcell®		HeartSheet®	JACC®	JACE®			
Male	10	7	21	na	na	12	5	15	7	14	2	1	4	1

NA: not applicable; na: not available.

Table 4. Comparison of regulatory development to support approval of RPs in Japan, and ATMPs in the EU and the US

	Japan	EU	US
Number of approved products	14	19[a]	14[b]
Number of approved indications	16[c]	20[d]	15[e]
Number of approved gene therapies	6 /14	12 /19	8 /14
Number of approved cells therapies[1]	8 /14	7 /19	6 /14
Number of products with ODD designation	10 /14	15 /19	10 /14
Number of products with Expedited development Designation[2]	3 /14	8 /19	11 /14
Number of products with Expedited MAA[3]	10 /14	9 /19	9 /14
Mean (SD) time to MA approval[3] (months)	13.4 (10.3)[h]	15.2 (6.0)[g]	10 (2.8)[f]
Mean (SD) time to MA approval of products with accelerated review[3] (months)	9.6 (3.3)	11.0 (2.9)	7.6 (2.0)[f]
Number of approved products with conditional and time-limited approval[4]	4 (28.6%)	7 (36.8%)	1 (7.14%)

[a] Approved ATMPs in the EU (until December 31, 2021): Glybera®, Imlygic®, Kymriah®, Yescarta®, Tecartus®, Strimvelis®, Luxturna®, Zynteglo®, Zolgensma®, Libmeldy®, Abecma®, Skysona®, Provenge®, Zalmoxis®, Alofisel®, ChondroCelect®, Holoclar®, MACI®, Spherox®.

[b]Approved ATMPs in the US (until December 31, 2021): Abecma®, Stratagraft®, Rethymic®, Breyanzi®, Tecartus®, Gintuit®, Kymriah®, Imlygic®, LaViv®, Luxturna®, MACI®, Provenge®, Yescarta®, Zolgensma®.

[c] 13 RPS have one indication, and 1 RP have three different indications; [d] 14 ATMPs have one indication, and 1 ATMP have two different indications; [e] 8 ATMPs have one indication, and 1 ATMPs have two different indications; [f] excluding Rethymic®, considered an outlier; [g] excluding Spherox®, considered an outlier.[h] 9.36 (3.32) considering JACC and one indication of JACE that might be considered as an outliers.

[1]Includes tissue-engineered products; [2]It includes any of those designations: PRIME (EU), Fastrack designation (US), breakthrough designation (US), RMAT (US) and Sakigake designation (Japan); [3]Include priority review for Japan and US and Accelerated Assessment for EU. The mean time required from submission of the MAA to its final approval (CHMP positive opinion in the case of EU); [4] It includes a conditional and time-limited approval (Japan), as well as a conditional approval and an approval under exceptional circumstances (EU), and accelerated approval (US).

MA: marketing authorisation; ODD: orphan drug designation.

Table 5. Comparison of clinical development to support approval of RPs in Japan, and ATMPs in the EU

	Japan	EU*
Number of products analysed	8[a]	17
Number of pivotal clinical trials	14	23
Mean (min-max) number of pivotal clinical trials	1-3	1-3
Phase of trials		
Phase I, Phase I/II, Phase II and retrospective trials	10 /14	10 /23
Phase II/III, Phase III	4 /14	13 /23
Type of control		
Non-controlled	13 /14	16 /23
Placebo or active-controlled	1 /14	7 /23
Type of objective		
Superiority or non-inferiority study	1 /14	7 /23
Other	13 /14	16 /23
Main outcome		
Intermediate variable	11 /14	18 /23
Final variable	3 /14	5 /23

*Based on data from previous analysis [Ref.23]. [a]Only products with a development specific in Japan were considered.

Supplementary Tables

Table S1. Post-marketing authorisation requirements for the approved regenerative medicine products

Product	Post-marketing commitments
Delytact Injection®	Prospective clinical to evaluate the efficacy and safety of Delytact in 14 patients with malignant glioma involving the lower brainstem (mainly cerebellum). use-results comparison survey to compare information between all patients receiving Delytact and patients not receiving Delytact in order to further evaluate the efficacy and safety of Delytact after the market launch.
Nepic®	Prospective clinical study to further assess the adverse events and efficacy in approximately 120 patients per year, and use-results surveys in all treated patients
Collategen®	Prospective clinical study to compare complete occlusion of ulcer rate between at least 120 patients treated with Collategen® and 80 patients in a control group, and use-results surveys in all treated patients
Stemirac®	Prospective clinical study to compare the improvement in American Spinal Injury Association Impairment Scale between at least 198 patients treated with Stemirac® and 414 patients in a control group, and use-results surveys in all treated patients
Temcell®	Use-results surveys in all treated patients
HeartSheet®	Prospective clinical study to compare time to cardiac event-related death between at least 60 patients treated with HeartSheet® and 120 patients in a control group, and use-results surveys in all treated patients
JACC®	Use-results surveys in all treated patients
JACE® (2018)	Use-results surveys in all treated patients
JACE ® (2016)	Use-results surveys in all treated patients
JACE® (2004)	An open-label, uncontrolled study to assess the epidermal replacement rate at four weeks with at least 10 patients, and use-results surveys in all treated patients

Table S2. Supportive clinical data to support the approval of regenerative products developed in Japan

Product	Delytact Injection®	Nepic®	Collategen®			Stemirac®	Temcell®	HeartSheet®	JACC®	JACE®		
Indication	Malignant glioma	Limbal stem cell deficiency	Critical limb ischemia of arteriosclerosis obliterans (ASO)	Buerger's disease	ASO and Buerger's disease	Neurological symptoms and functional disorders associated with spinal cord injury	Corticosteroid-refractory acute graft versus host disease (GVHD) following hematopoietic stem cell transplantation	Severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies	Symptoms of traumatic cartilage defect or osteochondritis dissecans (excluding gonarthrosis) of the knee*	Dystrophic Epidermolysis Bullosa and Junctional Epidermolysis Bullosa	Giant Congenital Melanocytic Nevus	Serious and Extensive Burns
Supportive clinical data to support the approval	Phase I/II study conducted as a non-GCP compliant study as reference data	Phase III follow up	2 US Phase 2 studies and 1 US Phase 2b study in ASO indication, 1 clinical research study in ASO and Buerger indication, 1 Phase 1 study in ischemic heart disease			None	Extension study (JR-031-202), foreign phase III study, an expanded access program study, and Emergency-Use Protocols	Reference data from 2 Japanese clinical studies	Results of research on the long-term safety clinical study and 1 Japanese clinical research	Efficacy and safety interim data from long-term follow-up study (patients treated in Study J-TEC-01-01)	Follow-up study (patients treated in Study J-TEC-GCMN001)	None

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Chapter 4: Market access of advanced therapy medicinal products in the European Union

4.1: Financing and reimbursement of approved advanced therapies in several European countries

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Abstract

The associated uncertainty on benefits and high cost of ATMPs is being a current setback for their reimbursement in health systems. The aim of this study was to provide a comparative analysis of NHAs recommendations issued in different European countries. The NHA reimbursement recommendations for the approved ATMPs were compared among 8 European Countries (EU8: Ireland, England/Wales, Scotland, Netherlands, France, Germany, Spain and Italy). The search was carried out until December 31st, 2021. A total of 19 approved ATMPs and 76 appraisal reports were analysed. The majority of the ATMPs were reimbursed, although with uncertainty on efficacy evaluation. Managed entry agreements such as payment by results were necessary to ensure market access. There is a divergent classification of added therapeutic value across the EU8. The main issue during the evaluation was to base the cost effectiveness analyses on assumptions due to the limited long-term data. The estimated incremental cost-effectiveness ratio among countries reveals high variability. Overall, the median time to NHA recommendation for the EU8 is in the range of 9-17 months. Transparent, harmonised and systematic assessments across the EU NHAs in terms of cost-effectiveness, added therapeutic value, and grade of innovativeness are needed. This could lead to a more aligned access, increasing the EU market attractiveness, and raising public fairness in terms of patient access and pricing.

Introduction

ATMPs are innovative drugs, based on gene, cell and tissues, offering potentially curative treatment options for a range of diseases. ATMPs are associated with high costs and for some of them uncertain efficacy claims, which is being a current setback for the market access of these drugs [1]. This is accentuated by the fact that an increased number of ATMPs are expected to enter the market in the coming decade, covering indications with higher prevalence rather than orphan diseases [2][3]. Once the European Commission approves an ATMP, the access to the treatment depends on the inclusion of the product in the public health care funding. Each European Member State has its own authority over the market access of new products and its reimbursement agreements, which are conditioned by the respective health-care resources. With this purpose the National Health Authorities (NHAs) of European Member States perform a relative efficacy and safety assessment, giving recommendations on whether a product should be considered for reimbursement and under which conditions, if necessary [4]. These NHAs appraisals usually consider several criteria to make their recommendations such as the burden and severity of the target indication, the relative effectiveness and safety of the new product compared to the SoC or best supportive care (BSC), the cost and economical effectiveness, as well as ethical, social and patient aspects [5].

The aim of our research is: i) to provide a comparative analysis of NHAs recommendations issued by 8 different European countries, ii) to analyse if there was any relationship between the type of EMA approval (conditional approval or under exceptional conditions vs standard approval) that could impact the reimbursement decision, and iii) to provide insights of the key considerations that played a role in the NHA reimbursement recommendations.

Methodology

An analysis of the of NHAs-reports of authorized ATMPs in 8 European countries (EU8) has been conducted using the following approach:

***Search strategy*:** Data collection was primarily extracted from available NHAs-reports, such as Health Technology Assessments (HTAs) and other official national reports of the EU8, i.e., Ireland, England/Wales, Scotland, Netherlands, France, Germany, Spain and Italy. The inclusion of countries was selected according to the largest European countries and HTA report availability written in a language understood by the researchers. The search was carried out until December 31st, 2021. In addition, a search for related publications was performed for pricing (i.e., grey literature: open search and non-peer review journals).

Eligibility criteria: Only products classified as ATMPs according to the EMA criteria [6][7] and authorised under centralised procedure in the EU have been considered for the analysis.

Data extraction and collected variables: The authors designed specific data extraction forms using Excel 2019 (Microsoft Corporation, Redmond, WA, USA) to collect information. A review was conducted of NHAs-reports of approved ATMPs published by national bodies in each country. The national bodies and the type of HTA reports analysed for each country are reported in Supplementary Material.

For each ATMP/indication and NHA body the following variables were collected: type of EMA approval, reimbursement recommendation, financing conditions, drug comparator used for the cost-effectiveness analysis and incremental cost-effectiveness ratio (ICER), reported price of the product (notified price or applicant´s requested price), date of publication of technology appraisal guidance and, date of recommendation implementation. Only reports describing the initial assessments were included, excluding resubmissions. For the ICERs, the base case accepted by the agency after corrections was chosen. Time from EMA approval to NHA recommendation in their appraisal reports and time from EMA approval to implementation (i.e., product available to the patients) were analysed.

It was assessed if there was any relationship between the type of EMA approval (conditional approval or under exceptional conditions vs standard approval) that could impact the reimbursement decision, given that less comprehensive data might be available.

The key considerations that played a role or might have influenced in the NHA reimbursement recommendation or final decision were collected for those products with an available NHA assessment report (where these considerations could be extracted). After identification of all HTA-reports of authorised ATMPs, considerations that had an influence on reimbursement were extracted - a consideration was defined as: "a value judgement of the HTA-body during the assessment". These key considerations were classified according to the 5 EUnetHTA HTA Core Model® (version 3) domains and the HTA Core Model for Rapid Relative Effectiveness Assessments domains (version 4.2) [8][9]. A review was conducted for the published reports of approved ATMPs to compare the aforementioned variables of the ATMP assessments across the 8 NHA bodies. The items or considerations included in the NHAs reports that might have had an influence on the reimbursement final decision were classified according to the pre-specified domains. In addition, these considerations were classified according to the ATMP type: gene therapies (chimeric antigen receptor T cell products, CAR-T), gene therapies that consist of viral vector delivered or cell-based therapies and cell- and tissue-engineered products. Data extraction and analysis was conducted by one author, and a second author validated it. Inconsistencies were discussed until consensus was reached.

Statistical analysis: A descriptive statistical analysis was made using means, median and range (minimum and maximum). The relationship between the type of EMA approval and the reimbursement decision was assessed by a chi-square statistic test with Yates correction. A p-value less than 0.05 was considered statistically significant.

Results

The analysed products and the type of approval granted by the EMA are listed in Table 1. A total of 19 approved ATMPs were included for 20 indications, 7 of those were authorised under conditional or exceptional circumstances. In addition, 7 ATMPs were withdrawn from the market. A total of 76 NHAs appraisal reports or summaries among the analysed countries were available and analysed. For some approved ATMPs, there is not publicly available information of the NHA assessment, and for the recent approved products the NHA are still performing the assessment with no recommendation published yet at the time this article was written.

Recommendations of reimbursement and type of reimbursement schemes

The majority of the ATMPs were initially reimbursed in most EU8, except in the case of Ireland (Table 2). Germany reimbursed all the 13 ATMPs for 14 indications, as well as Netherlands (6 ATMPs were reimbursed except for 1 indication of 1 product). England and Wales agreed the reimbursement of 11 out of 12 assessed ATMPs, similarly to France with 10 out of 14 and Italy with 7 out of 8 products. Ireland did not reimburse any of the 5 assessed ATMPs at an initial stage but did it later after re-assessment with CAR-T products.

England and Wales, Scotland, Netherlands, France, and Spain narrowed the authorized indication for the reimbursement of some ATMPs. Germany did not restrict any ATMP to specific conditions within the authorized indication.

Most countries established some types of reimbursement schemes, but the specific type of the schemes is divergent among the EU8. Managed Entry Agreements (MEA) or patient access schemes (PAS) are regularly used in Scotland and England, determining specific conditions for reimbursement, usually in a confidential manner. Payment based on outcomes (PBO) are more frequently used in Netherlands, Spain and Italy, where the financing is linked to achievement of certain clinical outcomes. This risk-sharing reimbursement approach might allow discounts and rebates.

The type of EMA approval did not have an influence on the reimbursement decision (chi-square 0.4742; p value = 0.4919).

Determination of product´s added therapeutic value

The determination of product´s added therapeutic value (ATV) has different implications in terms of recommendations, reimbursement negotiations and granting the drug innovativeness status. There is not harmonised or defined standard for ATV classification and the assessment criteria is different in each country. In France, Italy and Germany the ATV is assessed as a separate parameter according to several ranks and scales, while in Scotland, Ireland and Spain there is not publicly defined added therapeutic value classification and seems to be part of clinical effectiveness assessment. Netherlands uses a binary categorical classification system, classifying a product whether has ATV or not, which is called "established medical science and medical practice" [10].

In France, the HAS assesses the ATV or the called clinical added value (CAV) on a 5-point scale for pricing negotiations based on clinical data. The CAV is an assessment to measure the added value of the medicine compared with existing therapies and the punctuation is determined by i) the quality of the data, ii) the clinical relevance of product´s effect compared to the comparator, with special emphasis on the magnitude of quality of life (QoL), and iii) the medical need in the indication assessed [11]. A major to moderate CAV leads to the highest prices, a minor CAV leads to a higher price than the comparator, and no CAV leads to lower price than the cheapest comparator [12].

The Italian Medicines Agency introduced in 2017 a process to appraise innovativeness of medicines. Innovativeness status allows speeder market access and dedicated funds (one for cancer medicines and the other for non-cancer medicines). To obtain this status, which can be attributed only to drugs indicated for serious illnesses (life-threatening diseases; diseases producing frequent hospitalisations or causing disabilities that can seriously compromise quality of life), three criteria are assessed: therapeutic need, added therapeutic value and robustness of the scientific evidence submitted by the company [13],[14],[15]. The added therapeutic value can be rated in 5 categories (Table 2): maximum, important, moderate, poor and absent.

In Germany, the term "benefit" is defined as an "effect" and the term "added benefit" is defined as such an effect compared with the appropriate comparator therapy providing a higher quantitative or qualitative benefit [16]. The probability of the existence of an effect is examined for each outcome separately leading to a qualitative conclusion and depending on the quality of the evidence, the probability is classified as a hint, an indication or proof [17][18][19]. In the second step, the extent of the effect size is determined for each outcome to draw quantitative conclusions, which are classified

as: major, considerable, minor, and non-quantifiable. The overall conclusion on the added benefit is determined on the basis of all outcomes according to the 6 grades taking into account the probability and extent at outcome level [17][18]. The benefit for patients is assessed considering improvements in health status, reductions in the duration of the disease, survival gains, the reduction of side-effects and improvement in quality of life [20]. If the G-BA decides that the new medicinal product does not have any additional benefit over the appropriate comparator, it will be included in the reference price system, and if the drug without additional benefit cannot be allocated to a reference price group, a reimbursement price will also be agreed on [21].

In Netherlands, a new drug can be considered as a "substitutable" if it has similar therapeutic value or "non-substitutable" if the product has an added therapeutic value. This classification will have an impact on the type of reimbursement; the price of "substitutable" drugs will be calculated based on the similar prices for the products within the same cluster, while the ones with added therapeutic value will not be included in the common reimbursement system and the reimbursement will be decided based on magnitude of the added value and the cost-effectiveness evaluation [22]. For a drug to be included in the insurance package must comply with the "established medical science and medical practice" statuary criterion, which is assessed by determining the relative effectiveness in comparison to the standard or usual treatment [10].

The Scottish Medicines Consortium (SMC) committee uses the clinical checklists that summarise the key strengths and weaknesses to decide on drug reimbursement but there is no separate assessment of ATV. The methodological quality of the study, the appropriateness of the population, the relevance of clinical endpoints (including HQoL endpoints), the safety profile, the potential place of the medicine within the disease context and with respect to key comparators and any unmet need, among other factors are evaluated to determine the clinical effectiveness and therapeutic value of the drug [23]. In addition, for medicines used at the end of life and for very rare conditions, the sponsor may ask for the drug to be considered at a Patient and Clinician Engagement (PACE) meeting. PACE process gives the opportunity to patient groups and clinicians with regards to the added value of a medicine which may not always be captured in the company's submission and this output has a major weight on SMC decision making [24].

In Spain, the degree of innovation and the therapeutic and social value of the medicine is one of the key factors for the reimbursement decision-making, but there are no formal criteria for linking price to

ATV. In Ireland, there are also no grades to determine the ATV and the clinical effectiveness assessment are the main tool to compare the new drug with the best SoC [25]. In England, the ATV is more related with the health-economic analysis by the number of Quality Adjusted Life Year (QALY) gained [26][27].

Table 3 compares the ATV assigned per product in France, Italy, Germany and Netherlands. In Italy, of 6 indications (5 ATMPs) where innovativeness was assessed, 4 indications obtained the innovative status and for 2 were denied. For those products, the ATV was graded as "important" for 4 indications, 1 was graded as "moderate" and 1 as "low". In Germany, of the 14 indications (13 ATMPs) approved, 3 were classified as having the "added benefit not proven", 7 were classified as "hint for a non-quantifiable additional benefit" because the scientific data does not permit quantification, 1 product was classified as "hint for a considerable additional benefit" and 2 products were not subject to the scope of the benefit assessment. From the 7 available HTA reports in Netherlands, 5 assessed indications were considered "substitutable" or with similar therapeutic value, 1 was considered to be equal as SoC, and 1 was concluded to provide insufficient evidence of its intended effects. In France, most of approved product were classified as having a minor or moderate value. Overall, there is a benefit found in these drugs but with differences in how the magnitude of this benefit is considered among countries (Supplementary Material).

Some examples of alignment of differences among countries are discusses as follows.

In the first assessment of Kymriah® for diffuse large B-cell lymphoma indication (2019), Netherlands HTA did not recognise any ATV under the opinion that it was uncertain whether there was a clinically relevant difference in the overall survival compared to salvage chemotherapy (plus a stem cell transplantation). In the same line, in Germany it was considered that there was lack of proof of additional benefit since the data from the registries were insufficient for comparability between populations and due the observation periods were considered short. In contrast, Italy considered the rates of ORR and complete response (CR) observed in the pivotal study to be of clinical relevance, even if did not constitute an evident superiority with respect to therapeutic alternatives. The clinical relevance of the results with respect to possible comparators was found in the duration of the observed response compared to published projections suggesting the possibility of real long-term disease control. Finally, in France, in line with Netherlands, it was considered that the quantification of the clinical effect was difficult since no comparative studies with usual management were presented. Similarly

happened for the other Kymriah®´s indication (acute lymphoblastic leukaemia), but in this case, in Netherlands the data on survival was considered as clinically relevant in comparison with the one reported in the literature, and in France a higher ATV rated was assigned due to efficacy data showing a high percentage of complete remissions at 3 months (about 67% of the intended-to-treat population) maintained in approximately 40% of patients after a median follow-up of 9 months.

For Zolgensma®; in Italy although there was a lot of critical gaps found, e.g., sample size, product quality etc., it was considered that the product had the potential to modify the natural course of the disease. In France, Netherlands and Germany it is considered that Nusinersen would be the reference comparator and no comparative data was available, but while in France and Italy the ATV was only accepted for certain types of SMN mutations, in Netherlands the "state of science and practice" was considered met for all subtypes.

Aligned assessment can also be seen for Luxturna®; Italy considered that the ATV was important since data demonstrated clinical improvement maintained after 4 years, in France it was considered that the benefit at one year was already significant and in Germany data for after 3 years after baseline was available at the time of the assessment. Although in Netherlands it was considered that there was no recovery of normal vision and it was not clear how long the effect could last, it was noted the importance of halting the disease, which mean that the patient will remain self-sufficient longer. Aligned assessment can also be seen for Luxturna®; Italy considered that the ATV was important since data demonstrated clinical improvement maintained after 4 years, in France it was considered that the benefit at one year was already significant and in Germany data for after 3 years after baseline was available at the time of the assessment. Although in Netherlands it was considered that there was no recovery of normal vision and it was not clear how long the effect could last, it was noted the importance of halting the disease, which mean that the patient will remain self-sufficient longer.

Special funding process that impact on reimbursement decision

Most countries have special funding processes for reimbursement decisions related to orphan drugs, drugs target to treat patients in their last months of life (also called end-of-life medicine), the disease severity and/or to cover an unmet medical need.

In France, for those orphan drugs where there is therapeutic value and budget impact lower than €30 million a full reimbursement is granted [28]. In Ireland, in the case of orphan drugs and cancer

drugs, additional review committee advises on any additional benefit provided by the drug that may not have been captured as part of the HTA process. However, it has not been stablished if there is a correlation between this committee and positive recommendations [29]. In Scotland, ultra-orphan process provides reimbursement for a period of up to three years on the condition that further clinical effectiveness data are gathered. After this period, a reassessment is performed to decide on routine use of the medicine [30][31][32]. In Germany, the additional benefit for orphan medicines is considered to be already proven by the marketing authorisation, although manufacturers have to demonstrate the level of the additional therapeutic benefit in any case [20][33]. In Italy, for drugs that target rare diseases the "fully innovative" status is granted even with low quality of clinical evidence [15]. In Netherlands, for orphan drugs, or drugs approved under a conditional or exceptional approval for which there might not be sufficient data to prove this effectiveness, an inclusion in the basic health insurance is possible. This scheme allows carrying out further research into the effectiveness and appropriate use during a period no longer than 7 or 14 years. The patients are obliged to participate in the research in order to be eligible for reimbursement [34]. There are special research funds to cover orphan drugs in Spain and Italy [33] and for the later those drugs that obtain the innovative status are funded through dedicated national funds for innovative oncological and non-oncological medicines to provide immediate access to eligible patients [35],[36]. In England, the stablished criteria for end-of-life medicines by the National Institute for Health and Care Excellence (NICE) includes that the treatment can offer an extension of life of at least 3 months, compared with current National Health Service (NHS) treatment, and there is sufficiently robust data from progression-free survival or overall survival [37]. There is no additional flexibility in the case of orphan drugs, but NICE can evaluate certain type of drugs that meet several criteria under the Highly Specialised Technology evaluation (HST) process. NICE has set higher cost-effectiveness threshold in the case of for treatments that meet end-of-life criteria or for those very rare conditions evaluated as part of the HST procedure (see below) [38]. In Scotland, there might also be a greater flexibility in terms of a higher cost per QALY for end-of-life medicines [39] and Ireland has also set a higher threshold for medicines for ultra-rare indications [40][41].

Of the 7 ATMPs assessed in Scotland, all were submitted under the orphan or end-of-life processes. In England and Wales, 3 ATMPs (Kymriah® in diffuse large B cell lymphoma indication, Yescarta® and Tecartus®) met the criteria for life-extending treatments, but Kymriah® in acute lymphocytic leukaemia indication did not. From 13 analysed drugs, 4 were assessed under the Highly Specialised

Technology (HST) procedure (Strimvelis®, Luxturna®, Zolgensma® and Libmeldy®). In Netherlands, 3 ATMPs were reported to have an orphan drug agreement. In Germany, 3 out of 7 analysed and approved drugs obtained an orphan drug agreement to guarantee patient access.

Time to market access

The time from European Commission approval to the national NHA recommendation on financing decision and product market access is summarised in Table 4. Overall, the median time to NHA recommendation for the EU8 is in the range of 9 to 17 months, being the time to implementation the same as the time to NHA recommendation in Germany and +2 or +3 months in England. For the other countries analysed, the time to implementation cannot be determined due to limited data.

The reimbursement procedure itself should take no more than 90 days with a maximum of 180 days, as required by the European Transparency Directive (Directive 89/105/EEC of 21 December 1988). However, this deadline is variable given that does not consider the "clock stops" to allow the company to answer questions [42].

In England, when NICE recommends a treatment to be funded by the NHS, the regulations require that the period within which the health service must comply will be stated in the recommendations as 3 months, except when particular barriers to implementation within that period are identified [43].

In France, products can be reimbursed before central authorisation via the Temporary Authorisation of Use (ATU) on a named patient basis (nominal ATU) or for all patients for a given indication (cohort ATU) [28],[30]. From 10 analysed products in France, 4 received ATU; 3 cohort ATU (Kymriah®, Yescarta®, Luxturna®) and 1 product received nominative ATUs and a cohort ATU later in the Marketing Authorization indication (Zolgensma®). This allowed that once the CHMP opinion was positive the patients could already have access to the medicine without need of waiting EC Decision and the HTA full evaluation period. During the ATU validity, the company can set a free price before the negotiation, but subsequently, the ASMR will be a driver for price negotiation. The data generated during this period is used in addition to the clinical data from pivotal trials, to inform the subsequent HTA and reimbursement determination at the time of MA [30][44].

In Scotland, was introduced the "interim acceptance decision" in 2018, which also allows that the SMC should have the option to accept a medicine for use subject to ongoing evaluation and future reassessment for those drugs with a conditional marketing authorisation by the EMA or Medicines and

Healthcare products Regulatory Agency (MHRA) early access to medicines scheme or innovative licensing and access pathway [45]. Tecartus® and Holoclar® were accepted in the interim for use in NHS Scotland.

According to WAIT EFPIA Indicator study, there is a high variability on patient access to new medicines across Europe, with a 90% variance between Northern and Western European countries and Southern and Eastern European countries. It has been studied that the average time between market authorisation and patient access presents a variability across Europe, from as little as 4 months to 29 months (over 2.5 years) [46].

Comparators used for the cost-effectiveness analysis, notified prices and incremental cost-effectiveness ratio

In cases where a new medicine or intervention offers better health outcomes at a higher cost than the SoC or BSC for the same indication, an ICER needs to be estimated and justified. The ICER reflects the additional cost for an additional unit of the health effect. This unit, also called, QALY have different thresholds depending on the country.

The ICER thresholds varied depending on the country. In England, NICE has set a cost-effectiveness threshold of £20,000–£30,000 per QALY gained for a medicine to be reimbursed, £50,000 per QALY gained for treatments that meet end-of-life criteria and a threshold of £100,000 per QALY gained for those very rare conditions evaluated as part of the HST procedure [38]. The SMC has not specific threshold but refers to this NICE threshold of £20,000 [40]. Ireland has set a threshold of €45,000 per QALY gained and €100,000 for medicines for ultra-rare indications [40][41]. In Netherlands, there are three burden-of-illness categories with increasing ICERs based on the severity of the disease. The lowest threshold for low burden conditions is €20,000 per QALY gained [40]. In France and Italy, no established threshold in terms of incremental cost per QALY or per life-year gained is employed [47][48][49]. In Germany, the "efficiency frontier method" is used to determine an acceptable "value for money" [49][50]. Finally, in Spain a €24,000 per QALY threshold has been unofficially reported [49].

Table S1 shows the comparators used to determine the cost-effectiveness analysis of the analysed ATMPs. The comparators used in the analysed countries consists of similar SoC or BSC. This information was not available for Spain for any product. Most of the therapies are above the set

thresholds ranging from €45.000 per QALY to <€100.000 per QALY (Table 5). The estimated ICER for each product in each country and between countries reveals high variability. The notified prices are aligned across all the EU8 (Table 6).

Key considerations that influenced the reimbursement decision

The key considerations that might have influenced the reimbursement decision are summarised in Table 8 according to ATMP product, i.e., CAR-Ts, viral vector gene therapies and cell therapies. A total of 33 reports were analysed from Scotland, Ireland, England and Netherlands NHA bodies: 3 CAR-Ts for 4 indications (14 reports in total), 5 viral vector gene therapies (13 reports in total) and 3 cell therapies (6 reports in total). Several factors within EUnetHTA domains were considered.

The "clinical effectiveness", "safety" and "cost and economical evaluation" are three core domains with interconnected considerations. In terms of "clinical effectiveness" domain, generally, the treatments were found clinically effective, but the benefit could not be quantified because of the immature data and lack of trial data compared with SoC, as well as heterogenicity between (historical) control population and population included in the pivotal trial, which consisted of a comparability issue. In the same line, the treatments were seen as having potential long-term outcomes but there was substantial uncertainty and lack of demonstration regarding this long-term clinical efficacy. It should be mentioned that the limited collection of patient-reported health-related quality of life data in pivotal trials was also a consideration observed among the three ATMP categories analysed. In terms of "safety" domain, the lack of long-term safety data and the insufficient evidence on comparative safety were considered an issue for the HTAs. For the "cost and economical evaluation" domain, the considerations most repeated in the analysed HTA reports included the budget impact, above all related to the treatment's cost in relation to its health benefits remaining high, the uncertain assumptions applied to the cost-economic model in terms of long-term effects, and limitations to the modelling methodology and the data used to inform the model.

The other two domains "health problem and current use of technology" and "patient and social aspects" might have played an important role on the decision. In the "health problem and current use of technology" domain the main consideration consisted of the fact that these therapies offered a new treatment option for high unmet needs or where there is limited treatment options and no standard treatment. This consideration was consistent for the three ATMP categories analysed. In the "patient and social aspects" domain, the fact of targeted diseases being rare, serious, life-threatening and/or

debilitating conditions and, how this severely affects the lives of patients, families having a huge emotional, physical and financial impact was one of the key considerations mentioned by all HTAs, as well as experts and patients' groups when involved in the assessment. Given the potential benefit of these therapies where responders may be able to resume work, education, self-care and social activities and the fact that of consisting of a one-off treatment (single infusion), were seen as very important considerations. Within this domain an important aspect commonly considered by most HTAs for all ATMPs categories are the special service implications for these types of products, i.e., trained staff, infrastructure, monitoring, etc.

Discussion

Although the majority of the ATMPs were reimbursed in most EU8, the decisions are heterogeneous among these European countries based on how HTA agencies interpret evidence and the associated uncertainties. While in Germany, most of the approved ATMPs were reimbursed, in Ireland none of them was initially financed, mainly due to the highly uncertain on efficacy evaluation. Even Germany had the highest approval rate, this was mostly achieved with an unquantifiable benefit although this is common not only for ATMP and depends on how the appraisal is conducted. For other countries, there is a substantial tendency to issue a positive recommendation but restricting the approved indication. The type of EMA approval does not seem to have an influence on the reimbursement decision, probably due to the type of indications targeted, i.e., rare, last lines of treatment (where there is an unmet need) or serious conditions. Our results showed that the potential benefit of these therapies was acknowledged, but overall, the high degree of uncertainty associated with the magnitude of clinical efficacy and safety hampered the decision and made complex the evaluation. Some studies have confirmed that single-arm study, short-duration and indirect comparison were reported as a major efficacy uncertainty and it is suggested that the access to these therapies is lower in the EU compared to the US [51]. We found that considerations that might have influenced the decision could go beyond the three common core domains (clinical effectiveness, safety and cost-effectiveness), and include items related with "health problem and current use of technology" and "patient and social aspects" domains, because most therapies are targeting orphan and/or end-of-life conditions. Other studies have suggested that the incorporation of additional 'social value judgements' (beyond clinical benefit assessment) and economic evaluation could help explain heterogeneity in coverage recommendations and decision-making [49]. Budget impact, Gross Domestic Product, involvement of patient advocacy

groups, equity considerations, and different economic evaluations performed among European countries could also contributed to this heterogeneity.

In terms of the type of reimbursement scheme applied, the trends are divergent among the EU8 - different in each country with different special funding processes but with an extended use of MEAs. It has been recognised that a single payment model is unlikely in the case of ATMPs [52]. The use of MEAs, which are mainly negotiated when there is uncertainty on the drug clinical benefit, allows the introduction of new products with potential benefit but it is not seen as a solution to address high prices and uncertainties associated with the ATMPs [53][54]. The introduction of the two first CAR-T products, Kymriah® and Yescarta®, constituted the first examples of national reimbursement schemes involving outcomes-based staged payments for innovative therapies in Germany, Italy and Spain [44] [55][56]. However, the implementation of these agreements is not always easy, because the burden of monitoring this process is challenging, and can differ among countries. Different agreements arise for the same treatment in different jurisdictions, making it challenging for the sponsor, and inefficient in terms of sharing of outcomes data across jurisdictions which could facilitate more robust evidence for re-appraisal [57]. In those countries where payment by results is not used, a continuous re-assessment could be an approach to manage the decision uncertainties associated with these therapies (e.g., based on cohort data from a combination of follow-up from the pivotal trials and real-world evidence) [44][55]. Broad principles for innovative payment models for high-cost innovative medicines have already been addressed by the European Commission [58]. On industry side, a concrete list of recommendations has been proposed, which includes payment models that distribute costs over time [59]. It is still uncertain how, with the expansion of ATMPs to high-prevalent diseases, patients will have rapid access to innovation while health systems are financially sustainable. Value-based pricing methodologies are suggested to be an option to cope with the specific challenges of ATMPs [49][60].

For the NHAs, the ATV of a new drug compared with the best available treatment options is one of the key points to make their recommendation on reimbursement. Although no major significant differences have been found when the ATV for approved ATMPs has been compared among countries, not a comparable and unified criterion was used. Other studies have reported low rate of agreement on the ATV of ATMPs and non-ATMPs drugs compared to the SoC among Germany, Italy and France [61][62]. The main reasons for inconsistency were found to be related with a different appreciation of the subgroup analysis of efficacy data, the appropriateness of comparators, the surrogate endpoints, methodological differences, and the benefit/risk criteria that were used [62]. A study has already been

performed with the aim to investigate the feasibility of a harmonised EU approach concerning the assessment of the ATV of medicines in European Union [27]. In this report is suggested that the ATV should be measured on an ordinal scale, as well as it should be measured by a multi-disciplinary team of trained experts independently from the committees in charge of determining the reimbursement and product price. An harmonized definition of ATV would clarify the expected benefits of new drug, set rewards for higher therapeutic added value and promote the innovation [27]. On the other hand, it is also under discussion how the ATV of ATMPs in particular should be assessed. The challenges of the standard value and price assessment methods in the evaluation of ATMPs has already been analysed, and new elements to define their value have been proposed. These new elements are more focused on societal perspective and not only on comparative clinical benefit and economical aspects, e.g., value of hope, real option value and scientific spillovers [49],[63]. It has been reported that the assessments of additional values beyond QALY are often based on 'deliberative decision-making', which is criticised for the lack of a clear framework and transparency, as well as potential risks of double-counting of additional values that are already included as part of HTA reports [64]. It is important to mention that in January 2018, the European Commission proposed a new regulation with the aim to promote more alignment in terms of HTA assessments, which was approved in December 2021. This regulation aims to replace the current system of cooperation between Member States on HTAs with a permanent framework for joint work, allowing harmonised approach to clinical assessment of new medicines across EU Member States. With this new regulation that will be mandatory from 2025, a transparency and more alignment in terms of pricing is also foreseen, above all if is fairly defined in a consistent way among the EU Members States to reflect the added value that the product can bring to patients [65].

Drugs to treat orphan conditions, end-of-life medicines, and the disease severity and unmet medical needs are factors that have an influence in terms of a higher price, which is the critical feature of ATMPs that restrain the market access. It is generally recognised that drugs in these categories are unlikely to meet the pre-existing cost-effectiveness threshold [66], as well as higher degree of uncertainty in evidence and assessment outcomes are accepted [67]. This type of applications are increasing access to drugs for end of life and rare conditions in Scotland, while they might not otherwise have been accepted [68]. It was also suggested that in England, medicines for rare diseases not evaluated under the HST framework or with an appropriate modifier in the appraisal process are subject to disadvantages [33]. Cost-effectiveness analysis and incremental cost-effectiveness ratio are

variable among EU8, for most of ATMPs are above ICER thresholds set by the different countries, with a notified prices range comprising between 200,000 to 2 million €. Moreover, another concern aside of the price are the additional costs of treating and managing these patients, meaning clinical infrastructure and skills of the clinical staff. The pre-evaluation of the organizational impact of ATMPs and the need of health-care centres with the necessary resources are a suggested requirement to be adopted in preparation for the launch and deliver of these therapies [30][69]. Gene therapies for orphan hereditary diseases comprise a unique group of products, usually administered at an early age and expected to last for the entire patient's life. The economic burden at long-term of these type of diseases with the current SoC might be underestimated and some studies suggest that efforts are needed to reduce costs through improved drugs [70]. Similar analysis haven been performed with CAR-T products [71]. For this group of products, these increased ICERs and prices have been justified and the "willingness to pay" levels were exceeded on the assumption of improving long-term clinical outcomes and patient and caregiver quality of life. With this type of drugs, to help with the affordability, patient access and given uncertainty on effect durability, the long-term payment with risk-sharing models and a price without the premium addition have been proposed [72]. The partnership and join assessments across several countries to make the medicines more accessible to patients has already been applied for some approved ATMPs, as it was the case of Zolgensma® and Zynteglo® through Beneluxa Initiative [73][74], and which led to a successful reimbursement recommendation and an aligned agreement on the price. Other cross-country collaborations aim to negotiate affordable and sustainable prices for new and innovative drugs [75]. On the other hand, it should be noted that the gross domestic product, as well as the purchasing power of the population is not homogeneous among the different European countries. Therefore, it would also be necessary to adjust the prices for each country according to its gross domestic product [76].

Additionally, it has been extensively discussed the lack of transparency of the information on the NHA decision-making process, and in pricing since the "real" prices are often unknown due to agreed confidential discounts. The need of more harmonised, systematic, and reproducible assessment process has already been discussed at European Commission level [77]. A transparency and more alignment in terms of pricing is also foreseen, above all if is fairly defined in a consistent way among the EU Members States to reflect the added value that the product can bring to patients.

Study limitations

The limitations of this study are the small sample size given the limited number of ATMPs approved. In addition, for the latest approved products, the public reports are not yet available given the evaluations are still ongoing, which also reduces the sample size. Although 8 EU countries were evaluated, the lack of publicly available information and the lack of transparency for some countries, led that the study could not cover these 8 EU Members States for some of the analysed points. The conclusions cannot be generalised to other EU Member States, other than the ones analysed. For example, the Eastern European countries have not been included in the analysis, and it is likely that the decisions outcomes on ATMPs financing in these countries are not aligned as those observed in the EU8. Finally, the weight of each consideration that influenced the reimbursement decision could not be assigned for each domain given that is not publicly available.

Conclusion

Transparent, harmonized and systematic assessments across the EU NHAs in terms of evaluation of the different core domains, added therapeutic value and grade of innovativeness, as well as increased transparency of these assessments is needed. This could lead to a more aligned access to these innovative therapies increasing the EU market attractiveness, and raising public fairness in terms of market access and pricing. It is expected that the new EC regulation that came recently into force help to improve these points. Robust evidence on the clinical efficacy and safety of ATMPs, and the reduction of their costs over time are key elements for the future financing and reimbursement of these therapies.

Tables

Table 1. Analysed ATMP approved in the European Union

	Brand name	INN	Pharmacotherapeutic group	Orphan Drug designation	Type of authorisation and current status
GTMP	**Glybera®**	Alipogen tiparvovec	Lipid modifying agents	Yes	Exceptional circumstances. Withdrawn
	Imlygic®	Talimogene laherparepvec	Antineoplastic agent	No	Standard
	Kymriah® (DLBCL)	Tisagenlecleucel	Antineoplastic agent	Yes	Standard
	Kymriah® (ALL)	Tisagenlecleucel	Antineoplastic agent	Yes	Standard
	Yescarta®	Axicabtagene ciloleucel	Antineoplastic agent	Yes	Standard
	Tecartus®	Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured	Antineoplastic agent	Yes	Conditional
	Strimvelis®	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Immunostimulants	Yes	Standard
	Luxturna®	Voretigene neparvovec	Ophthalmologicals	Yes	Standard
	Zynteglo®	Betibeglogene autotemcel	Other haematological agents	Yes	Conditional. Withdrawn
	Zolgensma®	Onasemnogene abeparvovec	Other drugs for disorders of the musculoskeletal system	Yes	Conditional
	Libmeldy®	Atidarsagene autotemcel	Other nervous system drugs	Yes	Standard
	Abecma®	Idecabtagene vicleucel	Antineoplastic agent	Yes	Conditional
	Skysona®	Elivaldogene autotemcel	Other nervous system drugs	Yes	Standard. Withdrawn
SCTMP	**Provenge®**	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (Sipuleucel-T)	Other immunostimulants	No	Standard. Withdrawn
	Zalmoxis®	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low	Antineoplastic agents	Yes	Conditional. Withdrawn

	Brand name	INN	Pharmacotherapeutic group	Orphan Drug designation	Type of authorisation and current status
		affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)			
	Alofisel®	Darvadstrocel	Immunosuppressants	Yes	Standard
TEP	**Chondrocelect®**	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	Other drugs for disorders of the musculoskeletal system	No	Standard. Withdrawn
	MACI®	Matrix-applied characterised autologous cultured chondrocytes	Other drugs for disorders of the musculoskeletal system	No	Standard. Withdrawn
	Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Other drugs for disorders of the musculoskeletal system	No	Standard
	Holoclar®	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Ophthalmologicals	Yes	Conditional

ADA: adenosine deaminase; ALL: B-cell acute lymphoblastic leukaemia; DLBCL: diffuse large B-cell lymphoma; GTMP: gene therapy medicinal products; INN: international non-proprietary name; SCTMP: somatic-cell therapy medicinal product; TEP: tissue engineered medicinal product.

Table 2. Overview of initial reimbursement recommendations and financing conditions of approved advanced therapy medicinal products in the Europe Union (December 2021)

	Product/Indication	Scotland	Ireland	England & Wales	The Netherlands	Italy	Spain	France	Germany
GTMP	Glybera®								
	Imlygic®			MEA					
	Kymriah® (DLBCL)	MEA/OEP	*/ODM	MEA		PBO	PBO		
	Kymriah® (ALL)	MEA/OEP	*/ODM	MEA	OEP	PBO	PBO		
	Yescarta®	MEA/OEP		MEA	MEA	PBO	PBO		
	Tecartus®	MEA/OEP		MEA					
	Strimvelis®					PBO			
	Luxturna®	MEA/OEP		MEA	PBO/OEP		PBO		
	Zynteglo®				PBO/OEP				
	Zolgensma®	MEA/OEP		MEA	PBO				
	Libmeldy®								
	Abecma®								
SCTMP	Provenge®								
	Zalmoxis®								
	Alofisel®	OEP					PBO		
TEP	Chondrocelect®								
	MACI®			MEA					
	Spherox®								
	Holoclar®	OEP				PBO			
Available reports/ indication	20	8	6	13	7	9	7	14	14

Colour code: green (positive recommendation), orange (negative opinion), blue (positive recommendation with restricted indication).; ; ALL: acute lymphocytic leukaemia; CDF: use within Cancer Drug Fund; DLBCL: Diffuse large B cell lymphoma; GTMP: gene therapy medicinal products; MEA: managed entry agreement; PBO: payment based on outcomes; SCTMP: somatic-cell therapy medicinal product; TEP: tissue engineered medicinal product; OEP: ultra-orphan and/or end of life process; *Finally reimbursement following confidential price negotiations on July 2021.

Table 3. Product added therapeutic value and innovativeness status

	Product/Indication	Italy	France	Germany	Netherlands
GTMP	Glybera®		Insufficient clinical benefit	no added benefit proven	
	Imlygic®			no added benefit proven	
	Kymriah® (DLBCL)	INV/ important added value	CAV IV: minor added value	non-quantifiable added benefit	does not comply with established medical science and medical practice: insufficient evidence of the intended effects**
	Kymriah® (ALL)	INV/ important added value	CAV III: moderate added value	non-quantifiable added benefit	meets the statutory criterion of 'established medical science and medical practice'
	Yescarta®	INV/ important added value	CAV III: moderate added value	non-quantifiable added benefit	meets the statutory criterion of 'established medical science and medical practice'
	Tecartus®		CAV III: moderate added value	non-quantifiable added benefit	
	Luxturna®	INV / important added value	CAV II: substantial added value	hint for a considerable additional benefit	meets the 'current state of science and practice' criterion, but with great uncertainties on long-term effects and the cost-effectiveness
	Zynteglo®		CAV III: moderate added value	non-quantifiable added benefit	meets the 'current state of science and practice' criterion, but with great uncertainties on long-term effects and the cost-effectiveness
	Zolgensma®	INV / important added value	CAV III: moderate added value	no added benefit proven	meets the 'current state of science and practice' criterion but the scientific data does not permit quantification of added value with the comparator
	Libmeldy®		CAV III: moderate added value	non-quantifiable added benefit	
SCTMP	Zalmoxis®	non-INV / moderate added value	-	non-quantifiable added benefit	
	Provenge®			non-quantifiable added benefit	
	Alofisel®	non-INV / minor added value	CAV IV: minor added value	non-quantifiable added benefit	
TEP	Holoclar®	*unknown*	CAV IV: minor added value	*	
	ChondroCelect®		Insufficient clinical benefit		Therapeutic value equal to comparator

Colour code: green (positive recommendation), orange (negative opinion), blue (positive recommendation with restricted indication). ATV: added therapeutic value; CAV: clinical added value. INV: innovative status granted; SCTMP: non-INV: innovative status not granted; somatic-cell therapy medicinal product; TEP: tissue engineered medicinal product.

Italy – the 5 categories of ATV are as follows: maximum (the drug has proven larger efficacy than any possible existing alternatives to the point of cure or significantly alter its natural history), important (the drug has a proven larger efficacy measured on clinically relevant endpoints, decreases the risk of invalidating or fatal complications, avoids highly dangerous clinical procedures or has more favourable risk/benefit ratio than any available alternatives), moderate (the drug has a larger efficacy than any available

alternatives, but it is only moderate or only proven in some subsets of patients, with limited impact on the quality of life), poor (the drug has either a limited improvement of efficacy or has been proven on endpoints which are not clinically relevant, minor advantages, for example, more acceptable administration route), absent (the drug has no relevant benefit when compared with other available treatments). France - The CAV categories are: major (CAV level I), substantial (CAV level II), moderate (CAV level III), minor (CAV level IV) or no improvement (CAV level V), with the latter level corresponding to no therapeutic progress. Germany – the 6 categories of ATV are as follows: major, considerable, minor, and non-quantifiable added benefit; no added benefit proven; the benefit of the drug under assessment is less than the benefit of the appropriate comparator therapy. Netherlands – "established medical science and medical practice": product leads to relevant (added) value for the patient in comparison to the standard or usual treatment; 'net benefit' of the intervention being assessed is a relevant and sufficiently large benefit in comparison to all existing care.

* Ex-vivo expanded autologous human corneal epithelial cells containing stem cells are therefore not included in the scope of the benefit assessment according to Section 35a Social Code Book V.

**In a reassessment performed in January 2022, it was concluded that the Kymriah meets the legal criterion of 'established medical science and medical practice' in patients with r/r DLBCL.

Table 4. Time (*months*) from European Commission approval to the NHA recommendation and product market access

		EC approval date	HTA recommendation	HTA recommendation	Implementation	HTA recommendation	Implementation	HTA recommendation	Implementation	HTA recommendation	HTA recommendation	Implementation	HTA recommendation	HTA recommendation	Implementation
			Scotland		Ireland	England & Wales		The Netherlands		Italy	Spain		France	Germany	
GTMP	Glybera®	25-Oct-12												27	30
GTMP	Imlygic®	16-Dec-15	16	2		9	12				26			11	11
GTMP	Strimvelis®	26-May-16				20	23								
GTMP	Kymriah® (DLBCL)	22-Aug-18	12	12	34¥	6	8	6		15	4	4	6*	24	24
GTMP	Kymriah® (ALL)	22-Aug-18	5	18	34¥	3	5	3		15	4	4	6*	24	24
GTMP	Yescarta®	23-Ago-18	13			5	7	6	20	21	10	10	6*	8	8
GTMP	Luxturna®	22-Nov-18	14	21		10	13	14			29	29	6*	10	10
GTMP	Zynteglo®	29-May-19						25					9	11	11
GTMP	Tecartus®	14-Dec-20	7			2	4						4	7	8
GTMP	Zolgensma®	18-May-20	9	10		13	16	11		13			7**	17	17
GTMP	Libmeldy®	17-Dec-20											10§	10	10
SCTMP	Provenge®	06-Sep-13												18	18
SCTMP	Zalmoxis®	18-Ago-16											30	22	22
SCTMP	Alofisel®	23-Mar-18	15	18		9					17	17	11	7	7
TEP	Holoclar®	17-Feb-15	66			30	33				18		23	-	-
TEP	Spherox®	10-Jul-17				7	10						35		
	Median (months)		13	15	34	9	11	8.5	20	15	17	10	8	11	11
	Range Max (months)		66	21	-	30	33	25	-	21	29	29	35	27	30
	Range Min (months)		5	2	-	2	4	3	-	13	4	4	4	7	7

National Heath Authorities (NHA) recommendation: time (months) from EC approval to the date of publication of technology appraisal recommendation. Implementation: time (months) from EC approval to date of implementation of NHA recommendation. When information is not publicly available there is a blank gap. There is no information published for Abecma® and Skysona® as of 31st December 2021. MACI® and Holoclar® were evaluated via the medical procedure in Germany and not as a medicine, which undergoes the benefit assessment procedure. Colour code: green (<12 months), blue (between 12 and 23 months), orange (≥24 months). ALL: acute lymphocytic leukaemia; DLBCL: Diffuse large B cell lymphoma; EC: European Commission; GTMP: gene therapy medicinal products; SCTMP: somatic-cell therapy medicinal product; TEP: tissue engineered medicinal product. *Cohort temporary Authorisation of Use (ATU) granted in France; ** Received nominative ATUs in France from June 2019 and a cohort ATU granted by the ANSM on May 15, 2020 in the Marketing Authorization indication. ¥Finally reimbursement following confidential price negotiations on July 2021. §Early access scheme.

Table 5. Reported incremental cost-effectiveness ratio (ICER) for the approved ATMPs in the European Union

	Scotland	Ireland	England & Wales	The Netherlands	Italy	France
Imlygic®			• £23,900/QALY vs dacarbazine • £24,100/QALY vs BSC			
Kymriah® (ALL)	£25,238/QALY vs salvage chemotherapy	• €75,748/QALY - €116,506/QALY vs blinatumomab • €75,990/QALY- €107,163/QALY vs FLA-IDA	• £44,299/QALY vs blinatumomab • £74,322 per QALY vs salvage chemotherapy	*Estimated added costs vs blinatumomab ranging €1.8 - €2.1 million and €1.8 million allogenic bone marrow transplant	€32.543,80/QALY vs salvage chemotherapy	• €90,029/QALY vs salvage chemotherapy as reference and blinatumomab over a life time horizon • €189,822/QALY vs rescue chemotherapy baseline and blinatumomab over a 10-year time horizon.
Kymriah® (DLBCL)	• £44,330-48,116/QALY vs. [R-] Gem-Ox; • £44,151-47,903/QALY vs. [R-] GDP	• €1,035,700/QALY vs SCHOLAR-1 • €734,534/QALY vs CORAL extension studies	£42,991 - £55,403/QALY (with the discount agreed)		€60.680,63/QALY vs salvage chemotherapy	€ 294,381/QALY over 10 years.
Yescarta®	£49,136/QALY	€87,957/QALY	£50,000/QALY vs salvage chemotherapy	*€46,048/QALY - €600,262/QALY vs SOC	€54.699/QALY vs BSC	€97,015/QALY (€84,766/QALY before the technical exchange)
Tecartus®	£49,711/QALY vs SOC		£46,898 - £72,920/QALY			€111,649/QALY
Strimvelis®			£494,255 - £170,668 incremental costs when compared with an HSCT from a MUD and a haploidentical donor respectively.			
Luxturna®	£89,871/QALY vs BSC	€189,037/QALY vs BSC (a discount rate of 4% on costs and outcomes is applied)	£60,908 - £86,118/QALY (do not include the company's commercial arrangement)			€191,811/QALY vs BSC over a time horizon of 85 years (lifetime)
Zynteglo®				€90,000 per QALY		€ 151,003/QALY vs better supportive care (transfusions + iron chelators), a price of -15% results in a RDCR of 106,175 €/QALY.
Zolgensma®	£59,996 - £74,000/QALY vs BSC	€298,469/QALY vs Nusinersen €387,717/QALY vs BSC	ICERs cannot be reported	€263,389/QALY vs Nusinersen	€51.690/QALY vs Nusinersen	from €576,000/QALY - €2.6 million/QALY over a time horizon of 10 years and €212,226 / QALY- €1.5 million/QALY over a lifetime time horizon depending on the data source chosen.
Alofisel®	£20,930/QALY darvastrocel vs. surgical examination +/- seton placement plus curettage	€109,058 - €248,548/QALY.	£23,176/QALY			
Chondrocelect®			£14,000/QALY			

	Scotland	Ireland	England & Wales	The Netherlands	Italy	France
Spherox®			• £4,360/QALY vs microfracture • Lower than £20,000/QALY vs BSC			
Holoclar®	£3,483/QALY vs BSC		• £42,139/QALY vs conjunctival limbal allograft from a living related donor • £30,415/QALY vs keratolimbal allograft £6,948/QALY vs BSC			

The incremental cost-effectiveness ratio (ICER) is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.

One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.

The indicated costs of the table are per patient and QALY gained.

*No cost-effectiveness analysis was not carried out. For Yescarta®, comments on cost-utility analysis from NICE were considered. No economic analysis was performed; Information for Glyebra®, Libmeldy®, Abecma®, Provenge®, Zalmoxis® and MACI® is not available.

BSC: best supportive care; HSCT: hematopoietic stem cell transplantation; MUD: matched unrelated donor; SOC: standard of care.

Table 6. Comparators used to determine the cost-effectiveness analysis of the approved ATMP

		Scotland	Ireland	England & Wales	The Netherlands	Italy	France	Germany
GTMP	Glybera®							Unknown
	Imlygic®			Best supportive care and dacarbazine				Unknown
	Kymriah® (ALL)	Fludarabine, cytarabine and idarubicin (FLA-IDA). Blinatumomab in sensitivity analysis	Blinatumomab and Fludarabine with idarubicin (FLA-IDA)	Blinatumomab and salvage chemotherapy. *Blinatumomab preferred as a main comparator*	Cost compared with blinatumomab	Salvage chemotherapy	Blinatumomab and salvage chemotherapy. *Blinatumomab as a main comparator*	Unknown
	Kymriah® (DLBCL)	Salvage chemotherapy	Salvage chemotherapy	Salvage chemotherapy	-	Salvage chemotherapy	Salvage chemotherapy	Unknown
	Yescarta®	Chemotherapy used in SCHOLAR-1 study	Salvage chemotherapy	Salvage chemotherapy with or without rituximab	-	BSC	Salvage chemotherapy with rituximab	Unknown
	Tecartus®	SOC		SOC: rituximab, bendamustine, and cytarabine (R-BAC)				
	Strimvelis®			Haematopoietic stem cell transplants (HSCTs) from an HLA-matched unrelated donor				
	Luxturna®	BSC	BSC	BSC	-	Unknown	BSC	Unknown
	Zynteglo®				*Not specified*		BSC (transfusions and iron chelators)	Unknown
	Zolgensma®	Nusinersen and BSC for pre-symptomatic patients	Nusinersen and BSC for pre-symptomatic patients	BSC	Nusinersen and BSC for pre-symptomatic patients	Nusinersen	Nusinersen and BSC	Nusinersen
	Libmeldy®							BSC
SCTMP	Provenge®							SOC
	Zalmoxis®					Unknown		
	Alofisel®	Surgical examination under anaesthesia +/- seton placement plus curettage	Surgical examination under anaesthesia +/- seton placement plus curettage			Unknown	Unknown	
TEP	Chondrocelect®			Microfacture	Microfacture		Unknown	
	MACI®			-				Unknown

		Scotland	Ireland	England & Wales	The Netherlands	Italy	France	Germany
	Spherox®			Microfracture for defects up to 2 cm2 and BSC for defects larger than 2 cm2			Microfractures “plus” technique (combined with insertion of a membrane) is used for defects > 2 cm2 whereas the osteochondral allograft technique is reserved for very extensive (> 4 cm2) and deep defects.	Unknown
	Holoclar®	BSC		Conjunctival limbal autograft, keratolimbal allograft and BSC		Unknown	Unknown	Unknown

Colour code: green (economic analysis performed), orange (no economic analysis performed). For Spain no information on the cost-effectiveness analysis is public. No information is available yet for Abecma® in any country. BSC: best supportive care; GTMP: gene therapy medicinal products; SCTMP: somatic-cell therapy medicinal product; SOC: standard of care; TEP: tissue engineered medicinal product.

Table 7. Notified prices reported for the approved ATMPs in the European Union

	Scotland	Ireland	England & Wales	The Netherlands	Italy	Spain	Germany
Glybera®							€1.321,139 (26 vials per patient)
Imlygic®			£1,670 per vial				Annual therapy costs €72 287,80 - €289,151,20
Kymriah® (ALL)	£282,000 per infusion	Total cost including rebate is €301,762; VAT is not applicable.	£282,000 per infusion (company submission). Commercial arrangement.	The total cost of €320,000 per patient and per treatment	€320,000 (excluding VAT)	€320,000 euros (excluding VAT)	Annual therapy costs €282,419,28 – €283,244,95
Kymriah® (DLBCL)	£282,000 per infusion	Total cost including rebate is €301,762; VAT is not applicable.	£282,000 per infusion (company submission). Commercial arrangement.		€320,000 euros (excluding VAT)	€327,000 euros (excluding VAT)	Annual therapy costs per patient €283.062,13 - €291,815,14
Yescarta®	£282,451 per infusion	The total cost including rebate and VAT is €384,225	Price submitted as commercial in confidence	€327,000 per infusion (including conditioning chemotherapy)	€327,000 euros (excluding VAT)		2 single infusion bag €389,130
Tecartus®	£316,118 per infusion		Price submitted as commercial in confidence				1 single infusion bag €360,000
Strimvelis®			£505,000 (excluding VAT; company's evidence submission)		€594,000	€355,000 per vial	
Luxturna®	£658,946 (in each eye)	€690,000 (for two single-use packs, one for each eye)	£613,410 per patient (excluding VAT; company submission). Commercial arrangement.	€690,000 (for two single-use packs, one for each eye)			€321,000 (for both eyes)
Zynteglo®							1,929,926,88 € – 1,936,134,22 €
Zolgensma®	£1,795,000 single infusion	Price to wholesaler €1,945,000, €2,285,375 (inc. 23% VAT)	£1,795,000 (excluding VAT; company submission). Commercial arrangement		€2,155,124,65 (excluding VAT)	€1,945,000	2.314.550€
Libmeldy®			£2,875,000 (excluding VAT; company submission)				2,875,000 €
Provenge®							Annual therapy costs per €79,952,58
Zalmoxis®					€149,000	€60,000	Annual therapy costs per patient: 189,474,78 € - 757,899,12 €

	Scotland	Ireland	England & Wales	The Netherlands	Italy	Spain	Germany
Alofisel®		The cost per patient per year to the HSE (incorporating VAT and mandatory 5.5% rebate) is €70,500	£13,500 per vial. One course of treatment (4 vials) costs £54,000 (company submission). Commercial arrangement				71,400,00 €
Chondrocelect®			£16,000 (company submission)				
MACI®			£16,226 per implant (price excluding VAT). Negotiated discounts				
Spherox®			£10,000 per culture per patient, including cell costs and transportation				
Holoclar®	£80,000 (one treatment per limbal stem cell transplant)		£80,000 excluding VAT for 1 eye. Commercial arrangement.		€95,000		

No information for Abecma® was available at the time of the analysis.

Table 8. Key considerations that influenced the reimbursement decision

EUnetHTA Domain	Key considerations
Gene therapies (CAR-T products)	
Health problem and current use of technology	Offers a new treatment option
	High unmet need in these patients; limited treatment options and no standard treatment
	Treatment options are limited, often poorly tolerated and at best produce short remissions for the majority of patients
	Therapeutic advancement due to its different mode of action and considerable clinical benefit
	Likelihood of having an impact on public health
	Burden both on individuals and on society caused by the health problem
Patient and social aspects	Disease can have a huge emotional, physical and financial impact on both the patient and their families
	For patients and their families, the emotional and financial burden associated with this life-threatening illness could be reduced
	Devastating disease with significant symptoms and an extremely poor prognosis
	Available treatments with significant adverse events and are time intensive for patients
	Single infusion, versus several rounds of treatment involved in chemotherapy and allogenic stem cell transplants, may be preferable to patients and families/carers
	Patients who respond may be able to resume work, education, self-care and social activities
	Improvements in a patient's condition and prognosis will also have a wider impact on the lives of their family and friends
	Product need to be delivered by appropriately trained medical and nursing teams in a unit with access to intensive care and strict monitoring
	Impact on the service due to specialist requirements for manufacture, administration and monitoring (e.g., additional consultant and medical support, specialist nursing pharmacy and laboratory staffing)
Clinical Effectiveness	Clinical meaningful results compared to historical control
	Data available suggest that long term remission could potentially lead to many years of life gained or might be curative
	Study results are generalisable to patients in the EU country
	The treatment is clinically effective, but the benefit cannot be quantified because of the immature survival data and lack of trial data compared with SoC
	Insufficient evidence on comparative efficacy; single arm study with no control arm
	In the country, there is established clinical experience of using CAR-T cell therapies
	Indirect comparison: differences across the studies in design, baseline characteristics, maturity of data, measurement of outcomes and sample sizes
	No comparative data, naïve indirect comparison performed. This indirect comparison might be acceptable, but was subject to uncertainty as a result of the differences in the trial populations

EUnetHTA Domain	Key considerations
	The study was open-label, there is a potential for bias
	Immature clinical data
	Quality of the evidence will remain very low even with a longer follow-up duration
	The relevant comparator, SoC, for the disease is not well defined
	Uncertainties around the comparator in relation to country practice
	Data on patient reported quality of life outcomes are very limited to a small proportion of patients
	Heterogenicity between historical control population and population included in the pivotal trial
	Uncertainty around the generalisability of the results to clinical practice
	The indirect comparison did not include health related quality of life outcomes
	Due to a lack and immaturity of clinical data there is high uncertainty over the durability of benefit
	Longer term data insufficient to confirm curative treatment or sustained responses
	Uncertainties associated to the effectiveness of re-treatment
Safety	Insufficient evidence on comparative safety; open-label and uncontrolled study limits the assessment of safety
	The indirect comparison did not include safety
	Longer term safety data are as yet unavailable
Cost- and economical evaluation	The company's model is acceptable for decision-making
	The economic analysis based on a naïve indirect comparison
	The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise
	Budget impact and concerns that increasing experience with administration of CAR-T cells or adding new indications, which may lead to greater numbers of patients being treated and therefore, a greater budget impact
	Methodological quality of the analysis of cost-effectiveness supplied by the manufacturer is inadequate.
	Lack of directly comparative data and thus the economic analysis uses an indirect comparison method, which has a range of weaknesses
	There is no cost-effectiveness model of sufficient quality available
	The model has a long-time horizon relative to the limited available data on treatment, and thus there will be uncertainty associated with the extrapolations used
	Uncertain assumptions applied to the cost-economic model
	Cost-effectiveness needs to be improved relative to existing treatments
	Lack of comparison between CAR-T therapies on the same indication
	Uncertain whether long-term survivors have the same health-related quality of life as people in the general population of the same age and sex

EUnetHTA Domain	Key considerations
Gene therapies (viral vector- or cell- based therapies)	
Health problem and current use of technology	The treatment offers a new treatment option
	High unmet need in these patients; limited treatment options and no standard treatment
	The condition severely affects the quality of life of people with the condition
Patient and social aspects	Rare, serious, life-threatening and debilitating condition that also severely affects the lives of families and carers
	Patients who respond may be able to resume work, education, self-care and social activities
	Patients who respond could potentially have less disability burden over time
	Inherited nature of the condition; emotional toll attached to passing on or being at risk from a genetic disorder.
	Condition can affect opportunities in education, the labour market, and in day-to-day life
	Improvements in a patient's condition and prognosis will also have a wider impact on the lives of their family and friends
	Single infusion: It is a one-off treatment, which could be an advantage to patients and their families/carers
	Improvements to carer-related quality of life should be qualitatively taken into consideration in the committee's decision-making
	Service implications: in determining patient eligibility for treatment including genetic testing, infrastructure and subsequent monitoring of patients
Clinical Effectiveness	Substantial improvement in quality of life
	Significant clinical benefit compared to the control group (historical control or not)
	There is a biological rationale for the treatment effect to be maintained
	The primary endpoint that has not been validated and is potentially prone to bias, it is but acceptable endpoint because it captures a relevant clinical effect of the treatment
	No direct measure of HRQoL used in the clinical trials, considered that the lack of patient reported outcomes was a key limitation in the evidence
	High level of uncertainty relating to longer-term clinical effectiveness. Longer term data insufficient to confirm curative treatment or sustained responses
	Lack of QoL assessment or unclear how improvements in activities of daily living observed relate to QoL for patients
	No information on whether patients who may lose treatment effect would benefit from retreatment
	There is some uncertainty over what represents a clinically relevant improvement (in terms of primary endpoint)
	The overall treatment effect may not be generalisable in terms of benefit : risk ratio in individual patients
	Unclear what factors make some patients more likely to respond to treatment
	Heterogenicity between (historical) control population and population included in the pivotal trial
	Uncertain the relevance of the study results to clinical practice in other subgroups of patients with different disease grades/types/age
	The type of treatment received in the trial differed from what would be available for patients in clinical practice today

EUnetHTA Domain	Key considerations
	The natural history studies all had limitations, apart from being either exclusively or primarily based in the US, where there is a different approach in the BSC vs the EU countries
	Clinical-effectiveness data came from a small number of people and that follow-up data were limited
	The population under consideration was based on and derived solely from an analysis of an exploratory post-hoc subgroup
Safety	Safety data were only available for small patient numbers
	Longer term safety data are as yet unavailable
	Treatment generally well tolerated but potential risks and complications associated to the intervention
Cost- and economical evaluation	The pharmaco-economic analysis presented was comprehensive and the reporting was thorough and transparent
	The model was considered generally suitable for decision making, incorporating relevant health states and capturing fairly well the impact of disease progression on relevant costs and health outcomes important to patients
	The methods utilised in the modelling were generally robust
	The company presented an extensive and comprehensive list of sensitivity analyses which captured the uncertainty around the base case results reasonably well
	A model-based economic evaluation projected a substantial gain in quality-adjusted life years compared to best supportive care
	The economic analysis based on a naïve indirect comparison
	Analysis performed with a comparator chosen by the Applicant, while the HTA consider other comparator as more relevant
	Uncertain assumptions applied to the cost-economic model
	Uncertain assumptions applied to the cost-economic model in terms of long-term effects
	Budget impact: treatment's cost in relation to its health benefits remains high
	Budget impact: uncertainty associated with the Applicant's estimated on number of patients eligible to the treatment (incidence rate)
	The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise
	The study suffered from a number of limitations in terms of its applicability to the modelled population
	Uncertainty around the health-state utilities used in the model and that they had major effect on estimates of cost effectiveness
	The proxy health utility scores utilised were based on a very small sample of clinician responses and are subject to a number of limitations
	The primary outcome was not used in the economic evaluation as no data were available linking this outcome to costs, utilities or mortality and no data on the long-term change in this outcome were available either
	Considerable limitations to the modelling approach and methodology and the data used to inform the model
	The lack of suitable effectiveness inputs in the economic model prevented the committee from calculating a plausible incremental cost effectiveness ratio

EUnetHTA Domain	Key considerations
Cell- and tissue-engineered therapies	
Health problem and current use of technology	Considered therapeutic advancement
	Innovative technology which may offer the prospect of long-term healing
	Disease can be life-changing and severely debilitating condition
	The treatment is well tolerated and would provide another treatment option before invasive surgery
	Current treatment options are limited and suboptimal. There is no standardised treatment
Patient and social aspects	Disease can have a huge emotional, physical and financial impact on both the patient and their families
	Often diagnosed in younger patients who may subsequently have a lifetime of disease burden
	Service implications: training on administering as well as for training staff in the appropriate preparation
Clinical Effectiveness	Trial populations are generalisable to patients likely to be seen in the respective EU country
	Evidence shows that the treatment offered several advantages over existing treatments.
	Clinical results showed only a modest improvement in the proportion of people achieving complete remission compared with placebo
	Natural disease study does not contribute significantly to predicting the clinical effectiveness of treatment in clinical practice
	Indirect clinical evidence from a network meta-analysis is not relevant because the comparators are not licensed in the country
	Study results may not be generalisable to the treatment of patients in clinical practice
	Not clear how optimising the use of concomitant treatment would affect the generalisability of the study results to clinical practice
	The study was open-label and retrospective, there is a potential for bias
	Substantial uncertainty regarding the long-term clinical effectiveness
	Substantial uncertainty regarding the long-term clinical effectiveness compared to the SoC
	Heterogenicity between compared populations
	The treatment effects/results observed in the placebo group do not reflect country clinical practice, and therefore it is uncertain whether the treatment-benefit shown in the trial would translate to the same benefit over and above standard care in that country
	The pivotal did not collect patient-reported health-related quality of life data
Safety	Longer term safety data are as yet unavailable: long-term study are required to address missing data
	Lack of safety data in children and patients aged more than 65 years
Cost- and economical evaluation	The company's model structure is appropriate and suitable for decision making
	Only better data on long-term outcomes from the ongoing trial, or more robust information on the natural history of the disease, would make it possible to decide which is the most plausible ICER
	Company did not present a sufficiently robust economic analysis to gain acceptance

EUnetHTA Domain	Key considerations
	W52 outcomes were assessed on a post hoc basis and this outcome was not included in the original study design, the risk of a false positive finding may be inflated and the results may be less robust
	The plausibility of certain estimates used in the study, considered uncertain given the absence of robust clinical data
	Even though utility values were not a significant driver of cost-effectiveness in the analysis, the different sources do introduce uncertainty in the model
	The lack of observed long-term data also contributes to uncertainty in estimates of other parameters in the model
	The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise
	There was a high level of uncertainty with the clinical effectiveness evidence and as a result it was difficult to decide the most plausible estimate of cost effectiveness
	Considerable limitations to the modelling approach and methodology and the data used to inform the model
	Uncertain assumptions applied to the cost-economic model, also in terms of long-term effects

BSC: best supportive care; EU: European; SoC: standard of care; QoL: quality of life.

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Chapter 5: Discussion and Conclusion

Discussion

ATMPs, and above all gene therapies, are taking off and patients are already benefiting from them. In several countries, ATMPs are already part of standard treatment regimens in clinical practice. While the current outlook is still the treatment of monogenic and acquired diseases, the field is starting to evolve now in parallel to polygenic diseases. Most of the world's largest pharmaceutical companies have invested in advanced therapies, as well as many new biotech companies have been created as a result of potential therapeutic candidates [1][2]. The current landscape is promising but the field is facing critical questions in terms of manufacturing, safety setbacks and clinical trial results that did not meet expectations, which are ultimately holding back development and deploying these therapies [3][4].

This thesis has analysed: 1) the ATMPs regulatory development followed in different regions, 2) the clinical development that supported the MA of ATMPs; and 3) pricing and financing decisions on ATMPs issued by NHAs in the context of public health systems.

Regulatory development

In terms of regulatory framework, specific legislation and agency committees have been stablished for these types of products in both the EU and the US regions. The main difference among the EU and the US regions would be the involvement of European NCAa for the CT applications, while in the US these procedures are centralised through the FDA. The MAA in both regions implies a centralised procedure. The EU and US Agency guidance's recommendations are evolving and being updated over time in a non-parallel manner as the field evolves.

The findings showed that the criteria that must be met in both regions to classify a product as an ATMP are highly similar, and where the main groups, i.e., gene therapies and cell/tissue-engineered therapies would be classified in the same manner in both regions. Even if the regulatory terminology used on the criteria to define an ATMP and their sub-classification reveals some differences between these two regions, ultimately has no impact on overall classification as an ATMP. The main difference would be with the hematopoietic stem cells and adult and embryonic stem cells, classified in the US under the Section 361 or 351 of the PHS Act [i.e., as human cell, tissues, or cellular or tissue-based products (HCT/Ps) or biological products, respectively], and legislated under the

Directive 2004/23/EC in the EU. ATMPs are heterogenous class of products and within this innovative evolving field, in some cases, the assignment of a product in a particular ATMP subtype or as another type of biological product or under another legislation is not always trivial. The field is evolving to more innovative approaches, which can generate new uncertainties not resolved about product´s classification. The regulatory bodies provide support and advice for the correct classification through different available regulatory procedures. Being an optional procedure for the applicants, the advice from the Agencies allow to resolve doubts of borderline areas such as products combined with medical devices, biomaterials, scaffolds or matrices, or whether a product fall within the definition of an ATMP [5][6]. Keeping this knowledge available to the public contributes to the better understanding on ATMP classification as the field evolves.

Not many years ago, the EMA launched the "Reflection paper on classification of ATMPs (EMA/CAT/600280/2010 rev.1)" [7], which was a key guideline to better understand the classification of ATMPs. The line between an unauthorized HCT/Ps and an ATMP is not always easy to determine. Many products that were considered not to be "substantially manipulated" and in consequence did not go through the premarket requirements, are now required to have an approved BLA in the US [8]. More than 300 warning letters were issued by the FDA between 2018 to 2021 for these products to be lawfully marketed [9]. In the EU, the European Commission proposed the regulation of 'substances of human origin' (SoHO), advocating for the EMA to play a central role in resolving 'borderline' cases between SoHOs and ATMPs [10]. The regulatory concepts of "minimal manipulation" and "homologous use" have been used by several regulatory authorities to distinguish between human cells and tissues for medical use and ATMPs, which should be regulated more stringently [11]. However, opposite as for gene therapies, it has been recognised that for cell therapies might be a lack of alignment of regulations in high-income countries, while low- and middle-income countries have no experience with ATMPs or established regulatory frameworks for these therapies [12]. One of the current stablished priorities of WHO is to promote global convergence on the regulation of ATMPs in both developed and developing countries, by providing definitions for what is in and out of scope for a product to be classified as an ATMP and by defining key terminology relevant to the field [13]. For instance, Brazil published the first legislation to market ATMPs in 2020, defining these products as a category of special drugs subject to MA in conjunction with the regulations in the EU, the US and Japan [14]. It has been

stated that harmonizing the regulatory framework among high-income countries would facilitate the commercialization and use of ATMPs in low- and middle-income countries [12][13].

This study also analyses and compares the regulatory milestones achieved for the current approved ATMPs in different regions with the aim to provide a regulatory road map for ATMP development. As of end of 2021, there was 1.235 ongoing trials with ATMPs sponsored by academic and government institutions [15]. It is known that academic researchers are usually unfamiliar with regulatory processes and there is often a gap between academic drug development and the translation of study results into clinical practice and patient care [16]. Currently, the ATMPs mainly target rare and monogenic diseases, paediatric populations, and unmet needs. In consequence, the development of ATMPs may require a complete regulatory road map involving several procedures such as paediatric requirements, ODD, continuous (and joint) SA, and both expedited development and MAA designations. It is important to have a global regulatory strategy plan to coordinate similar procedures in different regions, to optimise the development and chances of MAA success in each region.

One major observed issue is the immaturity of the product dossier at the time of MAA. During the MAA process, the agency will assess the product's risk/benefit by evaluating the quality of its development, nonclinical data, clinical development data, and post-marketing proposals for demonstrating benefit. Agency interactions at each milestone of product development can help developers to anticipate potential objections and major issues that may arise during the MAA review, as well as address these issues proactively in the dossier or as part of the regulatory strategy plan. Therefore, developers of ATMPs should increase the use of early agency interactions and parallel interactions, especially during the early stages of ATMP development, when they are often led by academics, spin-off incubators, or small and medium enterprises who may be less familiar with the entire product development process.

Early interactions such as INTERACT or ITF meetings (with the FDA and EMA, respectively) are of special relevance to discuss and define aspects of the target product profile (TPP), to better tailor and target certain aspects of the development and help mitigating future regulatory and reimbursement challenges. For instance, it was observed that target indication and the clinical efficacy where the most common issues discussed

during the scientific advisory meetings at MAA stage. It should be noted, that it is advisable to reach a minimum development of the product, although not too much advanced, to make prospective decisions and take full advantage of these procedures [17]. In the case of US, INTERACT meetings might be denied if it is considered that the stage of the product development program is premature or too advanced. Moreover, given the resource constraints from the agencies, an increase on meeting denial rate has been observed [18]. Sponsors should avoid including broad or general questions in briefing packages that are already addressed in guidelines, as this may lead to meeting denial and contribute to agency overload. Among the European NCAs, several agencies also provide informal and expert regulatory advice to ATMPs developers, such as the MHRA Innovation Office in the United Kingdom, the Paul-Ehrlich-Institute (PEI) in Germany or the Federal Agency for medicines and health products (FAMHP) in Belgium, with the so-called "portfolio" meetings [19][20][21]. In the US, the FDA OTAT is conducting virtual town hall series to engage with product development stakeholders. The town halls have a question-and-answer format with the goal of providing regulatory information to developers [22]. This analysis revealed that half of the approved products did not seek advice from the EMA before starting the pivotal study, reporting more protocol amendments, but not implying an impact on approval success. It was observed the use of US special protocol assessment procedures to reach an agreement with the FDA on the design and size of a single clinical trial to support the MA.

Aside from the regular interactions with the regulatory agencies to obtain their feedback, and which are crucial to validate the development at critical points, joint interactions might be key to ensure a global strategy, early patient access and commercial success. This includes parallel consultation with the EMA and HTA bodies in the EU and parallel interactions between EMA-FDA. The lack of direct comparators and the uncertainty generated by the accelerated approval might have post-marketing consequences, as it has been seen for several approved products that had to withdraw from the European market [23][24]. The reimbursement uncertainty was mentioned most by large companies as one of the major hurdles in terms of financing and commercialisation [25]. For this reason, parallel consultation with the EMA-HTA might be considered as part of the development strategy and conducted before the pivotal clinical trial. This type of meetings will help to maximise the evidence-generation during drug development, to facilitate the EU reimbursement success, as well as obtain an early engagement on post licence evidence

generation [26]. However, our study revealed that parallel SA with the EMA-HTA bodies was not a common practice despite the importance of obtaining advice on the quality of evidence generation for future EU reimbursement decisions. In addition, parallel interactions EMA-FDA might also help to get more global alignment, avoid unnecessary and diverse testing methodologies, or discuss aspects where the guideline for both agencies and/or the clinical practice differ. Although achieving harmonization and increased convergence on a particular and punctual issue is a potential benefit outcome of this interaction, recurrent parallel interactions for the same product are not usually possible [27]. Further optimisation of this program by launching an ATMP-specific pilot has already been raised [28]. Moreover, whereas the EMA SA will usually have a stronger focus towards the pivotal CTs that will support the MAA, in the EU the clinical trials are under the remit of the NCAs. Since the advice on requirements prior to initiating clinical investigation may differ among agencies, a strategy for the exploratory trials would be to have more than one SA with the EU NCAs. With this purpose, a new pilot program that involve the advice of several EU NCAs was launched in 2020, i.e., simultaneous scientific advice (SNSA). However, the review of EU NCAs is independent and diverging opinion may still occur [29][30]. It is to be seen how this pilot will evolve, but previous agreement among the concerned EU NCAs and mutual recognition processes would ease EU clinical landscape. On the other hand, proposals to rapid advice between NCAs-CAT have already been suggested, which might be useful to sponsors, as well as increase NCAs knowledge-base [28].

The expedited designations in the EU, US and Japan allow opportunities for developers to further engage with regulators. Excluding the expedited MAAs assessment designations, the FDA has created three expedited development programs: Fast Track designation, the Breakthrough Therapy designation and the RMAT. The EMA launched the PRIME designation and the PMDA the Sakigake designation [31][32]. This study showed that the expedited programs were granted similarly in both agencies and PRIME and breakthrough designations were obtained consecutively for a particular product, when both designations were requested. Data from single-arm, non-controlled trial was not an obstacle to obtain these two designations. All the products with PRIME and breakthrough designation obtained expedited MAA review and no product was granted with an RMAT designation at the time of the analysis. The most recent approved products took more advantage of all these expedited designations. In 2021, Breyanzi® became the

first RMAT-designated therapy to reach the market, followed by Stratagraft® and Rethymic® (Annex 2.2-1). The number of PRIME and Sakigake designations for ATMPs also is growing in the last years [33][34]. In line with our findings, it was observed that products that had regulatory advice from PRIME support, had shorter assessment time and clock-stop duration than the average assessment time for all types of new active substances [33].

In terms of time to obtain the MA, our findings showed that the time required from the MAA submission to the approval was shorter in the US than EU; 5,44 months less. The same trend was observed for those products with an expedited MAA review. In general, the European MAA procedure was complex for most of the products approved. Almost all products with granted AA shifted to the standard timelines, denoting immaturity on submitted data. Moreover, more than half of the approved products required oral explanations during the EU MAA, attributed to the non-robust clinical development and due to product´s innovation and complexity. In both regions, there was also the need for an ad-hoc expert group consultation to clarify issues raised by the reviewers. Interestingly, these issues were different between the EU and US agencies, being mainly indication- and efficacy-related. The type of granted MA for the approved therapies in both regions was equivalent, except for one product.

The Japanese regulatory landscape presents similar trends as the one for the EU and the US. Similar number of ATMPs have been approved, more than half of these products target orphan indications, and there are expedited development designations available and expedited review processes to support the development of innovative therapies. Although with a lower number of the expedited development designations granted for the approved products in comparison with the ones granted in the EU and the US, the number of products under development granted with Sakigake designation is increasing. The MAA review period in Japan for the analysed products is slightly shorter than in the EU and three months higher than in the US.

At present, the majority of ATMPs are eligible for these designations in the three regions due to the target conditions. The generation of one designation that would cover the three regions, with common eligibility criteria and common documentation to be submitted would also facilitate the regulatory environment. Once granted, the designation could have specific benefits in each region. In terms of regulatory environment, streamlining

regulatory procedures and to achieve the maximum regulatory converge and harmonisation across regions, would be the aim to progress in advanced therapy field.

Due to the constant innovation in this field, it is possible that the existing guidelines do not cover some of the development challenges and questions. Hence, the developers might need to pave more risky approaches that are worth to share with the authorities. Moreover, there is an interplay between product quality and clinical evidence that can affect the clinical outcome. Manufacturing and controls are the most current challenge to advance in the field, and standard nonclinical developments packages cannot always be applied in the case of ATMPs. Agencies' recommendations are evolving and being updated slowly over time and in a non-parallel manner. The US seems to be ahead, launching new guidelines specific for the development of ATMPs aimed at certain types of conditions based on the experience acquired. The continuous identification of development challenges and how developers in collaboration with the agencies agreed on the potential solutions, could help to inform development strategies. Knowledge from SA or advice given through expedited designations (e.g., PRIME), objections or gaps found during MAA, are examples of regulatory intelligence that could be collected and shared. Therefore, points that might contribute to move forward faster in the field could include: i) capturing learnings and strategic recommendations, ii) the timely and dynamic dissemination of these challenges and guidance by the agencies, and iii) provide more detailed rather than broader recommendations, whenever possible [35].

Despite the fact that there is cooperation between Agencies to develop a common understanding in the field [36], the need for standardisation and more global regulatory convergence has already been claimed [37][38] and recognised by the regulatory bodies [39][40]. Efforts towards achieving such goal are currently in progress through the WHO [13] and by the ICH that is harmonising recommendations, e.g., nonclinical biodistribution studies [41]. Other organizations and international working groups and funded projects are developing manufacturing standards for AAV and lentiviral therapies, such as the US Pharmacopeia [42], the evaluation of pre-existing AAV immunity [42][43], or enhancing the acceleration of CAR T-cell therapy development through nonclinical and quality standards [44], among other several initiatives [45][46][47][48]. This harmonisation would facilitate and speed up the development, as well as submit regulatory applications more efficiently and in a time-saving manner across different agencies. Lessons learned from COVID-19 pandemic showed that the collective response

allowed a rapid development and availability of vaccines, as well as how EMA and FDA joint efforts let for a more unified nonclinical data requirements and regulatory convergence [49][50][51]. The implementation of the EU rolling reviews could remain permanent from now on to assess other products, instead of only be used as in a public health emergency [52]. Streamlining the development process may involve the use of single, unified templates to be used internationally for the clinical development [53]. On October 2022, a draft guideline on the harmonized trial protocol has been published by the ICH, along with template documents to unify the format and content of clinical trial protocols [54]. It is recognised that sometimes single templates may not meet the needs of all regulatory agencies, even if there is high convergence on the content. For example, the EMA has launched a template for the labelling and package leaflet of genetically modified cells, which includes regional particularities but should have homogeneous content across regions [55]. Finally, it has also been discussed the importance of other regulatory agencies form other regions to be familiar with the scientific principles and regulatory issues in this field, as well as the use work-sharing approaches to facilitate timely access to therapies [13][43][56]. Although it is understood that many countries will establish their own and new regulatory frameworks for gene and cell therapy development, this can lead to potential divergent frameworks across regions.

One of the regulatory challenges in the EU is the GMO legislation and its different implementation by the EU Member States. The ERA in the EU has been a subject of debate and has become a hot topic for many years now. In response to several multi-stakeholder pressure and proposals, a lot of efforts have been conducted to streamline the process and decrease the burden of the developers when applying for this procedure. This study discusses the ERA procedures in the EU, and its comparison with the US framework. In the US, the ERA is necessary for conducting clinical trials, only in specific cases, or even can be exempted for the BLA. In contrast, in the EU the ERA should be submitted during clinical development and MAA stages. Consequently, some data needs to be planned and generated at early stage: product´s characterization, shedding and biodistribution assessments, which will guide the ERA and design of clinical studies, as well as facilitate the MAA and defining the monitoring requirements. At MAA stage, risks are evaluated under a centralized procedure for both regions.

While our article has contributed to the position that significant improvements were needed in the EU for this procedure, some actions have been implemented since then. As

mentioned, the GMO legislation is present at two points of the development; during the product´s clinical development and during the MAA. On one hand, in terms of clinical development, good practice documents and common application forms have been endorsed by most of the EU Member States for those medicinal products consisting of or containing GMOs, i.e., AAVs and CAR T-cell therapies. This fact has allowed to standardise the information to be submitted. On the other hand, the EMA recognised the need to streamline both the technical requirements and the interactions with the ERA competent authorities during the MAA procedure. The consultation process with these competent authorities is now optimised, in a sense that is performed in parallel to the drug evaluation procedure by the CAT and CHMP members and it is more focused on practical minimisation measures. In addition, the dossier section to be completed for the MAA is based on the forms required during the clinical development, reducing then the MAA burden [57]. This streamlined approach has facilitated the procedure at each stage of development, i.e., clinical development and MAA, as well as provides a more consistent approach between these two stages.

Despite all these optimisations, further efforts are considered necessary to centralize or rationalize this procedure for all types of GMOs [58]. The bottleneck that EU environmental legislation may represent became more evident during the COVID-19 pandemic, when a temporary derogation of environmental requirements allowed clinical trials with GMOs intended to treat or prevent COVID-19 to start as soon as possible [59]. This derogation law, Regulation (EU) 2020/1043, recognises the complexity and workload that the ERA requirements imply to the developers. This derogation initiative was considered by the developers as a valuable measure for improving and enriching clinical research in the EU in the post-pandemic era [60]. Currently, in terms of number of clinical trials conducted with ATMPs by region, US is leading (~43.32%) followed by Asia Pacific (~34.31%), Europe (~17.64%) and other regions (~4.72%) [61]. It is under debate whether clinical development with GMO in the EU might be considered less attractive to sponsors than in US and Asia [62]. To implement the permanent derogation of GMO framework would be in line with the approach taken by the US, where most ATMPs are categorically excluded from submission of an ERA at the clinical development stage [59][63]. It has also been concluded that the environmental risks associated with certain types of ATMPs are negligible [62]. Whereas it is current subject of debate whether a permanent exemption from GMO requirements for ATMPs should

be applied or the assessment of all the potential risks that these GMOs might pose should continue, a simplified approach is still needed in the meantime. The new EU clinical trial regulation does not cover the authorisation under the GMO framework, which could have been an option to streamline the overall procedure, above all for multinational trials.

Applying the same approach as the US GMO framework for the development of ATMPs across regions has been suggested as a way to enhance harmonization. IND applications for the development of ATMPs are categorically excluded from the requirement to submit an ERA, unless other circumstances suggest that the specific action may significantly affect the environment, such as the use of virulent organisms or organisms that are ecologically more fit than their wild-type counterparts. Another principle for excluding ERA requirements during clinical development is the amount of product released, when the quantities of an investigational product and the limited number of patients in a clinical study should not have a significant cumulative effect on the environment in terms of GMO biomass shed from patients [59][63]. At the BLA stage, an ERA evaluation is required to address potential risks and agree on post-marketing minimisation measures. Some therapies, such as CAR-T cell products, which are known to be not viable in the environment, may also be categorically excluded. Therefore, the definition of a list of product class and circumstances where a product could be exempt of an ERA would be of value, similarly and aligned to the FDA "Guideline on Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products" [64].

Approved COVID-19 vaccines set an important precedent in the EU, exempt from the ERA requirements given the derogation and where millions of doses where administered. The risks to the environment for both vaccines during the EU MAA were assessed as negligible. This another indicative that nowadays, there is sufficient knowledge in the field as to determine the need of an ERA according to defined criteria, and with the aim to ensure the safety for human health and the environment. Given the expected amount of ATMP applications in the near future, it is clear that a pragmatic solution is required, and it is a good opportunity to harmonise requirements among regions.

Clinical development

The development of ATMPs is similar to the path experienced by monoclonal antibodies several decades ago, which faced many challenges but ultimately became best-selling

drugs in the pharmaceutical market due to scientific and technological advances [65]. The current authorised ATMPs target low prevalence, life-threatening, or seriously debilitating diseases. However, the ATMP field is starting to move beyond rare diseases, targeting prevalent and more complex diseases and expected going mainstream in a relatively near future. It has been reported that from a total of 2.406 clinical trials with ATMPs in 2021, 59% are targeting prevalent diseases [15] and preliminary promising results have already been shown for diabetes type 1 [66] and macular degeneration [67][68]. Since the approval of the first CAR T-cell products in 2018, the use of these therapies in earlier lines of treatment versus the standard salvage chemotherapy and stem cell transplant was seen as one of the future objectives of the clinical practice [69]. In 2022, axicabtagene ciloleucel (Yescarta®) and lisocabtagene maraleucel (Breyanzi®) received market authorization as a second-line treatments both in the EU and US [70][71][72]. On the other hand, allogeneic CAR T-cells are now under rapid development, and the next coming years will determine if the future is to have these therapies ready to use [73][74]. While studies evaluating the efficacy of CAR T-cell versus SoC therapy have already been performed [75][76], the future might consist of head-to-head comparison among autologous CAR T-cell therapies, head-to-head comparison between allogenic and autologous CAR T-cell therapies [69][73]. Moreover, CAR T-cell products are now expanding outside oncology indications; an IND for a novel CAR T-cell therapy to treat lupus nephritis was submitted in 2022 [77]. On the other hand, there has been a shift towards targeting polygenic diseases with AAV-based therapies such as Parkinson's and Alzheimer's disease [78], or targeting numerous infection diseases [79]. An autologous ex vivo CRISPR/Cas9 gene-edited therapy is being evaluated for patients with sickle cell disease and beta-thalassemia, and it is expected to be approved both in the EU and US in 2023 [80]. Finally, it is worth to mention that in 2022, two more gene therapies for rare disorders have been approved; elodacagene exuparpovec (Upstaza®) to treat the rare genetic nervous system disorder aromatic L-amino acid decarboxylase (AADC) deficiency, and valoctocogene roxaparvovec (Roctavian®) to treat haemophilia A [81][82]. Therefore, the ATMP space is evolving incredibly fast, and it is a priority to be prepared for this expansion.

This research has contributed to provide an exhaustive analysis of the level of clinical development robustness that supported the ATMP approval so far, and reviewed the

challenges associated to this type of developments. In addition, it has been also reviewed some of the current efforts to advance in the ATMP clinical development.

Aside from manufacturing issues, there are numerous methodological and clinical challenges, complicating the translation from research into patient access. As mentioned, most authorized ATMPs are targeting low prevalence, life-threatening, or seriously debilitating diseases. The clinical developments for these therapies are mainly based on adaptive, small, open-label, uncontrolled, and single-arm pivotal trials. Therefore, advanced therapies clinical development has initiated a shift from traditional clinical developments, i.e., controlled trials from Phase I to Phase III, towards an accelerated and highly product-specific ones. These types of designs are more common for gene therapies than for cell and tissue therapies. Two major challenges have been observed related to evidence generation during ATMP clinical development: i) demonstration of clinical benefit over the SoC and ii) lack of long-term data from pivotal trials. It is recognised that clinical development for diseases that have high unmet need and/or are orphan can be complex and robust trials might not be feasible. In these cases, speed up access and obtain an accelerated approval has been justified by sponsors and the regulatory agencies. On the other hand, and in the view on how the field is evolving towards prevalent diseases, achieving clinical trial designs that can demonstrate success over the current clinical practice and with clinically relevant endpoints, should be one of the main future goals.

To date, as most ATMPs target rare disorders, they are facing the same or similar challenges associated with orphan drugs. Many efforts have been carried out to launch recommendations on improved statistical methodology and innovative designs. On the other hand, the agencies are launching numerous draft guidelines on clinical development for ATMPs. The FDA is ahead guiding and establishing recommendations on how to move forward in the field in terms of clinical development [83]. One of the proposals is to improve clinical evaluation of product efficacy and safety through research on biomarkers and bioassays, as well as the use of PRO instruments is also encouraged [40]. The advantages of using biomarker-driven trials and multi-arm trials in rare disease settings, such as sharing control arms and facilitating recruitment, have been widely discussed in the literature. Although it requires more intensive collaboration between centres, cooperation of sponsors/industry and more preparation, is being promoted as a potential solution [84][85]. In May 2022, the EC, EMA, and Heads of Medicines Agency (HMA) released guidance on complex clinical trials, which also addresses the use of

biomarkers and biomarker assays and the design and conduct of master protocol studies [86]. Other approaches to increase efficiency in clinical development, such as master protocols, platform trials, umbrella trials, and basket trials, are being proposed. In November 2022, the FDA released a draft guideline on umbrella trials for cell and gene therapies [87]. As an example, the pharmaceutical company Kite Pharma is conducting a basket study design with separate indication-specific sub-studies to evaluate the efficacy of brexucabtagene autoleucel (Tecartus®) in four rare B-cell malignancies [88]. In a rapidly progressing field such as oncology and CAR-T products, the SoC might be updated during the course of the trial, and that is why these types of designs such platform trials are gaining more interest. In the future, studies similar to Lung-MAP (i.e., muti-arm biomarker-driven trial under a master protocol) with several CAR-T products might become the common approach [89]. Another example of increased development efficiency would be the PaVe-GT pilot program, which uses the same AAV vector produced through the same standardised manufacturing process, for four different rare diseases and under two master protocols grouped by therapeutic areas. The proof-of-concept studies will be conducted individually for each therapeutic indication, but some of the findings on biodistribution studies and potentially part of the toxicology, might be shared across programs [90].

The need for long-term data in the ATMPs field is important due to its link to safety and the persistence/durability of therapeutic outcomes. Long-term data for ATMPs is typically obtained through post-approval commitments. Some of the concerns of adverse events at long-term are related to genomic integration and off-target effects of gene-editing approaches, immunogenicity and pre-existing immune reactivity, potential liver toxicity due to viral load, etc. [91][92][93]. The current guidelines suggest that studies using integrating vectors and genome-editing products follow patients for at least 15 years, while for AAV vectors a minimum 5-year follow-up period is recommended [94][95]. Many approved ATMPs target paediatric population, where there is the need to evaluate growth, development, and sexual maturity as part of long-term safety assessments [96][97]. The lack of safety and efficacy long-term data is a factor that affects HTAs, which have to assess the potential durability and cost-effectiveness of a product based on short-term data available from accelerated clinical programs. Determining the ideal length for follow-up or how to harmonize data collection is a current topic of debate, especially as the field grows and patients in studies may be enrolled in the same registries

used for commercial purposes [98]. Continue working on effective ways of collecting and managing long-term data is necessary to gain insights into the safety and efficacy of these therapies and optimize long-term data requirements over time.

The use of RWE as a historical control in clinical development for rare diseases has been extensively discussed in the literature and has been widely used for the approval of ATMPs. The FDA has published draft guidance on the use of natural history information as a historical control [99]. The EMA has also published recommendations on the use of historical controls in trials for small populations [100]. Observational studies, patient registry databases, and medical chart extractions have been used as historical controls to provide complementary evidence to single-arm trial data, although it has been observed that the use of these controls to claim indirect benefit over the SoC may be challenged by payers and HTA bodies. It has been discussed how the bias of historical control groups can be reduced to be more acceptable by all stakeholders [101][102]. In cases where there are no alternatives, such as for genetic and rare diseases, an external control may be the only possibility. Then, robust comparative data, clear justification for a non-randomized trial and an early dialogue with regulatory agencies and HTAs at the design stage is encouraged. However, in fields such as oncology the comparison with the SoC should be the common approach. Similarly, with the use of surrogate endpoints, the true clinical effect may be overestimated and may condition the acceptability of the HTAs. Further guidance from the HTAs on the methodologies for validation and acceptability of surrogate endpoints has been already suggested [103].

The interplay between clinical data and product´s quality has also been discussed as a pilar to move forward in the field and to set principles to achieve translational success. Similar standards, e.g., investigation of immune responses through the same validated assays, would allow performing a comparison with valid pooling data, ensure consistency in clinical development, and the reproducibility of knowledge. Several organizations are working to define standards and the convergence of common requirements [45][104]. The development of databases to compile and analyse data, pre-existing immunity etc. are initiatives that would help to translational success.

Finally, the degree of specialization and clinical expertise in the management of ATMPs should be highlighted. The increasing interest on decentralised trials and the benefits in terms of improving recruitment and retention of subjects are being recognised and might

become the common way to operate in the future [105]. In the case of ATMPs, this is another added issue since these products usually need to be administered in highly specialised centres. There is the need of infrastructure for transporting and storing the treatment, accreditation to administer the treatment or trained staff and access to intensive care units to manage adverse events [106]. With the better knowledge and experience with these therapies is expected to have decrease and better management of adverse reactions. In addition, with the expansion of approved ATMPs, it is expected that its administration becomes the new normality and the patients and families do not have to travel significant distances to these centres for treatment. With the new technologies and decentralised trials is also expected that this might facilitate the follow up trials and post-marketing commitments.

Financing and reimbursement

Aside from ensure product´s safety and efficacy, the product must also be affordable to be accessible to the public health systems. If a therapy is approved but does not reach the patient, the whole product´s development fails in its primary purpose. The availability of medicines in the European markets is not homogeneous nor the time to reach the market. Multiple factors have been associated to this heterogenicity and delays on market access. Several measures to improve innovative drug availability are currently under debate: the generation of more robust evidence during clinical development, strengthen the early dialogue between HTA bodies and NHA/payers/patients, work on adapted payment models, face challenges of the cost-effectiveness analysis, increased transparency, harmonised and systematic evaluations across EU Member States, among others.

The achievement of greater transparency can be discussed both in terms of product´s cost and price and how the assessment of product´s value is performed. It is patent the lack of transparency in both the pricing mechanisms across the EU countries (where the "real" prices are usually unknown due to the agreed confidential discounts and managed entry agreements), and the development investment costs and profit levels from the pharmaceutical companies. Although the product´s ATV principals are similar among the EU countries, not all countries make public how these assessments are performed and what is the criteria used to stablish the product´s value and pricing/reimbursement decision-making in each case. All this asymmetry of information results in complex negotiations and no transparency on price-setting methods, which generates differences

on product accessibility and reimbursement uncertainties to the companies. This fact has been related to less attractiveness of the European market for sponsors. For example, the pharmaceutical company Bluebird withdrew its product betibeglogene autotemcel (Zynteglo®) from the market after failing to reach an agreement with health authorities on the treatment's price [107]. Therefore, to promote the innovation and build a sustainable system, there is the need for some reimbursement predictability to several stakeholders (both industry and health care systems), which leads to an increase transparency and more harmonised evaluation systems.

The assessment of medicines through a HTA, which is carried out by medical technology agencies or other medicine assessment bodies, is an evidence-based process that objectively assesses a new or existing drug and compares it with the current SoC or other relevant approved treatments, as a basis for decisions on the pricing and reimbursement. This evaluation is aimed to be a multidisciplinary and considers the medical, economic, social and ethical issues related to the use of the drug. There are certain differences in the national processes and methodologies used for the HTA evaluation, and how the evidence and the magnitude of drug´s clinical benefit is considered in these evaluations. Although no major significant differences were found when the ATV for the approved ATMPs was compared among the analysed countries, not a comparable and unified criterion was used. In line with our findings, in 2015, more transparency and unified evaluation for ATV assessment to clarify the expected benefits of new drug were recommended and studied by the EC [108].

Joint efforts started in 2004 with the recognition by the EC of an urgent need for establishing a sustainable European network on HTA [109]. Since then, the EUnetHTA Project has developed common assessment methodologies creating the HTA Core Mode and piloting, and other application of tools and approaches to cross-border HTA collaboration [110]. In this sense, we carried out a qualitative analysis of the consideration that might have influenced the reimbursement decision according to EUnetHTA domains (clinical effectiveness, safety, cost and economical evaluation, health problem and current use of technology and patient and social aspects). All domains have influenced the reimbursement decision in the products analysed, although the weight that each domain had on the decision is unknown.

In January 2018 and after several negotiations, the EC proposed a new regulation for HTAs. The proposal was finally adopted in June 2021 to enter into force in January 2025 after a transition period [111]. This regulation aims to replace the current system of cooperation between Member States on HTAs with a permanent framework for joint work, allowing harmonised approach to clinical assessment of new medicines and certain high-risk medical devices across EU Member States. The regulations establish that a European joint clinical evaluation report must be available. With this new proposal is expected a standardised HTA methodology to provide an equal basis for decision-making of member states across the entire EU through joint clinical assessments. This will also result in more transparent rules and the comparable assessments at individual member states level, which could lead to easier negotiations. In addition, it is expected that this facilitates the business predictability. The new regulation also makes clear that this report will have to be considered by the health authorities of each country for pricing and financing decisions, but the NHA will continue to be responsible for pricing and financing decisions in each country. It remains to be seen the benefits and impact on this new regulation in the coming years. In addition, it would be interesting to see how potential differences in SoC among Member States will be addressed in the joint assessments. Monitoring the implementation of this regulation, its impact on evidence requirements, decision-making, pricing alignments, and its iteration to optimise process will be key in the coming years.

The time lag between a MA and patient access also needs to be considered. The reimbursement procedure itself should take no more than 180 days, as required by the European Transparency Directive (Directive 89/105/EEC of 21 December 1988). However, this deadline does not consider the "clock stops" to allow the company to answer questions. According to our results, the average time to reimbursement is in the range of 9 to 17 months for the 8 EU countries analysed. Other studies that included other EU countries have reported a range from 4 months to over 2 years [112]. The root cause of unavailability and delay to innovative medicines has been analysed and attributed to: i) the need of a tailor-made dossier in local language and compliant with local rules, ii) the timing to apply for a reimbursement assessment (i.e., in some countries is possible prior to MA, but in others requires a positive opinion from CHMP or even the EC decision), iii) some countries only can start when a cohort of other countries have finalised their decisions at national level, iv) misalignment on evidence, v) delays in the applications

due to external reference pricing, vi) the availability of some countries to have tailored approaches for different types of medicines that can improve access (e.g., rapid assessments for orphan drugs), vii) difficulties absorbing innovative drugs when there is need for high quality health facilities, diagnostic centres and trained personnel, viii) among other factors identified [112]. With the new regulation is expected to reduce duplication of efforts for national HTA bodies and industry and avoid misalignment on clinical assessments. However, given that the members states may complement the joint clinical assessments with additional clinical analyses that may be needed in their national HTA process and with non-clinical analyses (e.g., on budget impact or cost-effectiveness), it remains to be seen whether there will be an improvement in terms of time to market access. The special funding and faster HTA processes in the case of orphan drugs, end-of-life medicines, and drugs that target unmet medical needs, as well as temporarily reimbursement schemes before EMA approval have been implemented in some of the analysed countries. The diversity of HTA procedures options depending on the drug and targeted disease and its specificities in each Member State is also factor contributing to this heterogenicity in the market access. Collaborative efforts could lead to faster and more homogeneous reimbursement systems across the EU countries, applying common rules for HTA procedures in terms of similar procedures for certain eligible drugs, common set timelines for both HTAs and sponsors, etc.

The high price of ATMPs has led to concerns about affordability for healthcare systems and patients. Payment models such as outcome-based agreements and spread payment models have been implemented to address this issue, but their implementation has been difficult due to challenges such as the definition of specific outcome variables, suboptimal data infrastructure, and a central platform to address these issues has been suggested [113][114][115][116]. The collection of RWE for ATMPs has become increasingly important in the context of outcome-based agreements [117]. On the other hand, the patient's quality of life may be improved with a single administration of ATMPs, which could also lead to long-term cost savings, rather than patients undergoing lifelong medical treatments and procedures [118][119]. RWE might play a critical role on confirming these estimations in the near future. Efforts on improving the quality of RWE have been conducted in the last years by the Agencies, to stablish its value and use for regulatory decision making [120]. The FDA issued five draft guidance in 2021, initiating the creation of a framework around the use of RWE [121]. In 2021, the EMA also published a

guideline on registry-based studies and plans to expand the use of RWE by 2025 [122][123]. In June 2022, an international workshop co-organised by EMA, FDA and Health Canada and with representatives from WHO and regulatory authorities of more than 40 countries, identified four areas of opportunities for regulatory collaboration to address common challenges and integrate RWE into regulatory decision-making [124].

The cost of producing ATMPs is expensive due to their complex manufacturing procedures, sometimes highly individualized, aside from logistically challenges. Global efforts are underway to improve and optimise the manufacturing platforms over time to reduce costs. Defining the product´s value and its price justification according to several factors related to costs and profits would be an objective approach. However, it has been recommended that sponsors should from an early stage in the product development, conduct analysis to assess the willingness to pay by consulting payers [113]. Pharmaceutical companies expect revenues to make for the investment costs of ATMP development, which are approximately around $1 billion [125]. To keep incentivising the research, the pricing and reimbursement framework should ensure the recognition and investment through a fair price (i.e., ensuring affordable access to patients, covering development, manufacturing, distribution costs and a fair and sociable acceptable profit to incentivize re-invest in new technologies) [126]. Some proposals for paying a fair price have been proposed, in which an amount of R&D costs for a new drug is used as the basis for calculating prices. Additional revenues for products considered innovative have also been discussed, which will be an incentive and offset by health and societal benefits [127]. Broad principles for innovative payment models for high-cost innovative medicines have already been addressed by the EC [128]. On the other hand, predictability of upcoming ATMP launches and associated funding and healthcare service requirements has been debated as a potential supportive tool, although pragmatically it is also seen as extremely time-consuming [129]. Interestingly, cost model for ATMPs which supports UK National Health Service (NHS) institutions to assess finance and resource implications arising from the adoption of CAR-T therapies into clinical practice has been launched [130].

The adaptation of cost-effectiveness frameworks used to assess ATMPs has also been discussed as a need to advance in the field. The incorporation of additional 'social value judgements' (beyond clinical benefit and economical assessment) has already been debated [113]. In addition, it is stated that a key limitation of the QALY approach is the inadequacy of capturing social value [131]. Our analysis showed how “health problem

and current use of technology" and "patient and social aspects" domains were considered in the ATMPs assessments in some countries, therefore having a more holistic perception of product´s value. The benefits associated with a one-time treatment offering curative potential, the reduction of healthcare utilisation, reductions in treatment administration burden, the patient and caregiver productivity gains, the improved adherence, or the value of hope provided by a cure were additional parameters capturing other dimensions of value included in the evaluation process. Therefore, there is a need to develop methodologies to adapt the cost-effectiveness frameworks used to assess ATMPs and to measure and capture the holistic product´s value during the HTA process. In addition, it is a fact that a multi-stakeholder approach, including patients, healthcare professionals and expert opinions, is increasingly being adopted during HTA value assessments to capture a holistic view of the value of treatment.

While to date the projected increase of ATMP approvals in the upcoming years will create a significant financial challenge, one of the expected long-term solutions for ATMP affordability is the biosimilar market. Biosimilar versions of ATMPs and competition will be essential to drive down prices and cope with affordability. The first concepts of "sameness" for ATMPs have already been addressed by the FDA in the context of ODD and orphan drug exclusivity [132]. However, there is the need for a well-defined regulatory framework when this situation comes, setting the reference standards to stablish similarity and for approval as it was done for mAbs. This is foreseen as another coming challenge, given the difficulty that might represent for highly individualized autologous and allogenic therapies to ensure clinical equivalence [133][134].

Finally, it should be mentioned that all these efforts being done are necessary to anticipate the expansion of ATMPs, not only on the orphan field but to high-prevalent diseases, and where it is expected that patients will have rapid access to innovation while health systems are financially sustainable. It has been estimated that in total, about 350.000 patients will have been treated with 30 to 60 products by 2030, and in 2030, about 50.000 patients per year may be treatable with ATMPs in the US [135].

Limitations and suggestions for future research

Some limitations of the studies presented in this thesis need to be considered.

First, this thesis represents a snapshot of the ATMPs field within the timeframe that this work was conducted. Given how rapidly this field is evolving, the outcomes of this research need to be interpreted within the context and time that this research was performed. In terms of the three pillars analysed – regulatory, clinical and market access – new approaches and more efficient ways to move forward are being proposed or already being implemented at the time that this work is being written, changing the landscape of the field, the agency recommendations and policies, and the manner to proceed of the developers.

Second, the limited number of approved ATMPs so far, made that the studies included a small sample size to be analysed. This fact might imply a higher variability of the results, as well as not sufficient evidence to compare these results with other types of biological or chemical therapies or within different therapeutic areas. On the other hand, this thesis focuses primarily on the approved ATMPs due to the aim of this work, excluding those in that are currently under development. Further analysis including therapies under development could provide with a more confirmatory outcomes of the findings for certain points. In addition, this research consists of cross-regional comparison and publicly available information is sometimes limited or not available for some of the regions analysed.

Third, for the analysis of the NHA evaluations of approved ATMPs, eight EU countries were analysed. Therefore, the study does not cover all the EU Members States and it cannot be generalised to other European regions. Moreover, the lack of transparency and publicly available information for some of the countries analysed reduces the sample size for some of the items analysed.

This study analysed the approved ATMPs until 2022. These drugs represent the "best-case" scenario of drug development given their approval, and despite all the challenges identified. Some ATMPs have submitted a MAA but have not reached the market given that were withdrawn or received a negative opinion. Analysing the major issues that led these therapies to a negative opinion or a withdrawal during the MAA assessment from a product´s quality, nonclinical and clinical perspective, would help to consider these challenges at an earlier stage for other developers. While some studies have been done in this line [136][137], an updated identification and a more detailed categorisation of those challenges, not only would provide a better understanding and the knowledge in the field

but would help the developers to inform optimised development strategies and help the agencies on suggesting re-designed or new recommendations. On the other hand, there are other advanced therapies that have withdrawn from development even before they could apply for an MAA. Analysing the causes of this failure by type of ATMP, i.e., gene therapies versus cell/tissue engineering therapies, and by therapeutic field would also contribute to further understand the development challenges of the field.

Finally, performing a study to analyse the key HTA considerations that influenced the reimbursement among all European Member States with a standardised methodology, would be the basis for understanding the differences of the NHA-frameworks and decisions in the EU. On the other hand, with the new EC regulation, studying the level of alignment obtained on clinical assessments across regions and how this regulation impacts at reimbursement level, and in terms of patient accessibility and optimisation time of market access is another analysis that would be key in the near future. To compare both proposed analyses would also help to have a more detailed picture on how this new regulation can contribute to the EU harmonisation.

Conclusion

1. ATMPs are regulated as biological products with specific regulatory framework for their development in the EU, the US, and Japan. Specific agency committees have been stablished for these types of products in the three regions.

2. The regulatory terminology used on the criteria to define an ATMP and their sub-classification reveals some differences between the EU, the US and Japan, but ultimately has no impact on overall classification as an ATMP.

3. ATMPs that are also GMOs undergo an ERA procedure to obtain the MA. The EU and Japan also require this procedure at multiple stages of development, while in the US might be exempted. The EU is currently attempting to streamline GMOs environmental procedures.

4. Although in the EU and the US the available regulatory procedures may differ, the main regulatory milestones achieved for the approved ATMPs are similar, except for the evaluation time for MAA, the type of MAA and the number of authorized products.

5. Japan has implemented a specific regulation for ATMPs (called regenerative products), including adaptive licensing and enabling shortcuts to speed up clinical development.

6. To date, most authorised ATMPs are targeting rare and life-threatening diseases, seriously debilitating diseases and/or unmet needs, which have justified accelerated clinical developments and authorisations in the analysed regions.

7. Most authorised ATMPs in the EU and Japan are based on small, adaptive, open-label, uncontrolled and single-arm pivotal trials using single and intermediate variables to evaluate primary efficacy outcomes. This fact has led to methodological weaknesses in their pivotal clinical trials, which in turn has resulted in less comprehensive clinical data to robustly assess the benefit/risk of the product.

8. The majority of the ATMPs were reimbursed in several Western European countries after complex and long negotiations, with uncertainty on added therapeutic value,

requiring managed entry agreements and requiring around 9-17 months to achieve a recommendation.

9. The considerations that influenced the reimbursement decision making included several domains, such as “health problem” and “current use of technology”, “patient and social aspects”, “clinical efficacy”, “clinical safety” and “cost- and economic effectiveness”, with unknown weight on decision for each of these domains.

10. Flexibility on conventional regulatory requirements for these therapies, lack of global harmonisation on development requirements, and lack of harmonisation across the EU countries in terms of market access and time to patient access to the product is the current situation.

11. There are several scientific, clinical, and regulatory challenges that need to be overcome to advance in the ATMPs field to ensure high-quality development and affordable treatments. These challenges include improving understanding of ATMPs' efficacy and safety, developing reliable manufacturing processes, optimizing real-world evidence, simplifying regulatory processes, and determining reasonable pricing, among others.

12. Progressive iteration of the science, establishing new standards for ATMPs development with the aim to ensure consistency in clinical development and the reproducibility of knowledge is required not only to increase the evidence generation for approval but to set principles to achieve translational success in this field.

Summary of the proposed recommendations:

- Definition and classification of ATMPs
  - ✓ Promote global convergence among health authorities on the definition and classification of ATMPs (for both developed and developing countries).
  - ✓ Stablish "universal" definitions and adopt globally the regulatory concepts of "minimal manipulation" and "homologous use" from the EU/US to distinguish between human cells and tissues for medical use and ATMPs.

- ATMP regulatory framework
  - ✓ Promote the adoption of regulatory frameworks from regions with experience in the field (e.g., the US/EU) in low- and middle-income countries with no stablished framework for these therapies.
  - ✓ Promote mutual recognition agreements, recognition/reliance routes from experienced regulatory agencies, such as the FDA or EMA, and the adoption of the current global guidelines by national health authorities with less experience in the field or less resources.

- Regulatory development
  - ✓ Encouraging that the developers plan a global regulatory strategy at early stage to maximise the benefits of current available procedures across different regions.
  - ✓ Regulatory fitness and convergence of regulatory procedures would facilitate this global plan.
  - ✓ Promote early interactions with the agencies (INTERACT, ITF and informal NCAs meetings), common SA interactions at each development milestone, EU SNSA, and parallel interactions (EMA-HTA and/or EMA-FDA).
  - ✓ Conduct risk-based approach during product development to design a tailor-made ATMP development program to determine the extent of nonclinical and clinical data necessary for an MA and to justify any deviation from the requirements.
  - ✓ Submission of mature dossiers at MAA stage to allow feasibility of accelerated MAA assessments.
  - ✓ Capturing learnings and developing strategic recommendations by the regulatory agencies to increase knowledge dissemination and to shape the regulatory requirements

as the field evolves. Timely and dynamic dissemination of this knowledge. Annual or bi-annual reports from main agencies (EU, US and Japan) categorising the issues by area and type of ATMP would be highly valuable.

- ✓ Extension, simplification and streamline the current regulatory procedures at national level and through global regulatory convergence. Optimise procedure timelines. Promote the harmonisation of regulatory requirements to facilitate the clinical investigation and global commercialization of ATMPs.
- ✓ Keep joint efforts to implement global standards for manufacturing, nonclinical and clinical development, to develop a common understanding in the field.
- ✓ Promote the harmonization of GMO framework across regions. Definition of "universal" principles as when an ERA is required during clinical development. Mutual recognition procedures of GMO risk assessment from reference regions to ease multinational trials.
- ✓ Encouraging the increase of specialists in all areas of the ATMP field and the increase of agencies resources.

- Clinical development
  - ✓ Achieving clinical trial designs that can demonstrate success over the current clinical practice, and with clinically relevant endpoints.
  - ✓ When randomised and controlled trials are not possible: encourage robust external comparative data, clear justification for a non-randomized trial and promote early dialogue with regulatory agencies and HTAs at the design stage.
  - ✓ Continued efforts on developing and promoting strategies to increase the efficiency of ATMP clinical development through:
    - o improved statistical methodology, innovative designs master protocol, platform trials or umbrella and basket trials, etc.
    - o dynamically disseminating recommendations and sharing lessons learned by the agencies.
    - o further guidance from the HTAs on the methodologies for validation and acceptability of surrogate endpoints and monitoring how the new EC regulation can contribute on the alignment and acceptability of surrogate endpoints across the EU HTAs.

- ✓ Acquire more knowledge on durability and long-term safety with ATMPs over time. Optimise long-term data requirements over time in terms of length for follow up or type of endpoints to be collected.
- ✓ Continued efforts on ways to optimise collecting and managing long-term data by the agencies and the sponsors.
- ✓ Continued efforts on stablishing new standards for ATMPs development with the aim to ensure consistency in clinical development, and the reproducibility of knowledge to increase the evidence generation and to set principles to achieve translational success in the field.
- ✓ Maintain efforts to develop an international and harmonised ATMP RWE framework.

- Market access
  - ✓ Keep working on harmonisation of evaluation systems and HTA assessments across the EU Member States. Monitoring the advantages of the new EC regulation (Regulation 2021/2282) in terms of market access, assessment of product therapeutic value and transparency.
  - ✓ Collaboration to reduce the lag time between EU MA and patient access to the drug. Incentivise collaborative efforts to improve faster and more homogeneous reimbursement systems across the EU countries, applying common rules for HTA procedures in terms of similar procedures for certain eligible drugs, common set timelines for both HTAs and sponsors, etc.
  - ✓ Development of new economic and payment models for ATMPs. Adapt the cost-effectiveness frameworks to assess ATMPs. Develop methodologies systematically measure the social value of these medicines during the HTA assessment.
  - ✓ Keep working on the development of standardised cost models for ATMPs to assess finance and resource implications of ATMP adoption into the clinical practice.
  - ✓ Increase transparency of price-setting methods from the authorities and development investment costs and profit levels from the companies.
  - ✓ Definition of a fair price concept to keep incentivising the research of innovative drugs and making drugs affordable.

Author´s note

As stated throughout this work, this thesis aims to take a snapshot of the current state of the field of ATMPs. Hopefully, the field will evolve to some point where the unmet needs will be covered by these therapies, where the high prevalence's diseases will be cured with universal and "off-the-shelf" therapies, and where these therapies will not be any longer a breakthrough but a clinical practice routine. It is then, when this thesis will become completely outdated, but it will live on as a reminder of how the field of advanced therapies has evolved and the challenges that had to face to get to this point… it is then when perhaps this thesis will serve as a reference for the introduction of other theses presenting the history of the field. My hope is to be able to see this within a few decades.

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ANNEXES

ANNEX 1: Publications Overview

Publications related to this thesis

Iglesias-Lopez C., et al. Regulatory Framework for Advanced Therapy Medicinal Products in Europe and United States. **Front Pharmacol. 2019**;10:921. doi: 10.3389/fphar.2019.00921. Erratum in: Front Pharmacol. 2020;11:766. doi: 10.3389/fphar.2020.00766

Iglesias-Lopez C, Obach M, Vallano A, Agustí A, Montané J. (2019). Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States, **Crit. Rev. Toxicol. 2019 Aug**;49(7):580-596. doi: 10.1080/10408444.2019.1689380.

Iglesias-Lopez C., et al. Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. **Cytotherapy. 2021 Jan** 19:S1465-3249(20)30959-2. doi: 10.1016/j.jcyt.2020.11.008. Epub ahead of print -

Iglesias-Lopez C., et al. (2021). Methodological Characteristics of Clinical Trials Supporting the Marketing Authorisation of Advanced Therapies in the European Union. **Front Pharmacol. 2021 Nov** 29;12:773712. doi: 10.3389/fphar.2021.773712.

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Other Publications

Iglesias-Lopez C. Temporary derogation from European environmental legislation for clinical trials of genetically modified organisms for coronavirus disease 2019. **Cytotherapy. 2021**;23(1):10-11. doi: 10.1016/j.jcyt.2020.09.005

Conference Abstracts and Communications

Iglesias-Lopez C., et al. (2019). Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: Comparison between the European Union and the United States. **Human Gene Therapy.** 00:A2–A221. DOI: 10.1089/hum.2019.29095.abstracts. **European Society of Gene and Cell Therapies (ESGCT) November 2019 (Barcelona).**

Iglesias-Lopez C., et al. (2021). Methodological features of pivotal clinical trials for the current authorised advanced therapies medicinal products in the European Union. **Cytotherapy 23 (2021)** S17–S207. **International Society of Gene and Cell Therapies** (**ISCT) 2021 (New Orleans Virtual).**

Iglesias-Lopez C. (2021). Clinical and regulatory strategies to support the marketing authorisation of regenerative medicine products in Japan. **European Society of Gene and Cell Therapies** (**ESGCT) October 2021 Annual Congress.**

Recognitions

- **Abstract among ones with the highest scores**
  International Society of Gene and Cell Therapies (ISCT) 2021.

  Abstract: Iglesias-Lopez C., et al. (2021). Methodological features of pivotal clinical trials for the current authorised advanced therapies medicinal products in the European Union. Cytotherapy 23 (2021) S17–S207.

ANNEX 2 - Chapter 2.3: Temporary derogation from European environmental legislation for clinical trials of genetically modified organisms for coronavirus disease 2019

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Abstract

Attempts to streamline environmental procedures for those products containing or consisting of GMOs among the EU Member States are ongoing but still need to be further developed. These procedures can be complex, resource-intensive and time-consuming. Some candidate vaccines currently under development for Coronavirus disease 2019 (COVID-19) include genetically modified viruses, which may be considered GMOs. Given the public health emergency caused by the COVID-19 outbreak, on July 15, 2020, the European Parliament approved a temporary derogation of the European environmental requirements to facilitate that those clinical trials with GMOs intended to treat or prevent COVID-19 can start as soon as possible in Europe. This measure has been very controversial, since it could entail risks to human health and the environment, as well as could be seen as unfair for other products targeting unmet medical needs. With the adoption of this measure, the bottlenecks and obstacles for the development of innovative GMO-based medicines in the EU that the environmental legislation entails have become even more evident.

Environmental legislation in the European Union

Biological therapies comprise a wide range of product types, including advanced therapies and vaccines. GTMPs are cutting-edge therapies and promise to treat indications ranging from rare genetic diseases to cancers. GTMPs treat disease by replacing, inactivating or introducing a recombinant nucleic acid sequence into the body, typically using a viral vector or through other carrier molecules. On the other hand, vaccines are a heterogeneous class of biological medicinal products aimed at the treatment or prophylaxis of infectious diseases and include not only classic vaccines consisting of attenuated or inactivated micro-organisms but also antigens produced through recombinant DNA technology, chimeric micro-organisms and live recombinant viral vectored vaccines. When a biological entity is capable of replication or of transferring altered genetic material, as is the case with many GTMPs and some vaccines, it is also considered a GMO. The clinical use of these therapies might pose a risk since these products may enter the environment by unintended dispersal or via excretion by the patient. This dissemination could potentially spread the GMO further, and it could undergo genetic or phenotypic changes, infect, reproduce, remain latent, compete with existing species or transfer its genetic material to other species, impacting human health and the environment. As a result, medicinal products consisting of or containing a GMO are regulated by environmental and human drug legislation in the EU, and all potential risks must be evaluated by conducting an ERA during the product's development. To conduct a clinical trial with a product based on a GMO, the sponsor needs to obtain not only authorization from the ethics committees and competent NHAs where the study is going to take place but also an additional authorization to "release" or administer the GMO-containing medicinal product in that trial. To obtain this authorization, an ERA must be assessed and endorsed by the government authorities of each Member State in charge of GMO evaluations and responsible for the environment in each country. In recent years, especially with the increased development of advanced therapies, the lack of harmonization among the European countries and the burden these environmental procedures entail for the sponsor have become notably evident. Although there is a common European framework in place, the environmental EU directives have been implemented differently across European countries. This fact has resulted in a resource-intensive process, above all for multicentre studies, as sponsors of clinical trials need to submit multiple requests for environmental authorizations to multiple competent authorities in different Member States, each with different requirements and ERA procedures that vary greatly from one Member State to another. The result is the generation of delays in clinical development, an increase in

logistical hurdles at country level and higher costs [1]. The European Commission recognized in 2018 the handicaps of these procedures in the EU and initiated several dialogues with the NHAs with the aim to unify the interpretation of the GMO framework. As a result, common position documents for genetically modified human cells and for products containing adeno-associated viruses were recently endorsed by most NHAs. Nevertheless, this approach is still not enough, and this procedure remains substantially burdensome.

Temporary changes in environmental legislation due to the coronavirus disease 2019 pandemic

Coronavirus disease 2019 (COVID-19) has rapidly developed into a worldwide pandemic with a significant health impact, and clinical trials that aim to discover an effective vaccine are ongoing. Potential vaccines currently under development include genetically modified viruses, which are classified as GMOs [2,3]. Given the public health emergency caused by the COVID-19 outbreak, on July 15, 2020, the European Parliament and the EU Council granted a temporary derogation from the environmental requirements to allow clinical trials with GMOs intended to treat or prevent COVID-19 to start as soon as possible, without the delays generated by the different national implementations of environmental Directives 2001/18/EC and 2009/41/EC and their diverse requirements [4,5]. Although these two directives aim to ensure the protection of human health and the environment through the assessment of the risks posed by the deliberate release or contained use of GMOs, it has been decided that the protection of public health—through accelerating the deployment of a COVID-19 vaccine - prevails in this unprecedented situation. Pivotal trials with promising candidates will be conducted in several countries, and without this measure, European clinical trials could fall behind those of the US or China, delaying early access to these product candidates. The derogation will apply as long as COVID-19 is regarded as a public emergency, but sponsors should implement appropriate measures to minimize the foreseeable negative environmental impact resulting from the release of the investigational medicinal product into the environment. Compliance with Good Manufacturing Practices and an ERA of the product will still be mandatory before marketing authorization is granted. This temporary derogation has been very controversial. On the one hand, some expert groups have pointed out that this measure could be irresponsible since the development of vaccines based on GMO viruses might involve risks to human health and the environment, and these risks are not necessarily covered by the general safety protocols aimed at protecting participants [6]. On the other hand, supporters of the measure argue that a clinical

study with only small quantities of an investigational product and a limited number of patients should not have a significant cumulative effect on the environment. The same

argument can be found in US environmental regulations [7], whereby most investigational products are categorically excluded from the requirement to submit an ERA, but this principle has not been applied in the EU thus far, and massive trials including thousands of participants are expected for phase 3 studies with these vaccine candidates. One of the potential measures that could have been taken is to shorten the period to get the authorization for COVID-19 clinical trials, as was suggested by the Netherlands, which is the second Member State with the highest number of experimental GMO medicinal products approved under deliberate release [8]. However, this proposal does not solve the time-consuming process of preparing and submitting multiple applications with different requirements to several EU Member States.

Finally, this temporary derogation could also be seen as unfair to other products and/or disease areas. There are promising advanced therapies and vaccines under development consisting of GMOs, targeting severe orphan indications for paediatric populations to highly prevalent diseases such as HIV and cancer, the latter being one of the top 10 causes of death in the EU and the second leading cause of death globally [9]. These products still have to deal with the intricacies of these environmental procedures and the delays this implies for the starting of clinical studies in the EU, ultimately postponing patients' early access to these products.

Conclusions

Attempts to streamline environmental procedures among EU Member States have so far been unsuccessful. With the temporary derogation from the environmental requirements for products intended to treat or prevent COVID-19, the bottleneck the environmental legislation represents in the EU for the development of innovative GMO-based medicines has become even more evident. Further efforts are needed to centralize or rationalize this procedure, with the main objective of enabling patients to benefit from innovative medicines for a variety of diseases as soon as possible.

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ANNEX 3: Original publications

frontiers in Pharmacology

POLICY AND PRACTICE REVIEWS
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Regulatory Framework for Advanced Therapy Medicinal Products in Europe and United States

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Advanced therapy medicinal products (ATMPs) are a fast-growing field of innovative therapies. The European Union (EU) and the United States (US) are fostering their development. For both regions, ATMPs fall under the regulatory framework of biological products, which determines the legal basis for their development. Sub-classifications of advanced therapies are different between regions, while in EU, there are four major groups, i.e., gene therapy, somatic cell therapy, tissue-engineered therapies, and combined advanced therapies; in US, the sub-classification covers two major groups of products, i.e., gene therapy and cellular therapy. The inclusion criteria that define a gene therapy are equivalent in both regions, and the exclusion criteria are directly related to the indications of the product. In the EU, there is a clear differentiation between cell- and tissue-based products regarding their classification as advanced therapies or coverage by other legal frameworks, whereas in US, there is a broader classification about whether or not these products can be categorized as biologic products. Both in EU and in US, in order to classify a cell- or a tissue-based product as an advanced therapy, it must be ensured that the processing of the cells implies a manipulation that alters their biological characteristics, although the term of manipulation in US differentiates between structural and non-structural cells and tissues. The regulatory terminology used to define ATMPs and their sub-classification reveals some differences between EU and US.

Keywords: genetic therapy, tissue engineering, cell- and tissue-based therapy, biological products, biological therapy, legislation and jurisprudence, United States Food and Drug Administration, Europe

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INTRODUCTION

Advanced therapy medicinal products (ATMPs) comprise a category of innovative and complex biological products, which in most cases require extensive and complicated preclinical and clinical developments. This complexity has been observed since the idea of transferring genetic material to cure a genetic disease was foreseen decades ago. The first ATMP product approved in the European Union (EU) came in 2009 with the authorization of ChondroCelect®, a tissue-engineered product indicated for the treatment of cartilage defects (European Medicines Agency, 2017a). In United States (US), the first approved ATMP came out 1 year later with PROVENGE®, a somatic cell therapy for the treatment of some prostate cancers (U.S. Food and Drug Administration, 2019a). The first authorized gene therapy was launched in 2012, when Glybera® achieved marketing authorization in EU (European Medicines Agency, 2012).

The delay between the theoretical concept of an ATMP and the first clinical trials that lead to a new treatment approval may be due to the multiple challenges that arise from the nature of ATMPs, including not only scientific and technical challenges but also regulatory ones (Ten Ham et al., 2018). The first step in their development is the definition of the product, and consequently, its classification. In both in EU and the US, there is a broad legal framework, ranging from medicinal products consisting of chemical substances to biological substances; the latter of which includes a wide range of possible products. In this sense, the classification of a potential biological product is often not so trivial, and in some cases, it may be difficult to discern the line between different biological subcategories. The correct classification of a product at an early stage of development is a critical point, since it will determine the regulatory framework and the European and American recommendations to follow throughout the whole development plan of the product in each region.

This article aims to review the legal frameworks in the EU and US for ATMPs, as well as the criteria to be met to define a product as such. The similarities and differences that exist between both regions are discussed in order to identify those nuances that may affect the development of an ATMP. A specific search for official regulatory documents concerning medicinal products for human use with a specific focus on ATMPs, such as legislation, guidelines, presentations, and reports, from the websites of the European Medicines Agency (EMA) and Food and Drug Administration (FDA) competent authorities was carried out until 31st December 2018. Key terms that covered the regulatory framework for advanced therapies and other products were used to navigate the websites of these competent authorities, including: terms describing advanced therapies (advanced therapy, advanced therapies, regenerative medicine, cell therapy, cell-based therapy, human cellular therapy, stem cells, gene therapy, tissue engineering, human cell therapy, human somatic cell therapy), information on the regulatory framework, and the definition and classification of advanced therapies in EU and US.

REGULATORY FRAMEWORK FOR THE CLASSIFICATION OF ADVANCED THERAPIES

Medicinal products for human use in EU are governed by Directive 2001/83/EC and Regulation 726/2004/EC. Biological products comprise many diverse product types, including immunological medicinal products (i.e., vaccines, toxins, serums, and allergens), medicinal products derived from human blood and human plasma (i.e., albumin, coagulation factors, and immunoglobulins of human origin), biotechnology products such as antibodies, and ATMPs, which are the focus of this paper (European Union, 2003a). ATMPs consist of products that contain recombinant nucleic acids or engineered cells and/or tissues. These products are divided into four subcategories: somatic cell therapy medicinal products (SCTMP), tissue-engineered products (TEP), gene therapy medicinal products (GTMP), and the combined ATMPs (cATMPs). These last ones consist of one of the first three categories combined with one or more medical devices as an integral part of the product (European Union, 2007). In EU, there is a clear differentiation between cell-based products considered as advanced therapies, and cell-based therapies covered by other legal frameworks such as the blood system or transplant laws, where these cells are not considered a medicinal product, and the active substance, i.e., human cells and tissues, cannot be commercialized or manufactured on an industrial scale for ethical and legal reasons (European Union, 2003b; European Union, 2004; European Union, 2010). The classification of an ATMP as a biological product will determine the wider regulatory framework by which the requirements of the development and the marketing authorization application are defined. These are to be read in conjunction with the specific framework for ATMPs, Regulation 1394/2007/EC, which came into force on December 30, 2008. This regulation provides the overall framework on ATMPs for those products, which are intended to be placed in the market of EU Member States. In addition, Directive 2009/120/EC updated the definitions and detailed scientific and technical requirements for advanced therapies. The cATMPs are not only regulated under the guidelines of medicinal products but also of medical devices. On 25 May 2017, two new regulations on medical devices came into force (European Commission, 2017a).

For the development of advanced therapies in EU, the clinical trial applications are submitted individually to the national competent authorities where the trial will take place. However, for the marketing authorization, all ATMPs are evaluated *via* centralized procedure ensuring that they benefit from a single evaluation and authorization applicable across the EU. There are two committees responsible for the validation and scientific evaluation for product approval: the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP) (European Medicines Agency, 2018a). The CAT is the EMA committee responsible for classifying; assessing the quality, safety, and efficacy of ATMPs; and following scientific progress in the field. This committee's main responsibility is to prepare a draft opinion on each ATMP application submitted to the EMA in order to support the final decision by the CHMP. This marketing authorization *via* the centralized procedure may be granted in three ways: standard marketing authorization, conditional marketing authorization (when an innovative medicine addresses an unmet medical need yet a positive benefit-risk balance by sufficient clinical data is demonstrated), and marketing authorization under exceptional circumstances in those extreme situations where a disease is rare or a clinical endpoint is difficult to measure (Detela and Lodge, 2019). Regarding classification, the CAT offers the confirmation that a medicine meets the scientific criteria to be classified as an ATMP. On the other hand, the regulatory authority in charge of medical devices is the national appointed bodies of each EU member. In the case of cATMP, the CAT interacts with the notified bodies in order to prepare the draft opinion on a cATMP (European Medicines Agency, 2011a).

In US, like in EU, advanced therapies are regulated as biologic products. In legislative terms, biological products comprise the following categories: i) the group of allergenics that includes allergen extracts, allergen patch tests, and antigen skin tests;

ii) blood and blood products, iii) vaccines, iv) xenotrasplants, and v) cellular and gene therapy products (CGTs), which constitutes the group of advanced therapies and encompasses two sub-categories of products. Advanced therapies should not be confused with other legislative category of products called "human cells, tissues, and cellular and tissue-based products" (HCT/Ps) and defined as "articles containing or consisting of human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient" (U.S. Food and Drug Administration, 2019). HCT/Ps are not considered biological products. On the other hand, combination products include products that are comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic. The definition is broad and takes into account the packaging and whether all components of the product are needed to achieve the intended use, indication, or effect (U.S. Food and Drug Administration, 2018a). In 2016, the 21st Century Cures Act (Cures Act) was signed into law in order to help accelerate medicinal product development and bring new therapies to the market faster and more efficiently. This Act established a new expedited product development program called the Regenerative Medicine Advanced Therapy (RMAT) (U.S. Food and Drug Administration, 2018b). Although it is not a type classification *per se*, yet a designation that offers a new expedited option for evaluation of the product, it is considered worth mentioning it here as a part of the US advance therapy classification. A regenerative medicine therapy is defined as: i) a cell therapy, therapeutic tissue-engineering product, human cell and tissue product, or any combination product using such therapies or products, explicitly excluding HCT/Ps; ii) that is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and iii) if the preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition (U.S. Food and Drug Administration, 2019b). Therefore, this definition implicitly includes advanced therapy medicinal products. A combination product can also be eligible for RMAT designation when the biological product component provides the primary mode of action. These products would be denominated as RMAT-based combination products. More than 30 out of 90 RMAT designation requests have been granted until 2019 (U.S. Food and Drug Administration, 2019c).

The US federal regulatory framework consists of two main statutes, Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Services Act (PHSA), which provide the Food and Drug Administration (FDA, the federal regulatory medicines agency in the US) with the legal authority to regulate human medicinal products including drugs, biological products, and devices. Biological products, and therefore advanced therapies, are regulated under section 351 of the PHSA and under the FDCA, because most biological products also meet the definition of "drugs" cited in this Act. FDA regulations are contained in the Code of Federal Regulations (CFR), which provides details on how the FDA implements the activities that are defined in the PHSA and FDCA. Regulations for biological and medical devices are found in Title 21 of the CFR (Lee et al., 2015; U.S. Title 42 The Public Health and Welfare, 2019). In US, the applicants need to submit an investigational new drug (IND) application in order to obtain a clinical trial approval (U.S. Food and Drug Administration, 2017a), and Biologics License Application (BLA) to obtain a marketing authorization (U.S. Food and Drug Administration, 2018c). The marketing authorization can be standard, under a Priority Review procedure or under an Accelerated Approval. In the Priority Review, the application is reviewed within 6 months compared to 10 months under standard review, and it is addressed to those drugs that, if approved, would bring about significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications. An Accelerated Approval allows drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint, if clinical benefit has been demonstrated (U.S. Food and Drug Administration, 2018d).

Within the FDA, responsibilities for drugs, biologic products and devices are organized in eight different centers. The Centre for Biologics Evaluation and Research (CBER) has jurisdiction over a variety of biological products, including blood and blood products, vaccines and allergenic products, and cellular, tissue, and gene therapies, as well as some related devices. Within the CBER, the responsibility for advanced therapies falls to the Office of Tissues and Advanced Therapies (OTAT), formerly known as Office of Cellular, Tissue, and Gene Therapies (OCTGT). OTAT comprises five divisions in addition to the Office of the Director (U.S. Food and Drug Administration, 2017b). Combination products are assigned to a FDA center that will have primary jurisdiction for its pre-market review and regulation. For combination products, CBER usually regulates medical devices related to licensed blood and cellular products by applying appropriate medical device laws and regulations (U.S. Food and Drug Administration, 2018e). This assignment is performed by the Office of Combination Products through a designation process (U.S. Food and Drug Administration, 2018f).

The current European and American legislations for biological products are summarized in **Table 1**. One of the main differences between EU and US is that the FDA oversees clinical trials, whereas the EMA does not. In terms of marketing approval, each region has specific legislations depending on the legal categorization of the product; in EU, they are licensed under article 8.3 of Directive 2001/83/EC, while in US, ATMPs are licensed under section 351 of the PHS Act. Both Agencies have their own specialized committees to evaluate advanced therapies. In US, the approval time for a standard BLA may extend up to 10 months from receipt date (U.S. Food and Drug Administration 2017c), while in EU, the assessment leads to an opinion from the CHMP by day 210 and European Commission by day 277 (around 7 months) (European Medicines Agency, 2016b). However, these timelines depend on the different types of marketing authorization available in each region. Among advanced therapies, product sub-classifications are slightly different between regions. While in the EU, an ATMP can be sub-classified into four major groups, i.e., GTMP, SCTMP, TEP, or cATMP, in the US the sub-classification groups are broader, covering two groups of products, i.e., gene therapy and cellular therapy products. Given that the sub-classification in the EU is more precise, there are products that could fall into two categories, and in some cases,

TABLE 1 | Legal and regulatory framework of biological products in United States and European Union.

European Union			United States		
Type of product	**Legal framework**	**Regulatory organism**	**Type of product**	**Legal framework**	**Regulatory organism**
Advanced therapy medicinal products: Gene therapy products Cell therapy products Tissue-engineered products	Directive 2001/83/EC (relating to medicinal products for human use) Directive 2009/120/EC (relating to medicinal products for human use as regards advanced therapy medicinal products) Regulation 726/2004/EC (community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency) Regulation 1394/2007/EC (on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004)	Clinical trials are under national competent authorities of each member state where the clinical trial will take place. Product positive opinion: CHMP Draft opinion: CAT	**Human somatic cell therapy and gene therapy products**	Section 351 of the PHSA and FDCA and Title 21 CFR 600-680 (Regulation on Biologics) (21 CFR 1271; prevent the spread of infection diseases) RMAT designation: section 3033 of the 21st Century Cures Act (21 U.S.C. 356[g](8))	CBER and OTAT

CAT, Committee for Advanced Therapies; CBER, Centre for Biologics Evaluation and Research; CHMP, Committee for Human Medicinal Products; FDCA, Federal Food, Drug, and Cosmetic Act; OTAT, Office of Tissues and Advanced Therapies; PHSA, Public Health Services Act; RMAT, Regenerative Medicine Advanced Therapy Designation.

the assignment in a particular subtype is not so trivial. In the case of US, the difficulty might arise when classifying the product as an HCT/Ps or as a biological product that falls beyond minimal manipulation and/or homologous use. Finally, another difference between regions is related with terminology; in the US, the term "advanced therapy" is not a common term used in legislative and regulatory documents, and these products are collectively referred as "CGT products."

To ensure a correct classification, both the EMA and the FDA have made scientific advice available to the applicants to clarify or corroborate this classification prior to further advancing the development. In EU, one of CAT's activities is to clarify the classification of a given product, above all when the product could fall in two different categories (European Medicines Agency, 2013a). It is always advisable to obtain CAT's opinion about a particular product, since the features of each product can be unique, and the corroboration of a product as an advanced therapy might add value to attract potential investors. On the other hand, in US, the Tissue Reference Group is the working group within the FDA that provides recommendations to stakeholders concerning the application of the criteria for HCT/Ps. For both consultations, a minimum of information on the product is required in order to obtain its proper classification, such as the source of the product, the intended use of the product, or description of how the product is processed from the time of recovery to the point of use of step-by-step (U.S. Food and Drug Administration, 2018g). Another consultation option at an early stage of development is to hold informal meetings with the Agencies in order to obtain informal exchange of information and receive advice and recommendations on the development process in terms of scientific, regulatory, and legal issues. For complex products, this type of meeting might also be helpful in order to obtain the first legal and scientific feedback on the classification of the product. For EU, these meetings are called Innovation Task Force (ITF) briefing meetings (European Medicines Agency, 2013a), while the equivalent meeting in US is called Initial Targeted Engagement for Regulatory Advice (INTERACT) meetings (U.S. Food and Drug Administration, 2018h). The ATMP classification procedures are valuable to address questions on borderline classifications, commonly raised for combined ATMPs, to confirm the medicinal product framework and determine what type of ATMP a product is, and therefore, develop the product under the specific dossier requirements and quality guidances.

Finally, it is worth noting that the main EU and US Agencies have launched expedited development programs in order to enable new medicines reach the market as early as possible. The medicines that are eligible to these programs are those that can justify a potential major public health interest, i.e., they target conditions where there is an unmet medical need or have the potential to bring a major therapeutic advantage to patients. Since ATMPs usually offer new treatments for currently incurable conditions or improve existing treatments, most ATMP are eligible to these types of accelerated programs. The FDA has developed the Breakthrough Therapy and Fast Track designation programs (U.S. Food and Drug Administration, 2018d), while the EU launched the adaptive licensing and afterwards the PRIority Medicines (PRIME) designation scheme. The difference between the Breakthrough Therapy and Fast Track designations falls on the qualifying criteria for the designation. In the former, clinical or nonclinical data should demonstrate potential to address an unmet medical need, whereas in the latter, preliminary clinical evidence indicates that it may demonstrate substantial improvement over available therapies on a clinically significant endpoint(s). The EU PRIME and the US Breakthrough Therapy designations share the same objective (timely patient access to innovative medicines) but have a different legal basis; hence, comparison and harmonization are difficult. However, since late 2016, FDA and EMA have worked together to track submitted requests for PRIME and Breakthrough Therapy designations and compare final review outcomes, including specific reasons for a designation request denial (European Medicines Agency, 2018b).

Throughout 2019, a database utilizing publicly available and company provided information to create a public list of RMAT recipients, as well as other expedited approval designations awarded in the US, EU, and Japan, is foreseen to be launched (Regulatory Affairs Professional Society, 2019).

CLASSIFICATION CRITERIA IN EUROPE AND UNITED STATES

Gene Therapies

Some examples of gene therapy products include *in vivo* therapies, such as nucleic acids or genetically modified microorganisms (e.g., viruses, bacteria, fungi), and *ex vivo* therapies like genetically modified human cells or human genome editing. In the EU, in order to classify a product as a gene therapy, all of the following inclusion criteria must be met (European Medicines Agency, 2015): i) the product has to be a biological medicinal product according to Directive 2003/63/CE; ii) the product must contain recombinant nucleic acid(s); iii) the recombinant nucleic acids should be of biological origin, regardless of the origin of the vector system used; iv) the recombinant nucleic acid is used in or administered to human beings in order to regulate, repair, replace, add, or delete a genetic sequence; and v) the recombinant nucleic acid(s) should be directly involved in the therapeutic, prophylactic, or diagnostic effect of the product (**Table 2**). It should also be noted that, according to the ATMP Regulation (European Union, 2007), a product that may fall within the definition of a SCTMP or a TEP, and a GTMP, shall be considered a GTMP, since it is the one that can pose the most safety concerns.

In the US, the inclusion criteria that must be met are the following (U.S. Department of Health and Human Services, 1993; U.S. Department of Health and Human Services, 1998): i) the product meets the definition of "biological product" in section 351(i) of the PHSA [42 U.S.C. 262(i)]; ii) the product has to be applicable to the prevention, treatment, or cure of a disease or condition of human beings; iii) the product mediates its effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences; and iv) the product can work through several mechanisms: replacing a disease-causing gene with a healthy copy of the gene, inactivating a disease-causing gene that is not functioning properly, or introducing a new or modified gene into the body. Recombinant DNA materials used to transfer genetic material for such therapy are considered components of gene therapy (**Table 3**).

Therefore, despite the different terminology used, the inclusion criteria that define a GTMP are equivalent in both regions: the product must be a biological product that contains "recombinant nucleic acid(s)" (term used in EU) or "genetic material" (term used in US), which through its action mechanism prompts the desired primary effect: addition, manipulation, or modification of gene expressions on human beings. Two autologous chimeric antigen receptor (CAR) T-cell therapies (Kymriah® and Yescarta®) were recently approved by the EMA and the FDA. These therapies are classified as cell-based gene therapies in both regions since they consist of genetically modified T cells expressing a CD19-specific CAR in order to lyse CD19-positive targets (normal and malignant B lineage cells). The fact that the product has to be a biological medicinal product is not a minor inclusion criterion, since chemically synthesized nucleic acid sequences will be excluded from being classified as ATMPs and will be considered chemical drugs that should be developed under another legal framework—as for example, antisense oligonucleotides and aptamers approved by the EMA and FDA as chemical drugs. Unlike the US, in EU, one of the inclusion criteria for GTMP establishes that the recombinant nucleic acids should be of biological origin, regardless of the origin of the vector system used. On the other hand, in both regions, the product has to be applicable to the prevention and treatment of a human disease. However, diagnosis is neither cited as one of the primary goals of these products in the US nor does the US definition of a biologic product, according to the PHSA Act, contemplates diagnosis as a purpose of the product (U.S. Title 42 The Public Health and Welfare, 2019). In EU, there is one exclusion criterion that explicitly vetoed a product from being classified as a gene therapy: those products aimed at the treatment or prophylaxis of infectious diseases. These products would be classified as vaccines, even if the product meets all of the necessary criteria to be considered an advanced therapy (European Medicines Agency, 2015). For instance, a modified vaccinia virus ankara (MVA) into which two genes have been placed for the treatment of non-small cell lung cancer is classified as a GTMP, but if these genes lead to foreign protein expression for the treatment of human immunodeficiency virus (HIV) disease, the product will not be considered an advanced therapy, but a vaccine (European Medicines Agency, 2016b; Draper and Heeney, 2010). The same principle applies to non-viral vectored products such as most plasmid DNA- or RNA-based products. For instance, Trimix is a mixture of mRNAs encoding for antigen presenting cell activation molecules. If this mixture of mRNAs is combined with tumor-associated antigens for the treatment of melanoma, the therapy is classified as a GTMP, but if these mRNA are combined with mRNA encoding for HIV antigens, the therapy will be considered a vaccine (European Medicines Agency, 2016b). In the US, it is not specifically mentioned as an exclusion criterion, but prophylaxis or therapeutic vaccines for infectious diseases have their own guidances for development, and these products are typically reviewed by the CBER/Office of Vaccines Research and Review (OVRR) and not by the OTAT (U.S. Department of Health and Human Services, 2007). Therefore, the criterion for excluding a product from being classified as a GTMP in both regions is directly related to the indications of the product. Although some regulatory and development requirements for both types of products overlap, since these vaccines may be gene-based, for either region, there are guidelines specifically addressed to the development of vaccines or gene therapy products independently. A consequence of this classification is that some of the available EU regulatory procedures that facilitate the development of ATMPs would not apply in the case of products classified as vaccines; for instance, the possibility of certifying the quality and non-clinical data for ATMP applications by the EMA (European Medicines Agency, 2010).

TABLE 2 | Inclusion/exclusion criteria in European Union.

Advanced Therapy medicinal products				
Product category	**Active substance**	**Purpose**	**Inclusions**	**Exclusions**
Gene therapy medicinal products (GTMPs)	Recombinant nucleic acid of biological origin	Administered to human beings with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence Therapeutic, prophylactic, or diagnostic effects that relate directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence	• Plasmids DNA • Viral vectors • Genetically engineered microorganisms • Human gene–editing technology • Patient-derived cellular gene therapy products	• Non-biological products (e.g., chemical synthetized nucleic acids) • Vaccines against infectious diseases
Somatic cell therapy medicinal products (SCTMPs)	Cells or tissues that have been subject to substantial manipulation or not intended to be used for the same essential function(s) in the recipient and the donor	Treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic actions of its cells or tissues	• Products containing or consisting of animal cells or tissues • Cancer immunotherapies • Other autologous and allogeneic cells therapies • Xenogeneic living cells • Stem cells and stem cell–derived products	• Products containing or consisting exclusively of non-viable cells or tissues and which do not act principally by pharmacological, immunological, or metabolic actions
Tissue-engineered products (TEP)	Cells or tissues that have been subject to substantial manipulation or not intended to be used for the same essential function(s) in the recipient and the donor The cells or tissues may be viable or non-viable.	Regenerating, repairing, or replacing a human tissue	• Products containing or consisting of animal cells or tissues • Products may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices • Products for cartilage or cardiac defects, among others • Stem cells and stem cells-derived products	• Products containing or consisting exclusively of non-viable cells or tissues and which do not act principally by pharmacological, immunological, or metabolic actions
Combined ATMPs (cATMPs)	Combines: • one or more medical devices within the meaning of or one or more active implantable medical devices and • its cellular or tissue part must contain viable cells or tissues, or • its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to	Therapeutic, prophylactic, or diagnostic effect Regenerating, repairing, or replacing a human tissue	–	–

Cell and Tissue Therapies

In the EU, SCTMP are distinguished from TEP. However, both class products share the same inclusion principle, i.e., the cells or tissues of the product must be "engineered," and the difference lays in the indication. To consider a cell or tissue as "engineered," it must fulfill at least one of the following criteria (European Union, 2007): i) the cells or tissues have been subject to substantial manipulation, or ii) the cells or tissues are not intended to be used for the same essential function(s) in the recipient and the donor, i.e., non-homologous use. Regarding the indication, in the case of SCTMP, the product is administered to human beings with a view to treating, preventing, or diagnosing a disease through the pharmacological, immunological, or metabolic actions of its cells or tissues, whereas in the case

TABLE 3 | Inclusion/exclusion criteria in United States.

Cell and gene therapy products

Product category	Definition	Purpose	Examples	Exclusions
Human gene therapy	Administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use	Prevention, treatment, or cure of a disease or condition of human beings	• Plasmid DNA • Viral vectors • Genetically engineered microorganisms • Human gene–editing technology • Patient-derived cellular gene therapy products	• Non-biological products (e.g., chemical synthetized nucleic acids) • Products that are destined for the treatment or prophylaxis of infectious diseases
Somatic cell therapy	Autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics *ex vivo*	Therapeutic, diagnostic, or preventive purposes	• Cancer vaccines • Cellular immunotherapies • Other types of both autologous and allogeneic cells • Xenogeneic living cells • Stem cells and stem cell–derived products • Gene therapy–modified cells	• HCT/Ps under section 361 of the PHSA

Combination products

Product category	Definition	Purpose	Examples	Exclusions
Combination products	Two or more regulated components, i.e., drug, device, biologic as a single entity or packaged together, packaged separately but intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect	Therapeutic, diagnostic, or preventive purposes	• Drug/device • Biologic/device: cells combined with medical devices such as natural or synthetic scaffold • Drug/biologic, or • Drug/device/biologic	–

Regenerative medicine advanced therapy designation

Product category	Definition	Purpose	Examples	Exclusions
Regenerative medicine advanced therapy (RMAT)	A cell therapy, therapeutic tissue-engineering product, human cell and tissue product, or any combination product using such therapies or products	To treat, modify, reverse, or cure a serious or life-threatening disease or condition; To address unmet medical needs for such disease or condition	• AT132 (Audentes Therapeutics, Inc.) • Romyelocel-L (Cellerant Therapeutics, Inc.) • AmnioFix® (MiMedx) • CAP-1002 (Capricor Therapeutics)	Products regulated solely under section 361 of the PHSA are explicitly excluded

Human cells, tissues, and cellular and tissue-based products

Product category	Definition	Purpose	Examples	Exclusions
HCT/Ps[1]	Articles containing or consisting of human cells or tissues	Implantation, transplantation, infusion, or transfer into a human recipient	• Bone • Ligament • Skin • Dura mate • Heart valve • Cornea • Hematopoietic stem/progenitor cells derived from peripheral and cord blood • Manipulated autologous chondrocytes • Epithelial cells on a synthetic matrix • Semen or other reproductive tissue • Amniotic membrane (when used alone (without added cells) for ocular repair)	• Vascularized human organs for transplantation • Secreted or extracted human products (e.g., milk, collagen, and cell factors) • Minimally manipulated bone marrow for homologous use • Ancillary products used in the manufacture of HCT/P • Cells, tissues, and organs derived from animals other than humans *In vitro* diagnostic products

[1]*HCT/Ps that meet the criteria contemplated in 21 CFR 1721.10(a).*

of TEP, the product is administered to human beings with a view to regenerating, repairing, or replacing human tissue. The key to ascertain the most appropriate subcategory is based on the predominant mechanism of action of the active substance and the claimed intended function. A problem arises when the dividing line for classifying a product as SCTMPs or TEP is not clear. Such is the case when the product exerts a pharmacological action in order to regenerate, repair, or replace a human tissue. For these cases, premises have been established in order to categorize a specific product: a product which may fall within the definition of a TEP and SCTMP should be considered a TEP according to ATMP Regulation, although the final classification should be considered on case-by-case basis, playing CAT's opinion a major role. In addition, those products that consist of engineered or manipulated cells that induce regeneration, repair, or replacement in the native tissue *via* secretion of paracrine factors also fulfill the definition of a TEP (European Medicines Agency, 2015). Finally, it is considered that a TEP may contain cells or tissues of human or animal origin, or both, and that the cells or tissues may be viable or non-viable, considering viable cells those that have a functional cytoplasmic membrane. Two considerations in this regard are made: i) an inclusion criterion that automatically classifies a product as an ATMP applies when products contain or consist of animal cells or tissues and ii) an exclusion criterion for not classifying a potential product either as a SCTMP or TEP includes those products containing or consisting exclusively of non-viable cells or tissues and which do not act principally through pharmacological, immunological, or metabolic actions (**Table 2**).

As mentioned, cell- and tissue-based products can be sub-categorized in the US regulatory framework as biologic products or as HCT/Ps. The definition of cell- and tissue-based products regulated as biologic products includes those that are "more-than-minimally manipulated," or for "non-homologous use," or have a systemic effect, or depend on its metabolic activity (except for autologous cells, allogeneic cells for 1st of 2nd degree relatives and reproductive cells) (U.S. Department of Health and Human Services, 2017a). The group of advanced therapies referred to as "human somatic cell therapy products" fall within this definition. Note that, in US, there is no product class defined for tissue-based advanced therapies. The definition and the inclusion criteria for human somatic cell therapy (SCT) include the following (U.S. Department of Health and Human Services, 1993; U.S. Department of Health and Human Services, 1998): i) SCT consists of administration to humans of autologous, allogeneic, or xenogeneic living cells; ii) the manufacture of products for SCT involves the *ex vivo* propagation, expansion, selection or pharmacologic treatment of cells, or other alterations of their biological characteristics, and therefore considered "more-than-minimally manipulated"; and iii) the aim of this cellular products is to be used for therapeutic, diagnostic, or preventive purposes (**Table 3**).

Therefore, the categorization or classification of human cells and tissue products between the EU and the US is different. On one hand, in the EU, there is a differentiation between products considered TEP, or SCTMP, in which the difference lies in the claimed indication, while in the US, cell and tissue products that constitute an advanced therapy will be labeled under the SCT's term. For instance, MACI (matrix-applied characterized autologous cultured chondrocytes) is a product approved both in EU and US which consists of autologous chondrocytes seeded on a collagen membrane of porcine origin indicated for the repair of symptomatic, full-thickness cartilage defects of the knee in adult patients. While in US, MACI is considered a cell therapy, a biologic-device combination product with the aim of being used for therapeutic purposes; in EU, it is classified as combined TEP, since the claimed primary mechanism of action of the product is the regeneration, repair, and replacement actions (European Medicines Agency, 2018d; U.S. Food and Drug Administration, 2018i). Finally, the FDA classifies xenogeneic living cells as SCT, as well as in EU, where these therapies can be assumed to be automatically classified as ATMPs from a regulatory point of view (European Medicines Agency, 2009; Schuurman, 2015).

Manipulation and Homologous Use

Both aforementioned inclusion criteria, manipulation and homologous use, have their own definitions depending on the region. In EU, "substantial manipulation" means to modify the biological characteristics, physiological functions, or structural properties relevant for the intended clinical use. For instance, cell separation, concentration, or purification does not represent a substantial manipulation if the cells performed the same biological activity as in the human body, whereas cell-culturing leading to expansion or cell activation with growth factors does. A non-exhaustive list of manipulations that is not considered substantial for ATMP purposes is provided in Annex I of Regulation EC (No). 1394/2007 and includes: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration, or purification, filtration, lyophilization, freezing, and cryopreservation. On the other hand, the "same essential function" (or homologous use) means that the cells or tissues (whether substantially manipulated or not) are used to maintain the original function(s) in the same anatomical or histological environment. By contrast, "different essential function" (or non-homologous use) for cells or tissues (substantially manipulated or not) are those not intended to be used for the same essential function(s) in the recipient as the original cell/tissue would perform in the donor (European Medicines Agency, 2015). Allogeneic human islets of Langerhans for the treatment of severe forms of type 1 diabetes is a common example of cell/tissue products that might be regarded as non-ATMPs, since these cells/tissues might be isolated, purified, and cultured by methods that do not result in a modification of the biological characteristics and are re-administered to fulfill their same essential function. In 2011, CAT considered that autologous/allogeneic human islets of Langerhans were not an ATMP (European Medicines Agency, 2011b), but are considered to fall under the provisions of the Tissues and Cells legislation. Under this legislation, these cells are neither considered a medicinal product, since the active substance, i.e., human tissues, cannot be commercialized or manufactured on an industrial scale for ethical and legal reasons. However, in 2013, a product that consists of viable alginate

encapsulated porcine pancreatic islet cells was classified as a SCTMP (European Medicines Agency, 2013b). In this case, the porcine islets were isolated from pancreases of neonatal piglets and cultured during 30 days, in which cell differentiation occurs by increasing the amount of insulin released from the cells, this being considered a substantial manipulation. Nevertheless, it should be noted that, since this product is based on xenogeneic cells, it is automatically considered an ATMP, as previously discussed. Finally, in 2018, the CAT considered an encapsulated allogeneic pancreatic islet–based product a non-ATMP. The consideration here is whether or not the encapsulation itself might change the characteristics of the islet (European Medicines Agency, 2018e).

In US, the definitions of manipulation and homologous use are defined for HCT/Ps, and by exclusion, the products based on cells and tissues that do not comply with these criteria established for a HTC/Ps could be considered a biological product, and consequently, an advanced therapy (U.S. Department of Health and Human Services, 2017a). The criteria for HCT/Ps include "minimal manipulation" and "homologous use," while "more-than-minimally manipulated" and "non-homologous use" are considered for cell- and tissue-based products considered as biological drugs.

Unlike the EU, in the US, there is a differential definition of minimal manipulation depending on whether or not the product consists of structural tissue. "Minimal manipulation" is defined as: "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement" for structural tissues, and "processing that does not alter the relevant biological characteristics of cells or tissues" for cells or non-structural tissues (U.S. Code of Federal Regulation Title 21, 2018a). For clarification, structural tissue is defined as human cells/tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion (e.g., amniotic membrane and umbilical cord). On the other hand, human cells/tissues that serve as metabolic or other biochemical roles in the body, such as hematopoietic, immune, and endocrine functions, are generally considered cells/non-structural tissues (e.g., hematopoietic stem/progenitor cells). It is considered that this differentiation between structural and non-structural tissues is required, since structural HCT/Ps generally raise different safety and efficacy concerns from those of cells or non-structural tissues.

As a result, the term "processing" is defined as any activity performed on a cell- and/or tissue-based product other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage. Processing includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization (U.S. Code of Federal Regulation Title 21, 2018a). Cell expansion, encapsulation, activation, or genetic modification are considered to be more than minimal manipulations. The aforementioned or any other additional processing steps should be considered in determining whether a product is minimally manipulated or not.

For products that contain structural tissues, "original relevant characteristics of structural tissues" generally comprise the properties of that tissue in the donor that contribute to the tissue's function or functions; for instance, the original relevant characteristics of amniotic membrane generally include the physical integrity, tensile strength, and elasticity of the tissue. Following with the same example, preserving and packaging amniotic membrane in sheets would be considered a minimal manipulation, yet more than minimally manipulated if the amniotic membrane is grounded, lyophilized, and packaged as particles, since it would imply the separation of structural tissue into components whose characteristics related to serving as a barrier are altered. However, ground bone adhered to form bone particles would generally be considered minimally manipulated since it can maintain its utility as a supporting structure. For products that contain cells (both structural and non-structural) and non-structural tissues, "original relevant characteristics" include differentiation and activation state, proliferation potential, and metabolic activity, e.g., for hematopoietic stem/progenitor cells, the ability to repopulate the bone marrow by self-renewal and by differentiating along myeloid and lymphoid cell lines. In this case, cell selection on peripheral blood apheresis products to obtain a higher concentration of hematopoietic stem/progenitor cells for transplantation would be considered a minimal manipulation, whereas differentiating the cells by culturing under specific conditions would be considered more than a minimal manipulation because the characteristics of multipotency and capacity for self-renewal are altered. The storage of the product should also be considered, since it can alter the original relevant characteristics of the cells and tissues. If a product is stored in a buffer solution or is cryopreserved, it would generally meet the minimal manipulation criterion.

Regarding "homologous use," there is also a differentiation between structural and non-structural tissues. The term of homologous use for a structural tissue defines that the tissue is intended to be used for a homologous function when used to replace an analogous structural tissue that has been damaged or otherwise does not function adequately. Therefore, it is defined as the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor (U.S. Code of Federal Regulation Title 21, 2018a). The Agency would consider structural tissue to be performing a non-homologous function when used for a purpose different from those that it fulfils in its native state, or in a location of the body, where such structural function does not normally occur. Similarly, cellular products are considered to be used for a homologous function when they are used to perform their native function, and for a non-homologous function when they are used to perform other functions (U.S. Department of Health and Human Services, 2017a; U.S. Department of Health and Human Services, 2017b).

As it has been discussed, it is important to have a product defined since, otherwise, the legal requirements for these could be violated. In the US, this was the case of some amniotic-/chorionic-based products, used for wound healing, which were considered HCT/Ps by some companies, when in fact, they were biological products. These products were therefore launched to the market without a premarket review, and after an inspection of the CBER Office of Compliance and Biologics Quality, an appropriate clinical development was requested in

order to demonstrate the safety and efficacy of the intended use of the product, as well as distribution of the product to test its clinical use in humans after IND application, and the subsequent submission of a BLA approval for its marketing. This implied that the cost of bringing this product to the market was very different from the one initially invested, given that the preclinical and clinical developments are much broader than for an HCT/Ps (U.S. Food and Drug Administration, 2018j; U.S. Food and Drug Administration, 2018k).

Therefore, both in the EU and in the US, in order to consider a cell- and tissue-based products advanced therapies, it must be ascertained that the processing of the cells implies a manipulation that alters their biological characteristics. In EU, the concept is referred as a "substantial manipulation," while in US, it is referred as "more-than-minimally manipulated." Regarding this term of manipulation in US, there is a nuance that differs from EU definitions and consists in the differentiation of structural and cells/non-structural tissues in the US. The European definitions of substantial manipulation and non-homologous use would encompass both structural and non-structural tissues under the same definition. Regardless of the examples of processing mentioned for either regions, for both, it is key to determine if the processing changes the original characteristics of the product. This requires a characterization of the product during the manufacturing process, as a part of development, to corroborate whether or not the phenotypic and physiological characteristics of a potential product have been altered. On the other hand, the European terminology uses the term "engineered" to denominate those cells or tissues that are substantially manipulated and/or used for a different essential function (or non-homologous use), which is mandatory criteria to classify a product as an advanced therapy. In the US, the term of non-homologous use is not explicitly mentioned in the definition of SCT, although it is to classify a product as biologic in the general definition of cell- and tissue-based products. Note that the nomenclature of "non-homologous use" is be common for both regions, although in Europe, the term "different essential function" would also be the one harmonized according to the EMA guidelines. All these mentioned differences in terminology can be important when submitting documents to the respective Agencies, since it is advisable to use the specific terminology used in each region (**Table 4**).

Combined Advanced Therapy Medicinal Products

In EU, there is a specific category for those products that consist in an ATMP combined with a medical device. A medical device is defined as any instrument, apparatus, appliance, material, or other article intended by the manufacturer to be used on human beings for the purpose of: i) diagnosis, prevention, monitoring, treatment or alleviation of disease, compensation for an injury or handicap, investigation, replacement, or modification of the anatomy of a physiological process, or control of conception and ii) which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but may assist its function by such means (European Union, 2017). Examples of medical devices in cATMP could be scaffolds, matrices, and encapsulation systems for cells, such as microspheres, among others. The criteria to meet in this category class are that the product must incorporate, as an integral part of the product, one or more medical devices. The medical device should be used in the combination, in the same way as its intended use without additional components. On the other hand, the cellular or tissue part of the product must contain viable cells or tissues, or if containing non-viable cells or tissues, it must be liable to act upon the human body with actions that can be considered primary to those of the devices referred to (European Medicines Agency, 2015).

In US, there is no specific category for cATMPs, but there are nine different types of combined products including drug/device, biologic/device, drug/biologic, or drug/device/biologic. The definition takes into account how the product is packaged, i.e., together in a single package or packaged separately, and if all components of the product are needed to achieve the intended use, indication, or effect. Among all of these categories, the type-5 combination product named "device coated or otherwise combined with biologic" constitutes the biologic/device combination where the device has an additional function in addition to delivering the drug and constitutes an "integral part" of the final product, e.g., live cells seeded on or in a device scaffold (U.S. Food and Drug Administration, 2018a). In US, a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which has at least one of the following three characteristics: i) it is recognized in the official National Formulary or the United States Pharmacopeia, or any supplement to them; ii) it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease; or iii) is intended to affect the structure or any function of the human body or other animals and does not achieve its primary intended purposes through chemical action within or on the human body or other animals and which does not depend on being metabolized for the achievement of its primary intended purposes (U.S. Code of Federal Regulation Title 21, 2018b; U.S. Food and Drug Administration, 2018l).

Therefore, while in EU, cATMPs are the fourth subcategory of products within the group of advanced therapies; in the US, the subcategory defined for combined products is very broad and includes drugs, biological, and medical devices. The category of type-5 combined products would constitute a group equivalent to what defines cATMPs in the US, where the product is a single-entity combination product, or the device constitutes "an integral part of the product" according to European definition. For both EU and US, the final combined product will be a biological and a medical device, where the definitions of medical device are equivalent: the medical device assists in the primary function of the biological component. Following MACI's aforementioned example, for both regions, the porcine collagen membrane is considered a device constituent of the product a CE-marked class III device in EU

TABLE 4 | Terminology and definitions for cell- and tissue-based products as advanced therapies.

European Union[1]		United States[2]	
Term	**Definition**	**Term**	**Definition**
Substantial manipulation	Biological characteristics, physiological functions, or structural properties have been modified to be relevant for their intended function during the manufacturing process.	**More than "minimally manipulated"***	For structural tissue, processing that alters the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement For cells or non-structural tissues, processing that alters the relevant biological characteristics of cells or tissues
Different essential function or non-homologous use	Cells when removed from their original environment in the human body are not used to maintain the original function(s) in the same anatomical or histological environment.	**Non-homologous use**	Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor, including when such cells or tissues are for autologous use. Basic functions of a structural tissue would generally be to perform a structural function for example, to physically support or serve as a barrier or conduit, or connect, cover, or cushion. Basic functions of a cellular or nonstructural tissue would generally be a metabolic or biochemical function, such as hematopoietic, immune, and endocrine functions.
Manufacturing	Defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of active substance(s) and the related controls	**Processing**	Any activity performed on an cell- and/or tissue-based product, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage
List of manipulations	Provided in Annex I of Regulation EC (No.) 1394/2007	**List of processing**	Provided in regulatory considerations for human cells, tissues, and cellular and tissue-based products: minimal manipulation and homologous use (2017) and proposed approach to regulation of cellular and tissue-based products (1997), and the United States pharmacopoeia (cellular and tissue-based products: 1046)
–	–	**Original relevant characteristics**	For products that contain structural tissues, "original relevant characteristics of structural tissues" generally include the properties of that tissue in the donor that contribute to the tissue's function or functions. For products that contain cells (both structural and non-structural) and non-structural tissues, "original relevant characteristics" include differentiation and activation state, proliferation potential, and metabolic activity.
Viable cell	A viable cell is a cell that has a functional cytoplasmic membrane. (The European Pharmacopoeia provides information on assays to demonstrate cytoplasmic membrane integrity and activity < 20729 >.)	**Living cells**	– (The United States pharmacopoeia cellular and tissue-based products <1046>)
Tissues	Defined in Directive 2004/23/EC (Art 3.b) as "all constituent parts of a human body formed by cells."	–	–

*[1]Definitions provided in EMA/CAT/600280/2010 Rev.1, CPMP/ICH/4106/00 and Regulation EC (No) 1394/2007; [2]Definitions provided in the Code of Federal Regulation (21 CFR 1271.3; 21 CFR 1271.10), Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (2017) and Proposed approach to regulation of cellular and tissue-based products (1997); *The definition provided is minimal manipulation. For advanced therapies the term that applies is "more than minimally manipulated".*

(European Medicines Agency, 2018d; U.S. Food and Drug Administration, 2018i).

The fact of combining a biological product with a medical product complicates its development, and in US, unlike in EU, there are guidances with some considerations to be taken into account during the development of these products (U.S. Food and Drug Administration, 2006; U.S. Food and Drug Administration, 2019d).

GENERAL DISCUSSION AND CONCLUSION

Our analysis reveals a difference between EU and US in the sub-categorization of advanced therapies and the regulatory terminology defining them. The criteria that must be met in both the EU and the US in order to classify a product as an advanced therapy is similar, although EU presents a more precise

sub-classification with more defined inclusion criteria between these subcategories. The criteria to determine if a product qualifies as a gene therapy may be simpler or more obvious than for cell therapies, although there are some relevant considerations for all defined subcategories of advanced therapies that can change the classification of the product both in EU and US.

EU and US are facing similar challenges regarding the regulation of ATMPs due to their inexperience in this specific medicinal product group, and because Europe covers a variety of overlaying jurisdictions and authorities on a member state level (Bender, 2018; Ten Ham et al., 2018). European and American legislation and regulatory guidelines launched by EMA and FDA show similarities and differences in the ATMP classification for both regions. It is unknown if these differences can be translated into divergent final recommendations by the regulatory authorities. Currently, the number and type of ATMPs approved differ between the two regulatory Agencies. In EU, up to 12 ATMPs have been authorized from 2009, but four of them have been withdrawn throughout the past 10 years. In US, nine gene and cell therapies haven't been authorized, and only six of them match in the two Agencies. The rationale behind these differences is unknown, but it seems feasible that a worldwide harmonization of the procedures involved in the development of ATMPs may allow to reach similar ultimate decisions. It is acknowledged that EMA and FDA have been collaborating for the past 15 years with the aim to ameliorate regulatory excellence. An ATMP cluster has been created under the umbrella of the reinforced EU/US collaboration on medicines with the aim to facilitate regulatory excellence of the new medicinal products (European Medicines Agency, 2018f). Yet, Agencies' recommendations are evolving and being updated over time in a non-parallel manner. In 2018, the FDA launched several guidances that include specific recommendations for the development of ATMPs aimed at certain types of diseases such as hemophilia or retinal disorders (U.S. Food and Drug Administration, 2019e), while the EMA guidelines published to date are more generalist, encompassing only the development of ATMPs according to the three main groups of therapies, GTMP, SCTMP, and TEP. In the future, it would be convenient to begin a progressive process of convergence between both Agencies in terms of terminology, legal recommendations, and characterization requirements. In this regard, some steps could be taken to reach this alignment between regulators—for example, common guidelines, increased number of EMA/FDA parallel scientific advice from the beginning of the lifecycle of the medicinal product, as well as similar post-authorization monitoring of the products or real-world evidence data generation.

AUTHOR CONTRIBUTIONS

CIL conducted the bibliographic search, analysed the data, drafted the manuscript and edits the final copy of this article. AA, MO, and AV analyzed and reviewed the data and edited the manuscript.

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FULL-LENGTH ARTICLE

Regulatory Policies

Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States

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ABSTRACT

Background aims: Regulatory agencies in the European Union (EU) and in the United States of America (USA) have adapted and launched regulatory pathways to accelerate patient access to innovative therapies, such as advanced therapy medicinal products (ATMPs). The aim of this study is to analyze similarities and differences between regulatory pathways followed by the approved ATMPs in both regions.
Methods: A retrospective analysis of the ATMPs approved by EU and US regulatory agencies was carried out until May 31, 2020. Data were collected on the features and timing of orphan drug designation (ODD), scientific advice (SA), expedited program designation (EP), marketing authorization application (MAA) and marketing authorization (MA) for both regions.
Results: In the EU, a total of fifteen ATMPs were approved (eight gene therapies, three somatic cell therapies, three tissue-engineered products and one combined ATMP), whereas in the USA, a total of nine were approved (five gene therapies and four cell therapies); seven of these were authorized in both regions. No statistical differences were found in the mean time between having the ODD or EP granted and the start of the pivotal clinical trial or MAA in the EU and USA, although the USA required less time for MAA assessment than the EU (mean difference, 5.44, $P = 0.012$). The MAA assessment was shorter for those products with a PRIME or breakthrough designation.. No differences were found in the percentage of ATMPs with expedited MAA assessment between the EU and the USA (33.3% versus 55.5%, respectively, $P = 0.285$) or in the time required for the MAA expedited review (mean difference 4.41, $P = 0.105$). Approximately half of the products in both regions required an Advisory Committee during the MAA review, and 60% required an oral explanation in the EU. More than half of the approved ATMPs (67% and 55.55% in the EU and the USA, respectively) were granted an ODD, 70% by submitting preliminary clinical data in the EU. The mean number of SA and protocol assistance per product conducted by the European Medicines Agency was 1.71 and 3.75, respectively, and only 13% included parallel advice with health technology assessment bodies. A total of 53.33% of the products conducted the first SA after the pivotal clinical study had started, reporting more protocol amendments. Finally, of the seven ATMPs authorized in both regions, the type of MA differed for only two ATMPs (28.6%), and four out of eight products non-commercialized in the USA had a non-standard MA in the EU.
Conclusions: The current approved ATMPs mainly target orphan diseases. Although EU and US regulatory procedures may differ, the main regulatory milestones reached by the approved ATMPs are similar in both regions, with the exception of the time for MAA evaluation, the number of authorized products in the regions and the type of authorization for some products. More global regulatory convergence might further simplify and expedite current ATMP development in these regions.

Introduction

Advanced therapy medicinal products (ATMPs) feature cells, genes or tissues. In the last decade, the first advanced therapies have been launched into the market, and as a result of the recent increase in research and development, regulatory agencies have adapted and launched new regulatory pathways compatible with the novelty, complexity and technical specificity of these products. It has been recognized by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) that the evaluation of ATMPs requires specific expertise that goes beyond the traditional pharmaceutical field [1].

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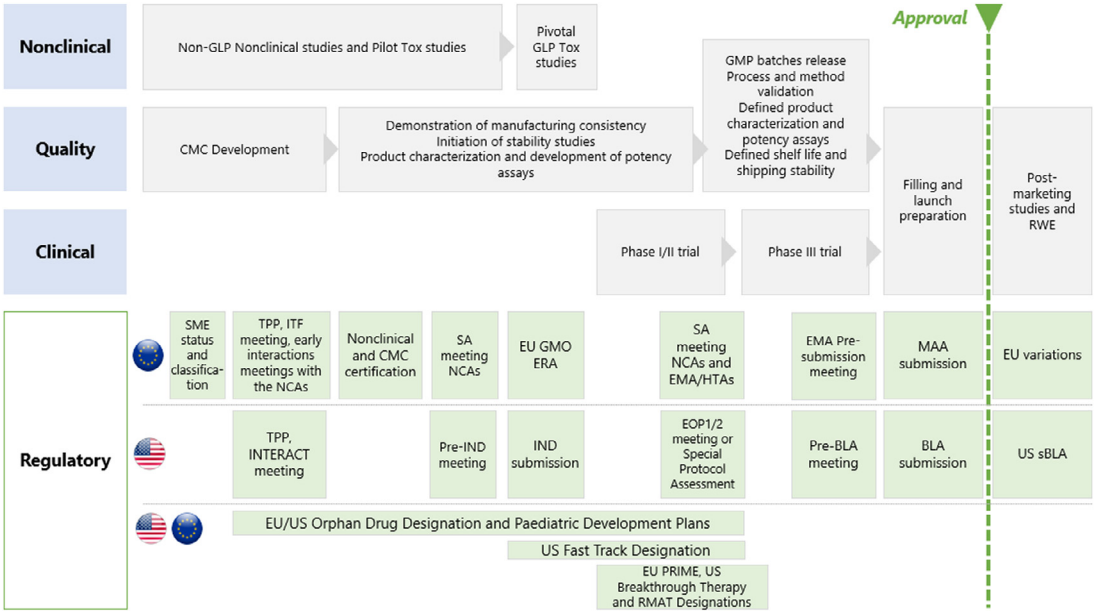

Figure 1. Overview of EU and US regulatory steps for advanced therapies during development. CMC: Controls Manufacturing Chemical; EOP1/2: End-of-Phase 1 or 2; EU: European Union; GLP: Good Laboratory Practices; GMO: Genetically Modified Organism; GMP: Good Manufacturing Practices; IND: Investigational New Drug; ITF: Innovative Task Force Meeting; INTERACT: Initial Targeted Engagement for Regulatory Advice; NCAs: National Competent Authorities; PD: Pharmacodynamic; SA: Scientific Advice; sBLA: Supplemental Biologics License Application; SME: Small and Medium Enterprise; Tox: toxicity; TPP: target product profile; RWE: Real World Evidence; US: United States of America.

In the USA, current Good Manufacturing Practice (cGMP) for phase 1 investigational drugs, which include biological drugs, is exempt from complying with 21 CFR part 211 (cGMP for finished pharmaceuticals) under 21 CFR 210.2(c) (referred to as phase 1 investigational drugs). However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or 3 study, as described in §312.21(b) and (c), or the drug has been lawfully marketed. In the EU, cGMP requirements are detailed in EudraLex, *The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice: Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products*. (Color version of figure is available online).

There are several optional and mandatory regulatory procedures to be followed throughout drug development (Figure 1). No studies have been conducted thus far to analyze the regulatory steps taken in the European Union (EU) and the in the United States of America (USA) for the approved ATMPs; thus, the aim of this study is to analyze and compare the regulatory pathways followed by these therapies in both regions.

Methods

To perform the retrospective study of the approved ATMPs in the EU and USA, the following approach was used:

(i) Search strategy: data were primarily extracted from the EMA and FDA websites (www.ema.europa.eu, www.fda.gov). European data were gathered from European public assessment reports, orphan designation product reports and publicly available EMA agendas, minutes and highlights. US data were collected mainly from FDA drug summary reports and "Summary Basis of Regulatory Action" documents and other approval history-related documents published for the approved cellular and gene therapy products. The search was carried out until May 31, 2020. In addition, a search for the main clinical trials of the approved ATMPs was conducted using the ClinicalTrials.gov database.

(ii) Eligibility criteria: medicine products classified as ATMPs according to EMA criteria and those classified as cellular and gene therapy products in the USA were included in the study [2,3]. To compare only those products that are considered ATMPs in both regions, the approved hematopoietic progenitor cell cord blood products in the USA were discarded from this analysis since they are not considered ATMP products in the EU but under transplantation laws. In addition, only products authorized under centralized procedures in the EU were considered, excluding those ATMPs approved under "hospital exemption" since these products are non-industrially manufactured and tailor-made for a single patient.

(iii) Data extraction and collected variables: the authors designed specific data extraction forms using Excel 2019 (Microsoft Corporation, Redmond, WA, USA) to collect information related to the approved ATMPs' regulatory development: scientific advice (SA) number and timing in EU and US pre-investigational new drug application (pre-IND) and pre-biological license application (pre-BLA) meetings, along with special protocol assessment procedure; timing and features of EU and US orphan drug designation (ODD), including significant benefit for the EU; and timing and features of expedited programs, marketing authorization application (MAA) and type of approval for the approved ATMPs in both regions. The expedited programs were classified as priority medicines (PRIME) designation in the EU and breakthrough designation, fast track and regenerative medicine advanced therapy (RMAT) in the USA. Information on expedited programs for other chemical and biological drugs was also collected. The types of marketing authorization (MA) were classified as standard approval, conditional approval and exceptional circumstances in the EU and standard approval and accelerated approval program in the USA. The date of EU approval was based on the positive Committee for Medicinal Products for Human Use (CHMP) opinion. Finally, the issues raised at the scientific advisory group meetings during the MAA evaluation were collected for both regions, and the categorization approach was sourced and adapted from Barkholt *et al.* [4]. ATMP classification and certification procedures were excluded from the analysis since they are European-specific. Environmental risk assessment procedures were also excluded, as they differ between the two regions [5].

(iv) Statistical analysis: analysis of categorical and continuous variables was performed by means of the distribution of frequencies, proportions, 95% confidence interval (CI), mean, standard deviation (SD), median, interquartile range (IQR) and range (minimum and maximum). Statistical differences were evaluated using the chi-square test for categorical variables and paired Student's *t*-test for continuous variables. Comparison of

temporal variables was made only for common ATMPs approved in both regions. A two-tailed significance was set at a level of 0.05. The statistical analysis was performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

In the EU, a total of 15 ATMPs were approved for 16 different clinical indications, whereas in the USA, a total of nine therapies were approved for 10 clinical indications. The ATMPs approved in both regions, year of submission and approval and clinical indications authorized are shown in Table 1. A total of seven of these ATMPs were approved in both the EU and USA (five being gene therapy medicinal products [GTMPs]), eight therapies were approved only in the EU and two were approved only in the USA. In the EU, eight (53.33%) ATMPs were GTMPs, three (20%) were somatic cell therapy medicinal products, three were tissue-engineered products (20%) and one (6.66%) was a combined ATMP. In the USA, five (55.55%) were GTMPs and four (44.44%) were cell therapies.

Orphan drug designation

Ten out of 15 approved therapies in the EU (67%) were granted an ODD during development (seven GTMPs, two somatic cell therapy medicinal products and one tissue-engineered product), whereas in the USA, five GTMPs out of nine approved ATMPs (55.55%) obtained this designation. In the EU, Yescarta, Kymriah and Luxturna each received two ODDs, whereas in the USA, Yescarta received three ODDs and Kymriah received two (Table 2). Of the seven products that were developed in both the EU and the USA, four obtained an ODD in both regions (57.14%).

In the EU, significant benefit did not need to be demonstrated for five medicinal products at the time of designation, as they targeted rare conditions lacking any approved therapies in the EU (33.3% of all approved ATMPs and 50% of those with an ODD). Only three ATMPs approved (30% of the approved products with an ODD) obtained the designation supported only by pre-clinical data (Glybera, Luxturna and Zynteglo). With regard to Alofisel, this information was not known, and the rest submitted preliminary clinical data (70%) (Table 2).

The mean ± SD time between having the ODD granted and the start of the pivotal clinical trial was 3.16 ± 26.93 months in the EU (median, −2.50, IQR, −15.75 to 30.25, range, −34 to 41) and −7.57 ± 28.72 months in the USA (median, −15, IQR, −25 to 14, range, −49 to 36), meaning that the main clinical trial started prior to having the ODD granted (Figure 2). When analyzing the four ATMPs with an orphan designation in both regions, the mean ± SD time between having the ODD granted and the start of the pivotal clinical trial was 1.50 ± 16.37 months in the EU (median, −2.50, IQR, −11.25 to 15.25, range, −15 to 28) and −5 ± 30.57 months in the USA (median, −3, IQR, −31 to 19.50, range, −49 to 36). This difference was not statistically significant (mean difference, 6.5 months, 95% CI, −20.14 to 33.14, $P = 0.558$).

The mean ± SD time between having the ODD granted and MAA submission was 55.53 ± 35.13 months in the EU (median, 51, IQR, 22–72, range, 12–123) and 27.14 ± 16.73 months in the USA (median, 36, IQR, 11–40, range, 5–48) (Figure 2). When analyzing the four ATMPs with an orphan designation in both regions, the mean ± SD time between having the ODD granted and MAA was 32.83 ± 19.02 months in the EU (median, 30, IQR, 20–47.25, range, 12–63) and 28.3 ± 14.29 months in the USA (median, 30.50, IQR, 13.25–39, range, 11–48). This difference was not statistically significant (mean difference, 4.50 months, 95% CI, −15.21 to 24.21, $P = 0.583$).

Of those therapies that were granted an ODD, none of them lost the designation after their MA, and only Alofisel needed an oral explanation during the EU MAA procedure to maintain the designation. Finally, Kymriah and Zolgensma (13.33% of the approved products) required the submission of a critical report addressing the possible similarity to other authorized orphan medicinal products in the EU.

Scientific Advice procedures

In the EU, all authorized ATMPs followed a SA or protocol assistance procedure (in the case of an orphan medicinal product) with the EMA. The mean ± SD number of SA procedures per product was 1.71 ± 0.75 (median, 2, IQR, 1–2, range, 1–3), whereas the mean ± SD number of protocol assistance procedures was 3.75 ± 1.05 (median, 4, IQR, 3–4.75, range, 2–5). The questions for all products pertained to quality and non-clinical and clinical development. A total of six (40%) of the approved therapies had the first EMA SA prior to the start of the pivotal clinical study, whereas a total of eight products (53.33%) had it later (Figure 3A). The mean ± SD time from the first SA to the start of the pivotal study was −2.50 ± 41.34 months (median, 6, IQR, −35 to 15.5, range, −74 to 85). The mean ± SD number of reported protocol amendments to the pivotal study for those products that had the SA after starting the main study was 5.60 ± 1.67 (median, 6, IQR, 4–7, range, 3–7), whereas it was 3.75 ± 1.67 (median, 4, IQR, 2.25–5, range, 1–6) for those products that had the SA prior to starting the main study. The mean ± SD time from the first EMA SA to MAA was 55.86 ± 33.23 months (median, 46, IQR, 40–70, range, 10–129). Only Zynteglo underwent a parallel advice procedure with health technology assessment bodies, whereas Kymriah benefited from the pilot version of this program (13.33% of the approved ATMPs in the EU).

With regard to the USA, Kymriah, Yescarta, Luxturna and Zolgensma had pre-BLA meetings. The mean ± SD time from the pre-BLA meeting to MAA was 7.40 ± 5.68 months (median, 5, IQR, 2.5–13.5, range, 2–14). Kymriah, Luxturna and Zolgensma also had reported pre-IND meetings, with a mean ± SD time from these meetings to the start of the pivotal study of 47.50 ± 34.78 months (median, 46.50, IQR, 15.50–80.50, range, 13–84) and 74.75 ± 47.30 months (median, 63, IQR, 36.75–124.50, range, 34–139) from the meeting to MAA. The applicants of Kymriah and Imlygic applied for the special protocol assessment procedure 1 year before the start of the main trial (Figure 3B).

Expedited program designations

In the EU, four approved ATMPs obtained priority medicines (PRIME) designation (26.67%), three of them—Kymriah, Yescarta and Zynteglo—the same year the scheme was launched, with Zolgensma obtaining the designation the following year. All the therapies, except for Zolgensma, obtained PRIME designation after having started the main clinical trial that was the basis of the submission. The mean ± SD time from the start of the pivotal clinical trial to PRIME designation was 5.25 ± 10.56 months (median, 6.50, IQR, −5.50 to 14.75, range, −8 to 16) (Figure 4A). The mean ± SD time from obtaining PRIME designation to MAA submission was 18.66 ± 4.46 months (median, 20.28, IQR, 14.61–23.19, range, 14.04–24.24). Both Kymriah and Yescarta obtained the designation just over a year before MAA submission, whereas Zynteglo and Zolgensma obtained the designation approximately 2 years before submission (Figure 4B). Although chimeric antigen receptor T-cell products were approved for the same indication, i.e. relapsed or refractory diffuse large B-cell lymphoma in adults, Kymriah obtained PRIME designation for the treatment of pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia, whereas Yescarta obtained the designation for the diffuse large B-cell lymphoma indication.

In the USA, four out of nine ATMPs approved were granted breakthrough designation (44.44%), (Kymriah, Yescarta, Luxturna and Zolgensma). With the exception of Zolgensma, all these therapies obtained breakthrough designation after having started the main clinical trial that was the basis of the submission. Kymriah obtained two

Table 1
Overview of approved ATMPs in the EU and USA (up to May 2020).

Product	Product description	EU indication and approval	US indication and approval
Axicabtagene ciloleucel (Yescarta; Kite Pharma)	Cell-based GTMP, autologous T cells transduced with gamma retroviral vector	• Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma • Treatment of primary mediastinal large B-cell lymphoma after two or more lines of systemic therapy Submitted: 29 Jul 2017 CHMP PO: 28 Jun 2018 Status: authorized	• Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and diffuse large B-cell lymphoma arising from follicular lymphoma Submitted: 31 Mar 2017 Approved: 18 Oct 2017 Status: authorized
Tisagenlecleucel (Kymriah; Novartis Pharmaceuticals Corporation)	Cell-based GTMP, autologous T cells transduced with lentiviral vector	• Treatment of pediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia that is refractory, in relapse post-transplant or in second or later relapse • Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy Submitted: 02 Nov 2017 CHMP PO: 28 Jun 2018 Status: authorized	• Treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse • Treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, high grade B-cell lymphoma and diffuse large B-cell lymphoma arising from follicular lymphoma Submitted: 27 Oct 2017 Submitted: 02 Feb 2017 Approved: 01 May 2018 Approved: 30 Aug 2017 Status: Authorized
Voritegene neparvovec (Luxturna; Spark Therapeutics Inc. & Novartis Europharm Limited)	Non-cell-based GTMP, AAV-2	• Treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells Submitted: 29 July 2017 CHMP PO: 20 Sep 2018 Status: authorized	• Treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy; patients must have viable retinal cells Submitted: 16 May 2017 Approved: 19 Dec 2017 Status: authorized
Spheroids of human autologous matrix-associated chondrocytes (Spherox; CO.DON AG.)	TEP, spheroids of human autologous matrix-associated chondrocytes	• Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (ICRS grade III or IV) with defect sizes up to 10 cm^2 in adults Submitted 03 Dec 2012 CHMP PO: 18 May 2017 Status: authorized	*Not approved in the USA*

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Table 1 (*Continued*)

Product	Product description	EU indication and approval	US indication and approval
Darvadstrocel (Alofisel; Takeda Pharma A/S.)	SCTP. Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue	• Treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn disease when fistulas have shown an inadequate response to at least one conventional or biologic therapy Submitted: 2 Mar 2016 CHMP PO: 14 Dec 2017 Status: authorized	*Not approved in the USA*
Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human ΔLNGFR and HSV-TK Mut2 (Zalmoxis; MolMed S.p.A.)	Cell-based GTMP, allogeneic T cells genetically modified with retroviral vector	• Adjunctive treatment in hematopoietic cell transplantation Submitted: 05 Mar 2014 CHMP PO: 23 Jun 2016 Status: withdrawn	*Not approved in the USA*
Autologous CD34+ cell-enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence from human hematopoietic stem/progenitor (CD34+) cells (Strimvelis; Orchard Therapeutics BV)	Cell-based GTMP, autologous CD34+ cells transduced with retroviral vector	• Treatment of severe combined immunodeficiency due to ADA deficiency Submitted: 01 May 2015 CHMP PO: 01 Abr 2016 Status: authorized	*Not approved in the USA*
Talimogene laherparepvec (Imlygic; Amgen)	Non-cell-based GTMP, rHSV-1	• Treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease Submitted: 28 Aug 2014 CHMP PO: 22 Oct 2015 Status: authorized	• Indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery Submitted: 28 Jul 2014 Approved: 27 Oct 2015 Status: Authorized
Ex vivo-expanded autologous human corneal epithelial cells containing stem cells (Holoclar; Holostem Terapie Avanzate s.r.l.)	TEP, *ex vivo*-expanded autologous human corneal epithelial cells containing stem cells	• Treatment of adult patients with moderate to severe limbal stem cell deficiency, unilateral or bilateral, due to physical or chemical ocular burns Submitted: 06 Mar 2013 CHMP PO: 18 Dec 2014 Status: authorized	Not approved in the USA
Sipuleucel-T (Provenge; Dendreon Corporation)	SCTP, autologous peripheral blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor	• Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated Submitted: 30 Dec 2011 CHMP PO: 27 Jun 2013 Status: withdrawn	• Treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer Submitted: 30 Oct 2009 Approved: 29 Apr 2010 Status: authorized
Autologous cultured chondrocytes on porcine collagen membrane (MACI; Vericel Corporation)	TEP, autologous chondrocytes expanded *ex vivo* expressing chondrocyte-specific marker genes, seeded onto a CE marked porcine-derived type I/III collagen membrane	• Repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3–20 cm^2 in skeletally mature adult patients Submitted: 01 Sep 2011 CHMP PO: 25 April 2013 Status: withdrawn	• Repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults Submitted: 04 Jan 2016 Approved: 13 Dec 2016 Status: authorized

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Table 1 (*Continued*)

Product	Product description	EU indication and approval	US indication and approval
Alipogene tiparvovec (Glybera; uniQure biopharma B. V.)	Non-cell-based GTMP, AAV-1/2	• Indicated for adult patients diagnosed with familial lipoprotein lipase deficiency and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions; indication is restricted to patients with detectable levels of LPL protein Submitted: 23 Dec 2009 CHMP PO: 23 Jun 2011 Status: withdrawn	Not approved in *the* USA
Characterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins (ChondroCelect; TiGenix N.V.)	TEP, caracterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins	• Repair of single symptomatic cartilage defects of the femoral condyle of the knee (ICRS grade III or IV) in adults; concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present Submitted: 01 Jun 2007 CHMP PO: 25 June 2009 Status: withdrawn	*Not approved in USA*
Betibeglogene autotemcel (Zynteglo; bluebird bio B.V.)	Cell-based GTMP, genetically modified autologous CD34+ cell-enriched population that contains hematopoietic stem cells transduced with lentiviral vector	• Treatment of patients 12 years and older with transfusion-dependent β-thalassaemia who do not have a $\beta 0/\beta 0$ genotype, for whom hematopoietic stem cell transplantation is appropriate but an HLA-matched related hematopoietic stem cell donor is not available Submitted: 21 Aug 2018 CHMP PO: 26 Apr 2019 Status: authorized	*Not approved in the USA*
Azficel-T (laViv; Fibrocell Technologies, Inc.)	Autologous cellular product	*Not approved in the EU*	• Indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults Submitted: 22 Dec 2010 Approved: 21 June 2011 Status: authorized
Onasemnogene abeparvovec-xioi (Zolgensma; AveXis, Inc., & Novartis Gene Therapies EU Limited)	Non-cell-based GTMP, AAV-9	• Treatment of patients with 5q spinal muscular atrophy with a biallelic mutation in the *SMN1* gene and a clinical diagnosis of spinal muscular atrophy type 1 or patients with 5q spinal muscular atrophy with a biallelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene Submitted: 09 Oct 2018 CHMP PO: 26 Mar 2020 Status: authorized	• Treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with biallelic mutations in the *SMN1* gene Submitted: 01 Oct 2018 Approved: 24 May 2019 Status: authorized
Allogeneic cultured keratinocytes and fibroblasts in bovine collagen (Gintuit; Organogenesis Incorporated)	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen	*Not approved in the EU*	• Indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults Submitted: 13 Mar 2011 Approved: 09 Mar 2002 Status: authorized

Indications according to labeling of each region. Date of EU marketing authorization application submission corresponds to the date when the application was received by the EMA.
ADA, adenosine deaminase; AAV, adeno-associated viral vector; cDNA, complementary DNA; HSV-TK Mut2, herpes simplex I virus thymidine kinase; ICRS , International Cartilage Regeneration & Joint Preservation Society; ΔLNGFR, low-affinity nerve growth factor receptor; PO, positive opinion; SCTP, somatic cell therapy medicinal product; TEP, tissue-engineered product.

Table 2
Summary of ODDs granted in the EU and USA for approved advanced therapies.

Product	Orphan indication		ODD at MA		EU prevalence to support the ODD	Data available to support the ODD	Significant benefit criterion in the EU	
	EU	US	EU	US			No satisfactory treatment was authorized in the EU	Designated with the need to justify significant benefit
Yescarta	Treatment of diffuse large B-cell lymphoma	Treatment of diffuse large B-cell lymphoma	Yes; COMP adopted an LoQ and required an OE	Yes	2.4 in 10 000	Preliminary clinical data showing a favorable response in patients with progressive disease who are refractory to previous treatments.	NA	Yes
	Treatment of primary mediastinal large B-cell lymphoma	Treatment of primary mediastinal large B-cell lymphoma	Yes; COMP adopted an LoQ and required an OE		0.3 in 10 000	Preliminary clinical data in patients affected by the condition who responded to treatment with the product as assessed by imaging	NA	Yes
	NA	Treatment of follicular lymphoma	NA		NA	NA	NA	NA
Kymriah	Treatment of diffuse large B-cell lymphoma	Treatment of diffuse large B-cell lymphoma	Yes	Yes	4.5 in 10 000	Pre-clinical data and preliminary clinical data showing antitumor activity of the proposed product	NA	Yes
	Treatment of B-cell lymphoblastic leukemia/ lymphoma	Treatment of acute lymphoblastic leukemia	Yes	Yes	1 in 10 000	Preliminary clinical data in patients	NA	Yes
Luxturna	Treatment of Leber congenital amaurosis	Treatment of inherited retinal dystrophy due to biallelic *RPE65* gene mutations	Yes; COMP adopted an LoQ and required an OE	Yes	1 in 10 000	Pre-clinical data supporting improvements in visual function	Yes	NA
	Treatment of retinitis pigmentosa			Yes	3.7 in 10 000			
Alofisel	Treatment of anal fistula	NA	Positive COMP opinion after appealing a negative opinion	NA	2.3 in 10 000	Not known	Yes	NA
Zalmoxis	Adjunctive treatment in hematopoietic cell transplantation	NA	Yes	NA	0.32 in 10,000	Clinical trials in patients were ongoing	NA	Yes
Strimvelis	Treatment of severe combined immunodeficiency due to adenosine deaminase deficiency	NA	Yes	NA	0.02 in 10 000	Clinical trials in patients were ongoing	Yes	NA
Imlygic	Not orphan drug in the EU	Treatment of stage IIb-IV melanoma	NA	Yes	NA	NA	NA	NA
Holoclar	Treatment of corneal lesions with associated corneal (limbal) stem cell deficiency due to ocular burns	NA	Yes	NA	0.3 in 10 000	Clinical trials in patients were ongoing	NA	Yes

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Table 2 (*Continued*)

Product	Orphan indication		ODD at MA		EU prevalence to support the ODD	Data available to support the ODD	Significant benefit criterion in the EU	
	EU	US	EU	US			No satisfactory treatment was authorized in the EU	Designated with the need to justify significant benefit
Glybera	Treatment of lipoprotein lipase deficiency	NA	Yes	NA	0.02 in 10 000	Evaluation of the effects of adeno-associated viral vector expressing LPL in experimental models was ongoing. At the time of submission of the application for orphan designation, no clinical trials in patients with LPL deficiency were initiated.	Yes	NA
Zynteglo	Treatment of ß-thalassemia intermedia and major	NA	Yes	NA	1 in 10 000	Pre-clinical results in a model of β-thalassemia intermedia	NA	Yes
Zolgensma	Treatment of spinal muscular atrophy	Treatment of spinal muscular atrophy	Yes	Yes	0.4 in 10 000	Clinical trials with the medicine in patients with spinal muscular atrophy were ongoing	Yes	NA

COMP, Committee for Orphan Medicinal Products; LoQ, list of questions; LPL, lipoprotein lipase; NA, not applicable; OE, oral explanation.

breakthrough designations, one for the B-cell precursor acute lymphoblastic leukemia indication and the other for diffuse large B-cell lymphoma indication. The mean ± SD time from the start of the main clinical trial to obtaining breakthrough designation was 10 ± 15.13 months (median, 11, IQR, −2.50 to 22, range, −15 to 23) (Figure 4A). The mean ± SD time from obtaining breakthrough designation to MAA submission was 20.2 ± 8.14 months (median, 19.56, IQR, 13.02–28.50, range, 11.04–30.96). Similar to the EU, both Kymriah and Yescarta obtained the designation just over a year before MAA submission, whereas Luxturna and Zolgensma obtained the designation over 2 years before MAA submission (Figure 4B). Three approved products (33.33%) received fast track designation (Provenge, Imlygic and Zolgensma). Zolgensma obtained fast track and breakthrough designations consecutively. The mean ± SD time from the start of the main clinical trial to obtaining fast track designation was −8.33 ± 35.64 months (median, 2, range, −48 to 21). The mean ± SD time from obtaining fast track designation to MAA submission was 58.96 ± 15.57 months (median, 60.12, range, 42.84–73.92). None of the approved ATMPs have been granted RMAT designation, and no product with this designation has yet been launched in the US market.

When analyzing the three most common ATMPs approved in the EU and USA, the mean ± SD time between having the expedited designation granted and starting the pivotal clinical trial in the EU was 6.33 ± 12.66 months (median, 11, range, −15 to 28) and 5.66 ± 18.58 months in the USA (median, 11, range, −15 to 21). This difference was not statistically significant (mean difference, −0.66 months, 95% CI, −23.75 to 22.42, $P = 0.912$). The mean ± SD time between having the expedited designation granted and MAA in the EU was 16.80 ± 3.02 months (median, 18, range, 14.04–20.04) and 19.68 ± 5.70 months in the USA (median, 18, range, 15–26.04). This difference was not statistically significant (mean difference, 0.24 months, 95% CI, −0.32 to 0.80, $P = 0.209$).

The number of cumulative PRIME designations granted for ATMPs from May 2016 to May 2020 was 32 out of 76 (42.10%) requested,

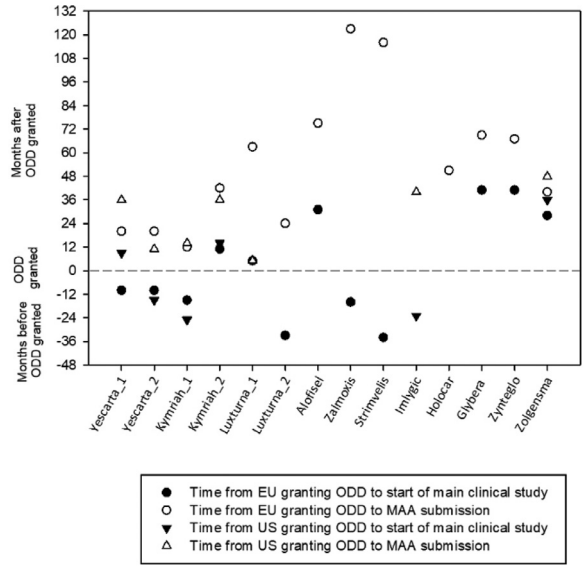

Figure 2. Relationship between date of granted ODD and start of main clinical study and MAA submission. No prospective clinical trials were conducted in support of Holoclar MAA. Yescarta_1 and Kymriah_1: treatment of diffuse large B-cell lymphoma indication in the EU and the USA. Yescarta_2: treatment of primary mediastinal large B-cell lymphoma indication in the EU and the USA. Kymriah_2: treatment of B-lymphoblastic leukemia/lymphoma in the EU and the USA. Luxturna_1: treatment of Leber congenital amaurosis in the EU and treatment of inherited retinal dystrophy due to biallelic *RPE65* gene mutations in the USA. Luxturna_2: treatment of retinitis pigmentosa in the EU. Yescarta received three ODDs in the USA: (i) treatment of diffuse large B-cell lymphoma, (ii) treatment of primary mediastinal B-cell lymphoma and (iii) treatment of follicular lymphoma. The two latest indications have been clustered (Yescarta_2) since they were granted almost at the same time.

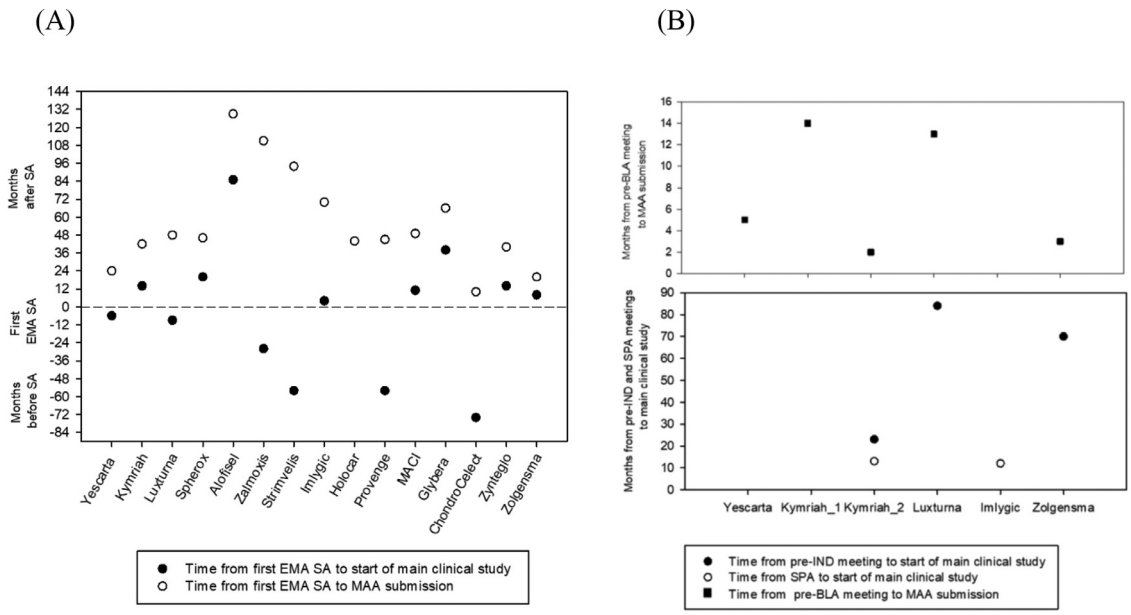

Figure 3. (A) Relationship between date of first EMA SA and start of main clinical study and MAA submission. (B) Relationship between reported meetings with the FDA and start of main clinical study and MAA submission. No prospective clinical trials were conducted in support of Holoclar MAA. Kymriah_1: treatment of diffuse large B cell lymphoma indication. Kymriah_2: treatment of B-lymphoblastic leukemia/lymphoma. pre-IND, pre-investigational new drug; SPA, Special Protocol Assessment procedure.

whereas it was 36 out of 199 (18.09%) requested for other chemical and biological drugs ($P< 0.0001$) (Figure 5). No cumulative data are reported for the breakthrough designation. The reported cumulative RMAT requests received from December 2016 until May 2020 add up to a total of 139; of these, 48 were granted (34.5%), 76 were declined (54.67%) and six were withdrawn (4.3%). Both RMAT and PRIME were launched in 2016, and the cumulative data indicate that slightly more PRIME designations are granted for ATMPs than RMAT designations (42.1% versus 34.5%, respectively).

Marketing authorization application

The mean ± SD time required from submission of the MAA to its final approval in the EU was 17.96 ± 10.97 months (median, 17.55, IQR, 10.78–21.42, range, 7.69–53.49) and 10.96 ± 4.62 months for those therapies with a PRIME designation (median, 9.30, IQR, 7.72–15.86, range, 7.69–17.55). The mean ± SD time of the first clock stop for all approved ATMPs was 6.56 ± 9.81 months (median, 3.65, IQR, 2.16–6.19, range, 0.85–43.70), whereas it was 1.59 ± 0.63 months for therapies with the PRIME designation (median, 1.66, IQR, 0.95–2.16, range, 0.85–2.20) and 9.03 ± 11.35 months for those without the PRIME designation (median, 5.55, IQR, 3.65–8.23, range, 2.86–43.70). The mean ± SD time of the second clock stop for all approved ATMPs was 2.03 ± 2.22 months (median, 1.05, IQR, 0.64–2.38, range, 0.03–7.75). After this second clock stop, there were second rounds of outstanding issues for nine of the approved ATMPs analyzed (60%), and even third and fourth rounds for ChondroCelect and Zalmoxis, respectively (13.33% of the approved products). For Zynteglo, there were no outstanding issues, although the European Commission requested clarifications on the label after the

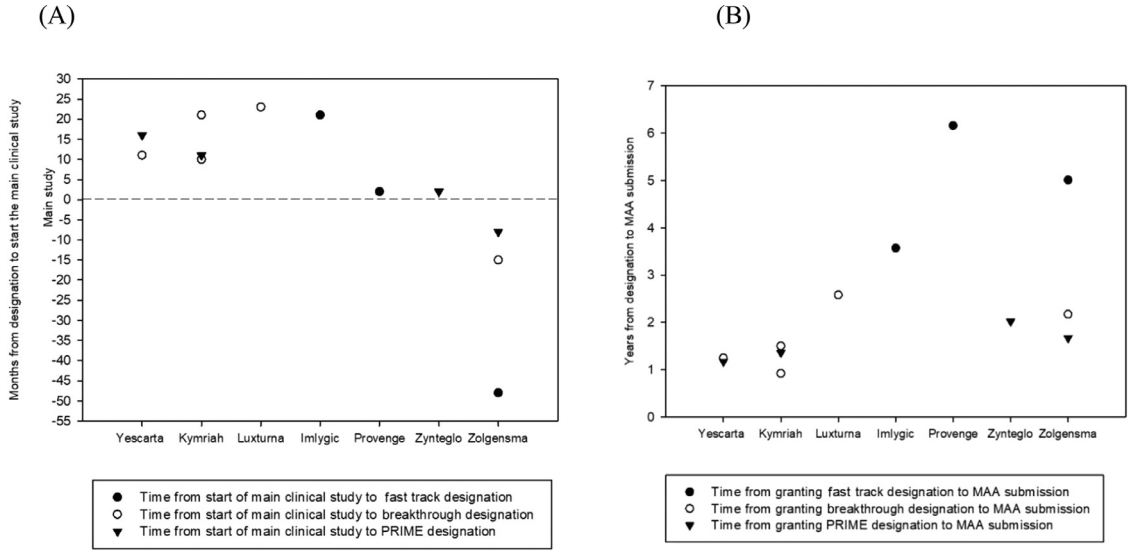

Figure 4. (A) Relationship between date of granting expedited programs and start of main clinical study. (B) Relationship between date of granting expedited programs and MAA submission. Kymriah obtained breakthrough designation for the following indications: treatment of adult patients with diffuse large B-cell lymphoma and treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

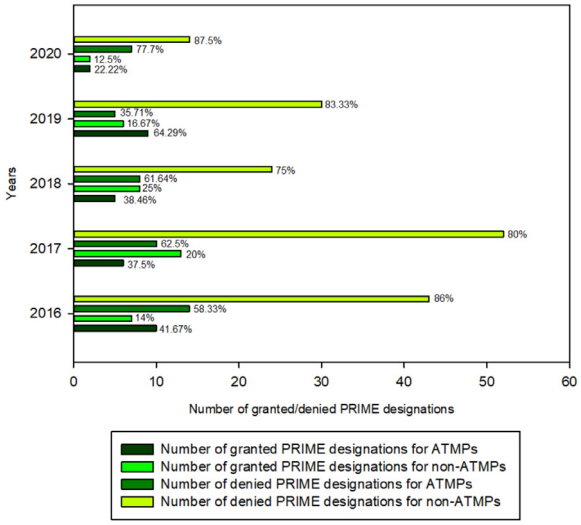

Figure 5. Number of PRIME designations granted and denied for ATMPs versus non-ATMPs (from May 2016 to May 2020). (Color version of figure is available online).

positive Committee for Advanced Therapies/CHMP opinion. Finally, nine of the approved products required an oral explanation (60%) to obtain the approval.

In the USA, the mean ± SD time required from submission of the MAA to its final approval was 8.16 ± 3.05 months (median, 6.98, IQR, 5.95–10.31, range, 5.13–14.98) and 6.85 ± 1.10 months for those products with breakthrough designation (median, 6.63, IQR, 5.49–7.56, range, 5.13–7.72). It took 7 months for Yescarta and Luxturna to obtain approval through a rolling submission.

The mean ± SD time required from submission of the MAA to its final approval among approved ATMPs in both regions was 13.64 ± 4.58 months in the EU (median, 13.76, IQR, 8.56–17.81, range, 7.82–19.78) and 8.20 ± 3.29 months in the USA (median, 6.98, IQR, 6.11–10.40, range, 5.13–14.98). The difference was statistically significant (mean difference, 5.44 months, 95% CI, 1.63–9.25, $P = 0.012$).

A total of seven products (46.67%) in the EU and six products (66.66%) in the USA required an advisory committee during the MAA. The issues raised to the advisory committees were different in the EU and the USA, and the most common questions were related to target population, evidence of clinical efficacy and clinical pharmacology (including dose and route of administration) (Table 3).

Expedited Marketing authorisation applications assessments

The MAAs of Strimvelis, Yescarta, Kymriah, Zynteglo and Zolgensma were reviewed under an accelerated assessment (AA) (33.33% of the approved products), being the mean ± SD time from submission to final approval 10.96 months in the EU (median, 10.78, IQR, 7.75–14.29, range, 7.69–17.55). Only Zynteglo could keep the AA until the end of the procedure.

A total of five (55.55%) of the approved products obtained a priority review in the USA, including all of the approved therapies that were granted breakthrough designation (Yescarta, Kymriah, Luxturna and Zolgensma). Provenge was granted fast track designation and also obtained a priority review since at the time of its development the breakthrough designation was not available. The mean ± SD time for approval under priority review was 6.56 ± 0.91 months (median, 6.73, IQR, 5.74–7.25, range, 5.13–7.72).

There was no difference in the percentage of ATMPs with an expedited MAA assessment between the EU (33.3%, 95% CI, 15–58.5%) and the USA (55.5%, 95% CI, 26.6–81.2%) ($P = 0.285$).

Kymriah, Yescarta and Zolgensma obtained expedited MAA review in both regions (42.86% of ATMPs authorized in both regions). The mean ± SD time from submission to final approval of these products was 10.99 ± 4.58 months in the EU (median, 9.3, IQR, 7.82–15.85, range, 7.82–17.55) and 6.58 ± 1.07 months in the USA (median, 6.73, IQR, 5.49–7.50, range, 5.13–7.72). The difference was not statistically significant (mean difference, 4.41, 95% CI, −1.70 to 10.53, $P = 0.105$).

Table 3
Comparison of the issues discussed in scientific advisory group meetings during the MAA for approved advanced therapies in the EU and USA.

	Kymriah		Luxturna		Imlygic		Provenge	
	EU	US	EU	US	EU	US	EU	US
Product potency								①
Pharmacology (including dosing and route of administration)						①		①
Pharmacokinetics (biodistribution)			①					
Target population and indication	②		③		②	①	①	
Choice of endpoints				①	①			
Sufficient clinical package to support the MA						①		
Clinical efficacy results	④				①		①	①
Clinical benefit	①		②					
Clinical safety							①	
Safety with regard to product administration		①		①				
Limited S&E follow-up, RM and post-marketing	①			①			①	
Risk-benefit assessment		①		①		①		
Regulatory pathway for approval						①		
Total	⑧	②	⑥	④	④	⑤	④	③

Categorization approach was sourced and adapted from Barkholt *et al.* [4]. LaViv and Gintuit were only approved in the USA. Issues discussed in scientific advisory group meeting during MA procedure for laViv were pharmacology (one issue), clinical safety (five issues), limited S&E follow-up and RM and post marketing (one issue). Issues discussed in scientific advisory group meeting during MA procedure for Gintuit were validation process and assays (one issue), impurities, microbiological contamination (two issues) and comparability and consistency issues (one issue). Glybera was approved only in the EU. Issues discussed in the scientific advisory group meeting during the MA procedure for Glybera were choice of endpoints (one issue), pharmacodynamics and drug interactions (one issue), target population and indication (one issue). Zolgensma required a scientific advisory group meeting in the EU. Issues discussed included pharmacology (including dosing and route of administration) (one issue), target population and indication (one issue) and clinical benefit (one issue). For Zolgensma, no advisory committee meeting was held in the USA because initial review of information submitted did not raise concerns or controversial issues that would have benefited from an advisory committee discussion. RM, risk management; S&E, safety and efficacy.

Types of Marketing Authorizations

In the EU, 10 (66.7%) ATMPs have been authorized under standard approval, four (26.7%) under conditional approval and one (6.7%) under exceptional circumstances. In the USA, six (66.7%) have been authorized under standard approval and three (33.3%) under an accelerated approval program. Of the seven ATMPs authorized in both regions, the type of MA differed for only two ATMPs (28.6%); Yescarta and Kymriah were authorized under standard approval in the EU but under an accelerated approval program in the USA. Four out of eight products non-commercialized in the USA had a non-standard MA in the EU. Five therapies were withdrawn in the EU, whereas two of those are still authorized in the USA (Table 1).

Discussion

The major finding of the current study is that the main regulatory milestones are similar between regions, although some differences

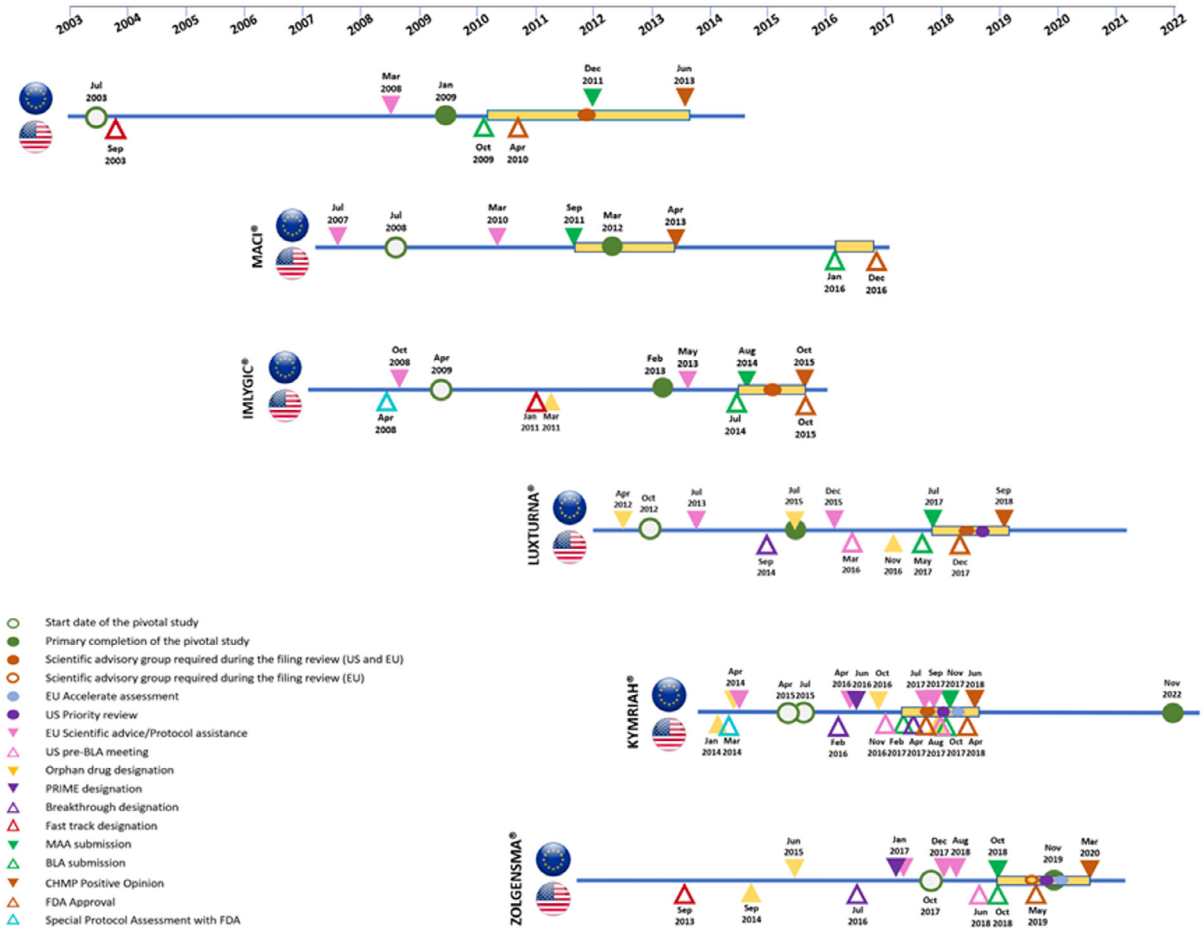

Figure 6. Comparison of regulatory pathways followed by ATMPs that were authorized in both regions. (Color version of figure is available online).

have become apparent (Figure 6). Over the last several years, a constant effort has been made to develop ATMPs focused mainly on orphan conditions. Almost 2100 clinical trials studying ATMPs were initiated between January 2014 and June 2019 worldwide, most of them cell and gene therapies in phase 1 or 2 of clinical development [6]. Interestingly, three times more of these interventional clinical trials were located in North America than in Europe. However, only 15 ATMPs in the EU and nine ATMPs in the USA had achieved MA by May 2020, representing 1.6% of overall approved products in Europe from 2009. These data reveal the necessity of understanding the gap between the large number of investigational products and the approved ATMPs and whether specific regulatory procedures were used to achieve their current status in the EU and the USA.

When analyzing all the steps involved in the procedure to achieve MA, the authors observed that more than half of the approved ATMPs obtained orphan status. With regard to the ODD programs in the EU and USA, medical plausibility and the prevalence of the disease need to be demonstrated. However, unlike in the EU, in the US there is no need to prove significant benefit over standard of care [7,8]. The authors' study indicates that in the EU, half of the approved ATMPs with an ODD targeted unmet medical needs, avoiding significant benefit demonstration and in part contributing to an open-label clinical designs. Moreover, the time analysis related to achieving orphan designation showed that there is no representative mean time to apply for the ODD; it is mainly product-specific and dependent on the duration of clinical development. Most of the approved therapies applied to the ODD once preliminary patient clinical data were available, possibly due to the fact that conventional non-clinical toxicological packages are not applicable to these therapies because of their patient specificity and lack of pre-clinical models [9]. By contrast, the therapies with a short period between granted ODD status and MAA submission might be in part due to the abbreviated clinical development, common in the case of advanced therapies, whereas those products with prolonged periods were probably attributable to recruitment issues, which are common in the case of rare diseases.

SA is a non-binding regulatory procedure offered to the sponsors at any stage of the ATMP development program. Although SA is not mandatory, it has been previously shown that products following SA recommendations at early stages of clinical development are more likely to achieve MA [10]. In the EU, advice can be provided by the EMA or the national competent authorities (NCAs). NCA SA is related to the suitability of early clinical development, whereas EMA SA will usually focus on the pivotal clinical trials that will support the MAA. Interestingly, half of the approved products did not seek advice from the EMA before starting the main study. This did not imply an impact on approval success, but a mean of two additional amendments to the protocol of the main study was observed. The fact that these therapies target unmet medical needs and the lack of clinical regulatory guidelines for specific medical conditions at that time might increase the need for this procedure. In 2020, the EMA has promoted a new pilot program to facilitate multiple SA procedures with the NCAs [11]. It should be noted that the review will be independent among the NCAs, and diverging opinions may still occur. Other options prior to a formal SA procedure include informal meetings with the NCAs in the EU focused on innovative therapies [12–14] or the so-called Innovation Task Force (ITF) and INitial Targeted Engagement for Regulatory Advice on CBER ProducTs (INTERACT) meetings with the EMA and FDA, respectively [15,16].

By contrast, the early development strategy should include discussions with the authorities regarding evidence generation. The abbreviated clinical development and non-controlled trials that accompany most ATMPs result in uncertainty about long-term efficacy and safety, which are the main constraints for obtaining product reimbursement [17]. Although approved through a standard authorization, Provenge, MACI and ChondroCelect were withdrawn because of poor commercial performance and/or lack of reimbursement in EU countries [18–20]. Despite the importance of this point, only 13% of the products conducted a parallel advice procedure with the EMA and European Network for Health Technology Assessment bodies [21].

In the USA, limited information with regards to meetings conducted with the FDA is available. Interestingly, in the case of ATMPs, special protocol assessment procedures were also reported, where the sponsors might reach an agreement with the FDA on the design and size of a single clinical trial to support the MA [22]. End-of-phase 2 meetings with the FDA are aimed at obtaining advice on pivotal study design and are similar to the EMA SA procedure when conducted with the same purpose. No comparisons between the two regions can be done for these SA procedures since there is no public information regarding when end-of-phase meetings were conducted with the FDA for the approved ATMP products.

Another milestone in the regulatory pathway in the EU and USA is the possibility of applying for an expedited program (see supplementary Table 1). These programs offer continuous support and guidance from the agencies during clinical development so as to optimize and speed up drug development plans and evaluation. Expedited programs are mainly aimed at those products that target unmet medical needs or serious conditions or bring a major therapeutic advantage to patients without treatment options. The FDA has created three types of expedited programs: the fast track designation in 1997, breakthrough therapy designation in 2012 and RMAT in 2016, whereas the EMA launched the PRIME designation scheme in 2016 [23–25].

The present data indicate that more breakthrough designations have been granted than PRIME designations for the approved ATMPs (44.4% versus 26.7%). Although a low number of approved ATMPs obtained PRIME designation, almost all of the approved ATMPs that were under development when these programs were launched benefited from them, except for Luxturna in the EU. The authors' results also demonstrate that the mean time from the start of the main clinical trial to obtaining PRIME or breakthrough designation and the mean time from obtaining these designations to MAA submission were similar for both regions. However, the time for obtaining PRIME designation might not be representative since, if this program was available at the time, it might have been granted earlier for these therapies based on exploratory clinical data. Further analysis is required to conclude the mean time for applying to this program, although, with regard to the current approved therapies, it was requested after the main clinical trial started. The fact that the breakthrough designation was available but obtained later during development might be attributed to the qualifying criteria of this program, where clinical evidence that demonstrates substantial improvement over available therapies is required.

With respect to Kymriah, Yescarta and Zolgensma, PRIME and breakthrough designations were obtained consecutively. Although the breakthrough therapy and PRIME designations are equivalent in the two regions, the development requirements and regulatory guidance may differ. However, the authors' data demonstrate that the access of ATMPs to expedited programs is approved or rejected similarly in both agencies.

In the USA, the RMAT designation includes all the benefits of the fast track and breakthrough therapy programs and does not require evidence to indicate that the drug may offer improvement over available therapies. Therefore, RMAT designation would have been an attractive option for these approved products, but it is assumed that development was already too far advanced at the time the RMAT designation was put in place by the FDA.

In the EU, there is a notable difference in the number of PRIME designations that have been granted for ATMPs in comparison with other products, including chemicals and other biological drugs. This fact emphasizes again the type of disease the current ATMPs target. Even if the clinical design for ATMPs is typically non-controlled, this does not seem to be an obstacle to getting the expedited designations.

The final step to achieving MA is the MAA. The standard timelines for a BLA review comprise 10 months of the 60-day filing date and around 11 months for the CHMP opinion in the EU (taking into consideration 210 days for the assessment and approximately 4 months for the clock stops). For priority reviews in the USA or AA in the EU, these standard timelines can be reduced to approximately 6 months (including a clock stop of 1 month in the EU) [26,27].

For the approved ATMPs, the time required from submission of the application to approval is shorter for the USA, requiring a mean of approximately 10 months less in comparison with the EU. In the EU, the median time required for the MAA evaluation under standard or accelerated review exceeds the theoretical standard timelines by approximately 7 and 5 months, respectively. In the USA, the median time of a priority review exceeds the theoretical timelines by only 0.56 months. It should be noted that all the products with PRIME and breakthrough designation obtained AA and priority review for the MAA, respectivetly.

The duration of the first clock stop in the EU MAA usually has an average of 3–6 months, and in the case of approved therapies, this tends to be toward the upper limit. Spherox is considered an outlier since it spent almost 4 years in clock stop, likely due to major issues related to quality. A similar case occurred with Holoclar, which had a clock stop of 13 months. The four therapies with PRIME designation had a considerably shorter clock stop compared with other therapies without these designations. Continuous guidance from the agencies during development might reduce the number of major objections during evaluation and help applicants anticipate the potential questions. In the case of the approved ATMPs, there were second rounds of outstanding issues after the second clock stop for half of the approved ATMPs and even third and fourth rounds for some products. This fact might reflect the immaturity of the data initially submitted. With the exception of Zolgensma, which had a second round of outstanding issues, none of the products with a PRIME designation had second rounds of questions after the second clock stop.

In the USA, those products with a breakthrough designation had shorter MAA review time, associated to a priority review. By contrast, the rolling review offers the possibility of submitting completed sections of the BLA, rather than waiting until the whole dossier required for the application is available [25]. Yescarta and Luxturna agreed on a rolling submission with the FDA, the latter also being eligible for priority review once the BLA was filed. The fact of having submitted this way did not shorten the BLA review timeline in comparison with other drugs that were submitted in a conventional manner.

In exceptional cases, during the EU or US MAA review there is the need for an ad hoc expert group consultation to clarify issues raised by the reviewers [28,29]. The fact that in both regions approximately half of the assessed products required this additional expert consultation indicates the complexity and specificity of these therapies, including the types of target diseases and clinical programs with alternatives designs. Interestingly, although the main development milestones are similar between the two regions, the issues raised to the external committees during the MAA for the approved ATMP differ between the agencies.

Regarding the milestone of obtainging an expedited MAA assessment, in the EU, an AA allows a reduction in the timeframe for the MAA if the product is of major interest to public health and therapeutic innovation. Under this procedure, a first 30-day clock stop is expected (compared with a standard 3- to 6-month clock stop), and a second clock stop should not occur [30]. Although four out of five products with a granted AA had the shortest review time compared with other approved ATMPs, with the exception of Zynteglo, the

timelines for approval did not meet the expectations of an AA, and there was a shift to the standard timelines. For Yescarta and Kymriah, the AA was no longer compatible because of major objections in the first and second clock stops, whereas Zolgensma presented deficiencies in many quality and clinical aspects of the dossier. Therefore, it would be advisable for the developers to present a mature dossier when requesting an AA and to anticipate potential questions that may arise during the clarification phase to shorten it as much as possible; otherwise, the AA loses its purpose.

The equivalent program in the USA is the priority review designation. Although the expedited review designations do not guarantee a priority review, most breakthrough therapy designation products are assigned priority status. The priority review involved a shorter review time in comparison with other approved therapies without this designation (i.e. Yescarta, Kymirah, Luxturna and Zolgensma vs laViv, Imlygic, MACI and Gintuit). For those products with an expedited MAA review in both regions, the time required from submission of the application to approval is shorter for the USA, requiring a mean of 4.4 months less in comparison with the EU, although this difference is not statistically significant.

Finally, with regards to the type of authorisation, a MA via the centralized procedure for an ATMP in the EU may be granted in three ways: standard, conditional or MA under exceptional circumstances [31,32]. In the USA, there are two types of MAs: the standard and the accelerated approval [33] (see supplementary Table 2). Although for most of the therapies approved in both regions the type of MA granted was equivalent, it might differ, as was the case with Yescarta and Kymriah. Half of the products commercialized not in the US but in the EU obtained a non-standard EU approval. Consequently, all of them required post-authorization studies to provide comprehensive and conclusive clinical data, which may sometimes also result in a negative benefit-risk balance. This was the case with Zalmoxis, which failed to show benefit on the primary endpoint, and the application had to be withdrawn [34].

The limitations of this study include the small sample size, above all for those ATMPs approved both in the EU and the USA, and further analysis is required to delineate differences between the two regions. In addition, this study was limited to approved ATMPs and did not include ATMPs under current development. The public information available is also not the same for the two regions, which hampered the analysis. Nevertheless, this is an exhaustive study that evaluates and compares, when possible, the regulatory steps taken for the ATMPs approved thus far, and no similar analysis was found in the literature by the authors.

Conclusions

The first ATMPs launched in the last decade mainly target orphan diseases. From a regulatory standpoint, there are multiple procedures available to facilitate and foster the development of these therapies, allowing an earlier MA. Although the EMA and FDA have their own regulatory recommendations with regard to pre-clinical and clinical development, the authors have demonstrated that the main regulatory milestones reached by the approved ATMPs are similar. Nevertheless, the number of authorized products and time for MAA evaluation, as well as type of MA for some products, differ between the two regions. Increased global regulatory convergence among the main regulatory agencies is a current topic of debate and might be one of the key factors in simplifying and expediting the approval of ATMPs.

Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article. The findings and conclusions in this article should not be construed to represent any agency determination or policy.

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Author Contributions

Conception and design of the study: CIL, AV, AA and MO. Acquisition of data: CIL. Analysis and interpretation of data: CIL, AV, AA and MO. Drafting or revising the manuscript: CIL. All authors have approved the final article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2020.11.008.

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Supplementary Material

Table S1: Expedited development and accelerate assessment programs in the EU and the USA

Expedited development programs		
	FDA	**EMA**
Program	***Fast Track Designation***	***(No equivalent)***
Qualifying criteria	• A drug that is intended to treat a serious condition AND • Nonclinical or clinical data demonstrate the potential to address unmet medical need	NA
Features	• Actions to expedite development and review (e.g. the product could be eligible for priority review if supported by clinical data at the time of marketing application submission) • Rolling review	NA
Program	***Breakthrough Therapy Designation***	***Priority Medicines (PRIME) designation***
Qualifying criteria	• A drug that is intended to treat a serious condition AND • Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	• Target conditions where there is an unmet medical need • Available data should support the claim that the product has the potential to bring a major therapeutic advantage to patients without treatment options (exploratory clinical trial phase)
Features	• Intensive guidance on efficient drug development (i.e. interactive communications to help the sponsor design and conduct efficient clinical trials that may require less time to complete facilitating coordinated internal interactions and communications with a sponsor) • Organizational commitment (i.e. assignment of cross-disciplinary project lead that will lease between members of the review team) All fast track designation features: • Rolling review • Other actions to expedite review	• Potential eligibility for accelerated assessment • Early appointment of a rapporteur from EMA's CHMP to facilitate continuity in support and building of knowledge in view of the submission of a marketing authorisation application • Kick-off meeting with a multidisciplinary group of experts from relevant EMA scientific committees and working parties to give preliminary guidance on the overall development plan and recommended regulatory pathway • Scientific advice at key development milestones with potential involvement of multiple stakeholders (e.g. health technology assessment bodies and patients), when relevant • Dedicated EMA contact point
Program	***Regenerative medicine advanced therapy (RMAT) designation***	***(No equivalent)***
Qualifying criteria	• A drug is a regenerative medicine therapy (a cell therapy, therapeutic tissue-engineering product, human cell and tissue product, or any combination product using such therapies or products*); AND	NA

Expedited development programs		
	FDA	**EMA**
	• it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; AND • if the preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition	
Features	• All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints • Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements	NA
Accelerate assessment and approval		
	FDA	**EMA**
Program	***Priority Review Designation***	***Accelerated Assessment Designation***
Qualifying criteria	• An application for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR • Any supplement that proposes a labelling change pursuant to a report on a paediatric study under 505A	• An application where the product is of major interest for public health and therapeutic innovation (usually the product addresses to an unmet medical by introducing new methods of therapy or improving the existing ones) • Applications under centralised procedure
Features	• Shorter clock for review of MAA (from 10 to 6 months)	• Shorter clock for review of MAA (from 210 to 150 days)

*Except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations. CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; FDA: Food and Drug Administration; MAA: marketing authorisation application; NA: Not applicable.

Table S2: Types and comparison of marketing authorisations in the EU and the USA

	FDA	EMA
Program	***Standard marketing authorisation***	***Standard marketing authorisation***
Features	● Comprehensive clinical data at the time of the MAA ● Positive benefit-risk balance ● Significant demonstration of safety and efficacy based on a therapeutically ● Relevant endpoint or when extensive clinical experience has been gained in the target patient population (including orphan drugs)	● Comprehensive clinical data at the time of the MAA ● Positive benefit-risk balance ● Significant demonstration of safety and efficacy based on a therapeutically ● Relevant endpoint or when extensive clinical experience has been gained in the target patient population (including orphan drugs) ● MAA valid for 5 years from the date of the EC decision, after which it may be renewed on application. Once renewed, the MA is valid for an unlimited period
Approved ATMPs	MACI®, Provenge®, Imlygic®, Luxturna®, Laviv® and Gintuit®	Chondrocelect®, MACI®, Provenge®, Imlygic®, Strimvelis®, Alofisel®, Spherox®, Luxturna®, Kymriah® and Yescarta®
Program	***Accelerate approval program***	***Conditional marketing authorisation***
Features	● Comprehensive clinical data may not readily be obtained ● Benefit-risk balance of the product must be considered positive pending confirmation from the comprehensive post-authorisation clinical data (phase 4 confirmatory trials) ● Serious conditions and unmet medical need based on a surrogate endpoint or intermediate clinical endpoints ● If the confirmatory trial shows that the drug actually provides a clinical benefit, then the FDA grants traditional approval for the drug.	● Comprehensive clinical data may not readily be obtained ● Anticipated positive benefit-risk balance of the product and requires confirmation from the comprehensive post-authorisation clinical data, which the applicant is expected to provide within a certain time frame. ● It may be possible to submit the application upon completion of Phase II studies or when initial efficacy, with a positive benefit-risk balance, is demonstrated through a surrogate clinical endpoint, such as a biomarker, rather than a direct therapeutic measure. ● MAA initially valid for 1 year, and may be renewed annually.
Approved ATMPs	Zolgensma®, Kymriah®, Yescarta®	Zalmoxis®, Holoclar®, Zynteglo® and Zolgensma®
Program	***(No equivalent)***	***Marketing authorization under exceptional circumstances***
Features	NA	● Extreme situations where comprehensive safety and efficacy data required are never expected to be obtained ● Specific obligations to monitor the ongoing safety of the product ● Accumulated clinical data are reviewed in an annual re-assessment procedure to continuously evaluate the benefit-risk balance ● MAA valid for 5 years, and continuation of the MA shall be linked to the annual re-assessment.
Approved ATMPs	NA	Glybera®

ATMPs: Advanced Therapy Medicinal Products; EMA: European Medicines Agency; FDA: US Food and Drug Administration; MAA: Marketing authorisation application; NA: Not applicable.

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REVIEW ARTICLE

Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States

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ABSTRACT

An environmental risk assessment (ERA) consists of an analysis of the risks to human health and the environment that a medicinal product may cause due to its release during clinical development or after entering the market. Regulators in European Union (EU) and the United States (US) require that advanced therapy medicinal products (ATMPs) that are also genetically modified organisms (GMOs) undergo an ERA in order to be approved for marketing authorization. This work aims to review the regulatory issues that need to be taken into consideration for carrying out an ERA, comparing the EU and the US. The European regulatory framework for environmental procedures and the dissimilarities in its implementation across the Member States and its implications at a logistical level are analyzed in detail. In addition, this review provides a brief insight into the non-clinical and clinical assessments that should be carried out during the development of the product in order to conduct a successful ERA, and thus facilitate its marketing authorization and post-marketing monitoring. Finally, the need for a European harmonization regarding environmental procedures for ATMPs is discussed.

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Table of contents

Introduction

Advanced therapy medicinal products (ATMPs) such as gene therapy medicinal products (GTMPs) are at the cutting edge of innovation and hold promise to cure or improve the quality of life for a variety of diseases for which there are no satisfactory therapies. In the case of medicinal products consisting or containing genetically modified organism (GMO), the requirement for conducting an environmental risk assessment (ERA) is regulated by the environmental and human drugs legislation. The clinical use of these therapies might bear a risk of inadvertent exposure of their constituents and/or derivatives into the environment with a potential impact on humans other than patients, causing potentially harmful effects on the ecosystem as well as on human health. GMOs contained in medicinal products may enter the environment by unintended dispersal of the product during administration, by accidental dissemination during product handling, by inappropriate disposal of waste or unused product, or via excretion by the patient. If the GMO is transmitted to other persons, such as medical staff or family members, or the environment at large, the GMO could potentially spread further, undergo genetic or phenotypic changes, infect, reproduce, remain latent, compete with existing species or transfer its genetic material to other species, altering human health and the environment. Therefore, the potential risks associated with such scenarios must be evaluated through an ERA. Both in European Union (EU) and United States (US), specific regulations were introduced around the end of the 1980s and early 1990s in order to guarantee the safe use of medicinal

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Table 1. Legislative and regulatory framework for environmental risk assessment for advanced therapies in the EU and the US.

Regulatory guidelines and legislation	
European Union	
Directive 2009/120/EC and Regulation (EC) No 1394/2007	Advanced therapy medicinal products regulation
Directive 2001/83/EC and Regulation 726/2004/EC	Procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing an EMA
Directive 2009/41/EC	Contained use of genetically modified micro-organisms
Directive 2001/18/EC	Deliberate release into the environment of genetically modified organisms Regulation
EMA (EMEA/CHMP/ICH/449035/2009)	General Principles to Address Virus and Vector Shedding
EMA (EMEA/CHMP/GTWP/125491/2006)	Guideline on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal products
EMA (CHMP/GTWP/60436/07)	Guideline on Follow-up of patients administered with gene therapy medicinal products
EMA (EMEA/CHMP/GTWP/125459/06)	Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products
EMA (CHMP/ICH/469991/2006)	General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors
EMA (EMEA/CHMP/BWP/135148/2004)	Environmental risk assessment for medicinal products containing, or consisting of, genetically modified organisms (Module 1.6.2)
EMA (EMEA/CHMP/BWP/473191/2006 – Corr)	Guideline on environmental risk assessment for medicinal products containing, or consisting of, genetically modified organisms
United States	
U.S. Food and Drug Administration (1998)	Environmental Assessment of Human Drug and Biologics Applications
U.S. Food and Drug Administration (2015)	Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products
U.S. Food and Drug Administration (2015)	Guidance document for industry on Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products
U.S. Food and Drug Administration (MAPP 5015.7 Rev. 1) (2017)	Manual of policies and procedures. Environmental Assessments and Claims of Categorical Exclusion
U.S. Food and Drug Administration (2015)	Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products
U.S. Food and Drug Administration (2018)	Long Term Follow-Up After Administration of Human Gene Therapy Products. *This guideline provides considerations for preclinical study design to assess biodistribution*
U.S. Food and Drug Administration (2008)	Content and Review of Chemistry, Manufacturing, and Control Information for Human Somatic Cell Therapy Investigational New Drug Applications. *A particular section of this guideline addresses how to the environmental impact should be addressed*
U.S. Food and Drug Administration (2018)	Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up. *This guideline provides recommendations regarding the testing for replication competent retrovirus during the manufacture and follow-up monitoring of patients: key factors to be considered in an ERA*
U.S. Food and Drug Administration (2016)	Recommendations for Microbial Vectors used for Gene Therapy. *This guideline considers biodistribution studies at preclinical level and shedding assessments as a part of clinical monitoring*
International guidelines	
ICH (2009)	General Principles to Address Virus and Vector Shedding
ICH (2006)	General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors
ICH (2009)	Oncolytic Viruses. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

EMA: European Medicines Agency; ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; FDA: U.S. Food and Drug Administration.

products containing a GMO (Anliker et al. 2010; Plan and Van Den Eede 2010; Acosta 2014).

This review briefly outlines the current regulatory framework in EU and US for the ERA procedures, and discusses the current divergences, hurdles and considerations for ATMPs clinical development relating to GMO applications in EU, bringing up the need for a harmonization. A brief outline of all reviewed legal acts is presented in Table 1.

Definition of genetically modified organisms and purpose of environmental risk assessment

In the EU and US, both GMO definitions are more focused on genetically modified plants and agricultural products rather in pharmaceutical products. According to Article 2 of the European Directive 2001/18/EC (Directive 2001/18/EC 2001), a GMO is defined as "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination", and in accordance with the same Directive, an "organism" is defined as "any biological entity capable of replication or of transferring genetic material". In the US, for the first time since 1986, are debating a possible change of the definition of a GMO due to the arrival of new techniques of genetic modification to ensure efficiently assessment of the risks of the future products of biotechnology (Barbero et al. 2017). According to the US Department of Agriculture (USDA), GMOs are organisms obtained through genetic engineering, defined as "the genetic modification of organisms by recombinant DNA techniques". The new definition proposed by USDA, genetic engineering would be a family of "techniques that use recombinant or synthetic nucleic acids with the intent to create or alter a genome" (FDA Code of Federal Regulations 2018). Therefore, many GTMPs such as recombinant oncolytic viruses, replication-incompetent viral vectors, and *ex vivo* genetically modified cells and other recombinant microorganisms fall within GMO definition. Not all ATMPs are by definition a GMO, for example peripheral blood mononuclear cells activated *ex vivo* with a recombinant fusion protein

(Sipuleucel-T) were excluded from this definition since the genetic material had not been altered (EMA/440011/2013 2013).

On the other hand, an ERA consists of an evaluation and estimation of the risks to human health and the environment that a medicinal product can pose due to its release during clinical development, or subsequently, once it is placed into the market. In this sense, the ERA identifies and evaluates the potential adverse effects of the medicinal product, either direct and indirect, immediate or delayed, and is a planning and decision-making tool in order to minimize or avoid these effects before they occur (Directive 2001/18/EC 2001). In EU, an ERA consists of a six-step process while in US is reduced to four-step, although the analysis is essentially the same (Table 2). Steps two and three of the European ERA are usually assessed simultaneously, and it is considered one single step in US. When an ERA is performed, it is important not to discount any potential adverse effect on the basis that it is unlikely to occur. Another consideration is that although the ERA should be based on quantifiable outcomes, it is likely that many of the results of the ERA will have to be qualitative (Directive 2001/18/EC 2001; European Commission 2002; FDA Center for Biologics Evaluation and Research (CBER) 1998).

Procedures for environmental risk assessment in the EU

Overview of the legislation and regulatory framework

During the lifecycle of a pharmaceutical product, an ERA is a mandatory procedure required by the regulatory authorities in order to further develop the products containing a GMO. This procedure is submitted prior to first-in-human clinical trial, during the subsequent clinical development and for the marketing authorization application (MAA). The documents to be submitted at these stages, and the regulatory authorities that will assess the procedure are different; during clinical development, the ERA, is conducted according to the requirements of the EU member state in which the trial will be performed, whereas for MAA it is centralized and reviewed by the Committee for Advanced Therapies (CAT), along with the Committee for Medicinal Products for Human Use (CHMP), at the European Medicines Agency (EMA).

The European legislative framework contemplates two possible ways in which a GMO can come into contact with the environment: a "contained use" and a "deliberate release". *Contained use* refers to any activity in which micro-organisms are genetically modified or in which such genetically modified micro-organisms (GMMs) are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment, for instance the use of GMOs in confined laboratories (Directive 2009/41/EC 2009). By contrast, *deliberate release* refers to any intentional introduction into the environment of a GMO for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment, i.e. in the context of research purposes when a product that consists/contains a GMO is tested in clinical trials, or when this product is placed to the market. Although the term GMM is used within the legal framework of contained use, and in the case of deliberate release, the term is GMO, the definitions of these two terms are virtually the same (Directive 2001/18/EC 2001). In both cases, before any GMO can be used in any of these contexts, the ERA should have been submitted and an authorization must have been granted. The requirements and the procedures for performing an ERA in each case are laid down in Directive 2009/41/EC (2009) and in Commission Decision 2000/608/EC10 for contained use of GMOs, and in Directive 2001/18/EC (2001) and in European Commission Decision 2002/623/EC11 for deliberate release. On one hand, the focus of Directive 2009/41/EC (2009) is on the assessment of the biosafety level classification of the GMO and the implementation of physical, chemical and biological barriers in order to limit the contact of the GMO with the environment. The risk classification has consequences for the procedure and review period of the application, and usually requires clinical site-specific notifications. On the other hand, Directive 2001/18/EC (2001) seeks to conduct an ERA that considers the effects on human health and the environment prompted by an intentional introduction of a GMO into the environment aiming to provide the safety measures necessary to minimize the potential risks. This Directive was primarily addressed for genetically modified plants and agricultural products, raising difficulties on preparing the ERA since the application forms are generally not designed for medicinal products (Buechner et al. 2018).

In terms of clinical development, two types of authorizations should be obtained in order to conduct a clinical trial with a GMO-containing medicinal product: one for the clinical trial application (CTA) reviewed by the ethics committees and competent national health authorities, and another one for the GMO application in order to "release" or to administer the GMO-containing medicinal product in that trial. The competent authorities (CAs) of each Member State in charge of GMO evaluations are the Ministries or agencies responsible for the environment in each country, along with a scientific advisory committee, which usually provides a recommendation to the CA on the ERA assessment (Table 3). The GMO application is usually submitted in parallel with the CTA, yet in some Member States such as Bulgaria, Poland, Romania, Slovenia and Slovakia, sponsors are required to obtain the GMO authorization before the CTA can be submitted. The information to be submitted comprises the comparison of the characteristics of the parental and the modified organisms, details on the genetic modifications, effects of inserted or deleted sequences, details on the release and the receiving environment, possible interactions between the GMO and the environment, and information on the monitoring, control, waste treatment and emergency response plans. The GMO framework does not apply in those cases where the product has been granted a marketing authorization and the use of the GMO in an intended clinical trial is in accordance with the summary of product characteristics, which aims to administer the product for the same indication, route of

Table 2. Environmental risk assessment step procedure in the EU and the US.

Region	ERA step process	Environmental analysis	Examples and/or Comments	Comparison
EU	1. Identification of characteristics which may cause adverse effects	• Characteristics of the GMOs linked to the genetic modification that may result in adverse effects on human health or the environment • Comparison of the characteristics of the GMO(s) with those of the non-modified organism under corresponding conditions of the release or use will assist in identifying the particular potential adverse effects arising from the genetic modification	• Location of the construction in the genome of the GMO where the transgenes were inserted • Potential interaction of the different transgenes • Phenotypic and genetic instability. • Spread of the GMO(s) in the environment (e.g. pathways of dispersal, biological fitness, etc.) • Interactions with other organisms	Equivalent to steps 1 and 2 of the ERA in US
	2. Evaluation of the potential consequences of each adverse effect, if it occurs	• For each adverse effect identified, the consequences for other organisms, populations, species or ecosystems exposed to the GMO have to be evaluated • In quantitative terms the magnitude should be expressed as "high", "moderate", "low" or "negligible"	• One single hazard could have more than one adverse effect, and the magnitudes of the individual adverse effects could be different	Equivalent to step 2 of the ERA in US
	3. Evaluation of the likelihood of the occurrence of each identified potential adverse effect	• Estimate how likely it is that adverse effects will actually occur. In some cases, both the likelihood and the frequency should be addressed. • The likelihood of the occurrence of an effect will depend on the specific risk management measures that may prevent that risk from occurring	• The relative likelihood of the consequence can probably not be assessed quantitatively, but it can be expressed in terms of "high", "moderate", "low" or "negligible"	Equivalent to step 2 of the ERA in US
	4. Estimation of the risk posed by each identified characteristic of the GMO(s)	• Estimation of the risk to human health or the environment posed by each identified adverse effects, given the state of the art, by combining the likelihood of the adverse effect occurring and the magnitude of the consequences, if it occurs • The overall uncertainty for each identified risk has to be described	• To include assumptions and extrapolations made at various levels in the ERA, different scientific assessments and viewpoints, uncertainties, the known limits of mitigation measures	Equivalent to step 2 of the ERA in US
	5. Application of management strategies for risks from the deliberate release or marketing of GMO	• The ERA may identify risks that require measures to manage them, and a risk management strategy should be defined	–	Equivalent to steps 3 and 4 of the ERA in US
	6. Determination of the overall risk of the GMO	• An evaluation of the overall risk of the GMO(s) should be made taking into account any risk management strategies which are proposed	–	Equivalent to step 3 of the ERA in US
US	1. Identification of substances subject to proposed action, which includes a description of the drug product and its potential metabolites, degradants, or by-products released into the environment	–	• Identify degradation products to be released • Identify known and potential variants of the GMO released into the environment (e.g. replication competent product may be present as an impurity) • Data to demonstrate the release of vector DNA into the environment (detectable by PCR at the injection site and/or in excreta)	Equivalent to step 1 of the European ERA

(*continued*)

Table 2. Continued.

Region	ERA step process	Environmental analysis	Examples and/or Comments	Comparison
	2. Identification and assessment of potential environmental effects	Assessment of the magnitude and likelihood of each environmental effect should be presented, and a conclusion should be given regarding the overall risk to the environment • To be based both on events known to occur and those that may be reasonably foreseeable • The likelihood of environmental effects may be assessed experimentally: amount of GMO and their metabolites released from patients into the environment, environmental decay and half-life measurements, frequency of uptake by susceptible species and estimates of infectious dose	• Identification of characteristics which may cause adverse effects: phenotypic attributes of the parental strain and/or vector, environment into which the GMO may be introduced, attributes of the genetic alteration • Assessment of the magnitude of each environmental effect combined with the likelihood of the effect occurring • The risk may be described in qualitative terms ranging from high, moderate, and low to negligible	Equivalent to steps 2, 3, and 4 of the European ERA
	3. Mitigation measures	• This section should describe any measures taken to avoid or mitigate the overall environmental risk and may include procedures to inactivate, contain, limit exposure, or monitor release of a product	–	Equivalent to step 5 of the European ERA
	4. Alternatives to the proposed action, which discusses alternatives that offer less environmental risk if potentially adverse environmental impacts are identified	• Measures may be proposed to mitigate individual effects and depending on the adequacy of these measures, they may lower the overall risk level	–	Equivalent to step 5 of the European ERA

Table 3. ERA framework for GMOs in some EU member states.

Member state	Competent authority	Scientific advisory committee	ERA Framework for clinical trials with GMOs
Netherlands	The Ministry of Infrastructure and Water Management (IenW) and the Office for Genetically Modified Organisms (GMO Office)	Netherlands Commission on Genetic Modification (COGEM)	Deliberate release
Germany	The Federal Office of Consumers Protection and Food Safety (BVL)	Central Commission on Biological Safety (ZKBS) and Paul-Ehrlich-Institute, residing with the Ministry of Health	Deliberate release
Spain	Ministry of Environment	The Spanish Biosafety Commission (CNB) and the Interministerial Advisory Committee (CIOMG)	Deliberate release
Italy	Italian Medicines Agency (AIFA), Ministry of Health (Competent Authority for the contained use), Ministry for Environment, Land and Sea Protection (Competent Authority for the deliberate release)	–	Depending on the potential for releasing the GMO in the environment and its capacity replicate, transmit and disseminate into the environment, clinical trials are handled as contained use or deliberate release activities
Belgium	Regional authorities from the Flemish, Walloon and Brussels-Capital Region are responsible for the contained use The Federal Agency for Medicines and Health Products (FAMHP; Competent Authority for the deliberate release)	Biosafety and Biotechnology Unit (SBB; responsible of the scientific evaluation of clinical trials regulated under the "contained use" framework) Belgian Biosafety advisory Council (advisory body for deliberate release)	For clinical trials in all cases an authorization must be obtained according to the contained use legislation. However, if there is a probability of possible release that may confer a risk to human health or the environment which cannot be avoided by proper management procedures or working practices, a notification under "deliberate release" is also required
France	Ministries of Environment, Agriculture, Research, Health and Consumer Affairs	Haut Conseil des biotechnologies	Depending on the potential for releasing the GMO in the environment, clinical trials are handled as contained use or deliberate release activities
Denmark	Working Environment Authority (WEA), Ministry of Employment, is responsible for the safety regarding contained use. Environmental Protection Agency (EPA), Ministry of Environment and Food of Denmark	–	Contained use
Finland	Board for Gene Technology	–	Depending on the potential for releasing the GMO in the environment and its capacity replicate, transmit and disseminate into the environment, clinical trials are handled as contained use or deliberate release activities
Poland	Ministry of the Environment	–	Contained use
Portugal	Portuguese Environment Agency (APA)	–	Depending on the potential for releasing the GMO in the environment and its capacity replicate, transmit and disseminate into the environment, clinical trials are handled as contained use or deliberate release activities

administration and pharmaceutical form. Otherwise, an evaluation would be required in terms of new potential risks that are not covered by the ERA performed for the MAA. In these cases, a special submission form should be provided (European Commission 2018).

Regarding marketing authorization, the MAA submitted to the EMA has to include an ERA, which corresponds to Section 1.6.2 of the MAA dossier included in Module 1, in accordance with the principles of deliberate release and assessed as part of the centralized procedure. This ERA, in accordance with Annex II of the Directive 2001/18/EC (2001), should follow the following general principles: the GMO should be compared to the non-modified organism from which it is derived, the ERA should rely on data derived from specific testing of the GMO during the development and performed on a case-by-case basis, and the ERA needs to be reevaluated if new information on the GMO or its effects on human health or the environment becomes available. The information to be submitted is outlined in the Annex IIIA, which applies to releases of all types of GMOs other than higher plants, and Annex IV of Directive 2001/18/EC (2001). The EMA has developed two guidelines to provide guidance on the preparation of the ERA for MAA (Table 1) (EMEA/CHMP/BWP/473191/2006 – Corr 2006; EMEA/CHMP/GTWP/125491/2006 2008). At the EMA, committee members from various states meet to make decisions about marketing approval, and the designated GMO CAs of all Member States are also consulted for review of the ERA (Anliker et al. 2010). Due to the procedural and scientific complexities associated with the ERA evaluation, the EMA recommends to request pre-submission meetings one year in advance of submission of the MAA (EMEA/CHMP/BWP/135148/2004 2005). Finally, after marketing authorization GMO-containing medicinal product is subject to traceability and a monitoring plan is to

be performed (Table 4). This monitoring plan should include systemic distribution and shedding in some cases, surveillance of long-term side effects, information about adverse or unexpected effects, monitoring effects in individuals other than the patient, if applicable, and information about off-label use (EMEA/CHMP/BWP/473191/2006 – Corr 2006).

Divergences across EU countries during clinical development

Although the mentioned European Directives define the legal framework and objectives to be met by the Member States regarding ERAs, these Directives have been implemented differently across European countries leading to different GMOs procedures and requirements. This lack of harmonization entails an impact on the logistics of product development that might affect times, costs and managerial burden. In a recent study conducted among commercial ATMP developers, where challenges experienced during various development phases were shared, the most often mentioned challenges were related to country-specific requirements, mainly driven by issues with the GMO legislation raised by GTMP developers. Developers experienced the GMO procedure as a confusing and resource-intensive process, leading to duplicate applications or additional inspections that result in time delays and consumption of extra resources (Ten Ham et al. 2018).

Different applicability of GMO definition

The applicability of the GMO definition has not been so trivial for some investigational products, such as naked nucleic acid or engineered cell therapies. For instance, so far, the European Member States have held diverging views on the inclusion of plasmids as GMO, and for a multinational clinical trial with the same investigational product there were contradictions regarding the need to submit an ERA procedure. Recently, 23 out of 28 countries of the European Economic Area (EEA) in 2018 along with the CAT, have agreed a common interpretation for GMO classification, although it has not been adopted yet by the European Commission (European Commission 2018). The most recent consensus establishes that a medicinal product for human use that consists of one (or more) plasmid(s) does not fall under the scope of the GMO framework, unless it might represent a potential risk; for example, a delivered plasmid encoding for an anti-HER2 antibody for the treatment of HER2-positive breast cancer (Schenk-Braat et al. 2007) does not require an ERA procedure, while a plasmid-based therapeutic vaccine for HIV is subject to an evaluation since it contains a viral sequence that might have an impact if released to the environment (European Commission 2013). Similarly, cell therapies need to be analyzed case by case, but those consisting of human cells that have been genetically modified with plasmids will generally not be considered as a GMO, provided that the plasmids are not integrative and non-replicative nor contain a viral sequence (European Commission 2018). On the other hand, investigational human cells genetically modified with viral vectors are regulated as GMOs, and the differences arise when some countries consider that both the viral vector (a starting material in *ex vivo* transductions) and the genetically modified cells (the drug product) are GMOs, whereas other countries consider that only the viral vector is a GMO (Alliance for Regenerative Medicine 2017). In addition, for modified cells expressing a therapeutic transgene, there might be slight differences when the organism(s) from which this insertion is derived (also called "donor organisms") needs to be defined, creating inconsistencies and confusion in the application process. For instance, it is common for chimeric antigen receptor T-cells (CAR-T) to be transduced with a replication-deficient viral vector carrying a CAR gene insert. The CAR receptor is usually derived from the murine monoclonal antibody fused to a human hinge region of an antibody and to human intracellular regions. Some countries consider that the donor organism is the viral vector, while in others the donor organism might be the viral vector and/or the *Homo sapiens* and *Mus musculus* species due to the genetic origin of CAR receptor (European Commission 2019b). The percentage of trials using genetically modified cells, such as CAR-T, is dramatically increasing (Acosta 2014; Sermer and Brentjens 2019), most of these cells being genetically modified *ex vivo* using retroviral or lentiviral vectors (Poorebrahim et al. 2019). For this reason, at the end of 2018, these 23 countries of the EEA endorsed a specific ERA with a common application form for clinical research with human cells genetically modified by means of retro/lentiviral vectors, reducing the administrative burden of the process and unifying the requirements for ERA. This common procedure is addressed to those cases in which it can be justified that there is no risk of formation of replication-competent viruses, and the finished product is free of infectious viral vector particles that can potentially be released in the environment (European Commission 2019a).

Finally, cells that have been modified with CRISPR/Cas9 technology should be considered a GMO by definition since the genetic material of the cells has been altered, even if no vector has been used. Some controversy has been generated regarding this issue and it is still under discussion. According to the publicly available information, two recent clinical trials that tested autologous CRISPR/Cas9-modified CD34+ human hematopoietic stem and progenitor cells were authorized after undergoing a GMO procedure (Kim et al. 2016; European Commission 2019b). In these cases, there is no donor organism since the genetic modification creates an insertion–deletion mutation by endogenous non-homologous end-joining following Cas9. As mentioned, the Directive 2001/18/EC 2001 on the deliberate release is focused on genetically modified plants and agricultural products, and contains what is known as a "mutagenesis exemption", which exempts organisms obtained by mutagenesis from the obligations imposed by the directive on GMOs. On 25 July 2018, the Court of Justice of the European Union ruled that the GMOs created using gene-editing technologies such as CRISPR/Cas9 are subject hereinafter to GMO regulations, although it does not specify if it is addressed to gene-edited crops and/or pharmaceutical products (Callaway 2018; Court of Justice of the European Union 2018). More clarifications

Table 4. Considerations of environmental risk assessment for the approved advanced therapy medicinal products in the EU and the US.

			Environmental assessment considerations in EU		Environmental assessment considerations in US
Product name	INN	Type of product	MAA	Post-marketing considerations/surveillance	MAA
Glybera	Alipogene tiparvovec	Non-cell-based GTMP: AAV-1 capsid with AAV-2 backbone expressing the S447X variant of the human lipoprotein lipase (LPL) gene. The virus is replication deficient and non-integrating.	• Discussion of the effects of over-expression of LPL in an otherwise healthy human, including an estimation of the exposure that an accidental self-inoculation would result in • Discussion of the risk of integration and potential insertional mutagenesis • Describe the origins of each of the vector genome sequences and provide details of these small intervening DNA sequences • Clarify if WPRE expressing X protein may be associated with oncogenesis • Since WHV is endemic to marmot species found in the EU were concerns whether the WPRE might be a novel sequence for this environment • Submission of batch release tests to preclude the presence of replication competent vector • Justification of pathogenicity of baculoviruses in humans since vector particles may contain fragments of baculovirus DNA which could encode for ORFs expressed late in baculovirus replication[a] • Justify the recombination events that might occur between baculovirus vectors during manufacture of Glybera and their potential to result in the formation of replication-competent AAV[a] • To justify the frequency of homologous recombination with sequences in the environment (horizontal gene transfer) and the possibility of uptake of vector DNA by microorganisms • Shedding and biodistribution studies were submitted • Discussion of possible gem line transmission • Discussion of potential dissemination of infectious disease or the creation new reservoirs or vectors • Justification for not conducting a post-marketing monitoring plan	• Long term monitoring was conducted on the health of patients and any healthcare workers accidentally exposed to the product	Not approved in US
Imlygic	Talimogene laherparepvec	Non-cell-based GTMP: Disabled recombinant HSV-1 encoding for human granulocyte macrophage	• Describe the tropism, pathogenicity and infection capability of talimogene laherparepvec in comparison to the wild type HSV1	• Evaluate the disseminated herpetic infection in	• An ERA was prepared pursuant to 21 CFR part 25. The ERA provided a quantitative assessment

(*continued*)

Table 4. Continued.

Product name	INN	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
			MAA	Post-marketing considerations/surveillance	MAA
		colony-stimulating factor (hGM-CSF) gene	• Discuss the potential recombination of talimogene laherparepvec with wild-type HSV-1 virus. Clinical data investigated whether talimogene laherparepvec after being injected intratumorally could also distribute to the site of natural HSV-1 infection and establish infection, latency and reactivation • Discussion of the potential transmission of talimogene laherparepvec to an unintended human recipient and establishment of latency/ re-activation • Discussion of the risks from inadvertent transmission, the likelihood of transmission to occur at the site of talimogene laherparepvec administration and the potential for exposure from the environment • Discussion of the magnitude of consequences of talimogene laherparepvec transmission to immune-compromised and pregnant individuals • The clinical pharmacology program was focused on the assessment of the viral clearance of talimogene laherparepvec by analyzing the biodistribution in the blood and urine, and viral shedding of the infectious virus (from the surface of injected tumor(s) and the exterior occlusive dressing)	immunocompromised patients • Monitor the potential transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Monitor symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients • Assessment of accidental exposure of HCP to talimogene laherparepvec • Additional clinical biodistribution and shedding data in melanoma	of Imlygic environmental exposure and environmental stability. • Evaluation of the biodistribution and shedding was subject of a postmarketing requirement (PMR) • Imlygic-associated herpetic infection in non-tumor tissue of treated patients (primary infection or reactivation/ latency) and contacts (transmission/accidental exposure) was a PMR requirement
Strimvelis	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Cell-based GTMP The viral vector is a replication deficient gamma-retroviral vector based on MoMLV	• Long-term monitoring of potential RCR in clinical trials. Discussion of homology with human endogenous retroviral sequences (HERV) • Two biodistribution studies were submitted • Discussion related to risk of germline transmission • Justification for not conducting shedding studies • Discussion of the probability of introducing surface-bound retroviral particles • Product-related manufacturing materials are tested for recombinant virus formation in line with good manufacturing practice	• Pharmacovigilance plan: development of RCR	Not approved in US
Zalmoxis	Allogeneic T cells genetically modified with a retroviral	Cell-based GTMP The γ retroviral vector	• Analysis of the characteristics of Zalmoxis and its components and their	• Pharmacovigilance plan: development of RCR	Not approved in US

(*continued*)

Table 4. Continued.

Product name	INN	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
			MAA	Post-marketing considerations/surveillance	MAA
	vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2))	used for *ex vivo* transduction is an integrative, replication defective vector	possible interaction with the environment, in particular any potential adverse effects due to survival, multiplication or dispersal • No specific studies on viral shedding were performed since no direct *in vivo* administration of the retroviral vector was foreseen • Discussion of possible gem line transmission of vector related sequence to the progeny and justification for not conducting studies • Discussion of the possibility to release free retroviral vectors or RCR and infection of non-target human and animal species		
Kymriah (tisagenlecleucel)	Patient's T cells are engineered *ex vivo* to express the anti-CD19 CAR using a CTL019 (murine) HIV-1 replication-defective vector, (recombinant third-generation self-inactivating lentiviral vector derived from the HIV-1 lentiviral genome)	Cell-based GTMP	• Assessment of the likelihood of presence of RCLs in the final product and subsequent transmission of RCRs to thirds • Assessment of the likelihood of formation of RCL in patients • Assessment of the likelihood of transmission of replication-incompetent vectors • Assessment of the likelihood of transmission of genetically modified T-cells by accidental administration to thirds or after bleeding	• Monitoring of RCR • Long-term safety	Categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c)
Yescarta (axicabtagene ciloleucel)	Patient's T cells are engineered *ex vivo* to express the anti-CD19 CAR using a replication incompetent γ-retroviral vector containing the CAR transgene	Cell-based GTMP			Categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c)
Luxturna (voretigene neparvovec)	Naturally-occurring AAV2, replication deficient, requiring co-infection with helper viruses to replicate. The vector genome contains the therapeutic gene expression cassette	Non-cell-based GTMP	• Justification for not performing sequencing of each batch, testing product identity on import into the EU, and testing for gene product expression and potency • Justification of the p5 promoter position and potential for minimizing homologous recombination between vector plasmid and packaging plasmid • Proof of absence of an ability to transform bacteria and possibly confer resistance to bacteria in the environment	• Long-term safety (> 9 years) • Third party transmission	• The ERA provided a quantitative assessment of the product environmental exposure based on data from biodistribution and shedding studies, lot release testing and related nonclinical studies, and a worst-case assumption in each case. (Studies were developed in parallel with EU)

(*continued*)

Table 4. Continued.

Product name	INN	Type of product	Environmental assessment considerations in EU		Environmental assessment considerations in US
			MAA	Post-marketing considerations/surveillance	MAA
			• Clinical shedding studies were performed analyzing samples of tears and serum in Phase III trials. • Biodistribution justification after sub-retinal injection of the product. The assays used to detect virus and immune response to the capsid and the transgene were not validated to an acceptable standard, and these data were not considered to be definitive		
ZOLGENSMA (onasemnogene abeparvovec-xioi)	Recombinant form of self-complementary AAV9, which contains human SMN protein-encoding transgene	Non-cell-based GTMP	Not approved yet in EU	No data available	• The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The Agency determined that approval of the drug product will not result in any significant environmental impact • Vector shedding after infusion with the drug product was investigated at multiple time points during the clinical study. Samples of saliva, urine and stool were collected the day after infusion • Biodistribution was evaluated in nonclinical studies and in two patients who died

AAV1: Adeno-associated virus serotype 1; AAV2: Adeno-associated virus serotype 2; ERA: environmental risk assessment; HSV-1: herpes simplex virus serotype 1; MAA: Marketing Authorization Application; MoMLV: Moloney murine leukemia virus; ORF: open reading frame; RCR: replication competent retrovirus; RCL: Replication Competent Lentivirus; WPRE: Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element; WHV: Woodchuck Hepatitis Virus.

[a]The GMO is manufactured using a system of three-recombinant baculoviruses in an insect cell line.

regarding this issue are expected from the European Commission throughout the coming years.

Different legal framework across EU countries

Another hurdle for applicants in the authorization of multinational clinical trials are the dissimilarities in the implementation of legislation among the Member States. The release of a GMO within the context of a clinical trial can be included within "contained use" or "deliberate release" regulations depending on the country (Table 3), resulting in wide variability on how the risk is assessed, the requirements and the documents to be submitted, as well as the procedure to be followed. Some Member States decide, on the basis of several factors of a clinical trial, whether a notification for deliberate or contained use is needed. Some of the factors are related with the features of the GMO (e.g. replication-deficient), probability of shedding (i.e. when the GMO is released into the environment via the patients' excreta), if proper management procedures and/or working practices are taken to prevent any possible release of the GMO, or if patients are hospitalized in a room that fulfills the contained use criteria or treated on an out-patient basis. For the other Member States, a clinical trial where GMO-containing medicinal products will be administered falls under the deliberate release legislation, regardless of the specific circumstances of the clinical trial. A European repository of national requirements has been created in order to disseminate the national GMO regulatory requirements and facilitate the development of these medicinal products (European Commission 2019c).

For some countries, the sponsor must decide into which category the GMO falls based on a preliminary risk assessment and considering the interpretation of national legislation for each procedure. In these cases, it is highly recommended to determine with the competent body which are the GMO classification and/or the procedure to follow before proceeding with the GMO evaluation. Since the CTA and the GMO procedures are reviewed by separate national agencies, some countries offer the possibility of coordinating a scientific advisory panel between both competent bodies, such as the case of Belgium (Willemarck et al. 2015). Other countries like the Netherlands offer an informal preliminary consultation of the draft GMO application in order to discuss whether sufficient information for a full risk assessment has been included, avoiding time delays after its submission (Gene Therapy Office 2019).

Considerations at logistical level

Although the same GMO is used at different phases of clinical development or in multiple parallel clinical trials, each clinical trial usually requires a separate GMO evaluation and authorization. The possibility of integrating one GMO assessment for a whole clinical development may be considered, but needs to be assessed by a CA on a case-by-case basis (European Commission 2018). This option might be feasible in cases where there are no contemplated changes throughout the clinical development plan that may alter the overall risk assessment. Changes during the clinical development plan may include variations in the indication or target population, manufacturing or formulation aspects that may alter the characteristics of the product or when the overall dose and exposure to the GMO per subject is likely to change. Obtaining this single authorization might also be easier in cases where the full clinical development is intended to be conducted in a single clinical site, and the analytical procedures to detect and identify the GMO are also carried out at the same site. By doing so, the technical aspects regarding the GMO manipulation by the hospital staff and the methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release will be the same or highly similar throughout the development. On the other hand, it should be considered that planning a full development program in advance is not common or trivial, since at early stage there is uncertainty as to the performance of the investigational medicinal product, and for some countries, final clinical protocols might be required. In addition, the measures to minimize risks when the product is administered/released should be established in advance, being more complicated for multicentre clinical trials where the hospital activities, including transport, storage, preparation, administration, disposal of the product (including patient samples) and the analytical procedures, should be defined.

From a scientific standpoint, the principles to be addressed for the overall GMO risk assessment are common among all EU member states since they are under the European legal framework. However, the documentation and requirements to be submitted, as well as the administrative fees and timelines differ for each country, adding complexity in the case of multinational clinical trials where several interactions with different regional stakeholders are needed; interactions with CA bodies, the investigators, biological safety officers, hospital pharmacy services of the clinical sites, etc. The duration of the procedure to obtain authorization may also depend on several regional factors and may differ across countries: the quality of the initial assessment provided by the sponsor in accordance with the requirements of each country, the timing of each CA body to perform the evaluation, or the time that it might take the sponsor to clarify the deficiencies dictated during the assessment. The latter point might require additional time-consuming studies, such as method validation or shedding studies. In addition, certain information related to the clinical trial and the GMO to be released is subject to 30 days of public evaluation through EU register, although this is usually done in parallel to the evaluation of each Ministry and competent committees. Finally, another point to consider is the coordination and the fees of all the necessary translations into the national languages of the documents.

Additionally, there are other specific considerations depending on the member state where the clinical trial will take place. For instance, in Germany the long-term storage of the GMO-containing product or contaminated materials at the study site are not covered by the release authorization, and interaction with the local GMO authorities are required (German Genetic Engineering Act 1993; Anliker 2016). In Belgium, the sponsor has to deliver to the Service Biosafety and Biotechnology (SBB) a control sample of the GMO along

with related scientific documentation, at the latest 15 days after the start of the trial, with the aim of detecting and identifying the recombinant virus or micro-organism in case of inspection or accidental release. The detailed protocol for the method of conservation and analysis of the control sample should be provided to a specific laboratory that will evaluate the data (Belgian Biosafety Server 2019).

In conclusion, multinational clinical trials involving a GMO should be carefully planned, not only taking into account the studies that may be required for the environmental risk evaluation, but also in terms of the specific documentation and requirements by each country and the estimated duration of each national procedure, in order to coordinate the intended start date of the trial and the overall costs, which include both the regulatory fees and translations.

The need for harmonization

The new Clinical Trials Regulation facilitates to conduct clinical trials in the EU, above all those that are multinational. Under this regulation, the requirements for clinical trials are harmonized across the EU and CTAs are submitted, centralized and assessed by a single authorization procedure (European Commission 2014). However, this new regulation does not consider the requirements of the GMO legislation and several initiatives have started to encourage the need for GMO harmonization, which is a current topic of debate. A multi-stakeholder meeting at EMA took place in 2016, where the divergences in the implementation of GMO procedures in Member States were discussed, as well as the need for changes to the GMO directive itself (EMA/345874/2016 2016). In 2017, the European Biopharmaceutical Enterprises (EBE), the Alliance for Regenerative Medicine (ARM), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the European Association for Bioindustries (EuropaBio) published a position paper proposing possible solutions to improve the European regulatory procedures for clinical trials with ATMPs consisting of or containing GMOs, bringing this topic into focus (Alliance for Regenerative Medicine 2017). In 2018, the European Commission along with the EMA initiated a dialogue with national CAs to address the discrepancies across the EU regarding the application of GMO Directives, with the aim to create coherent approaches without changing the basic legislation (EC and EMA Action Plan 2017; EMA/CAT/614550/2017 2017). So far, as previously discussed, a common position document has been launched in order to unify the interpretation of the GMO framework and the applicability of the GMO definition (European Commission 2018), and a common application form has been endorsed by the most CAs for human genetically modified cells and for those products containing AAV vectors (European Commission 2019a).

Procedures for environmental risk assessment in the US

In the US, environmental impacts from pharmaceuticals are assessed under the National Environmental Policy Act (NEPA) and NEPA regulations by the Food and Drug Administration (FDA; the federal regulatory medicines agency in the US). FDA's NEPA policies and procedures can be found under the Code of Federal Regulations (CFR) (21CFR Part 25) (Table 1). According to FDA, those products that consist of gene therapies, vectored vaccines, and related recombinant viral or microbial products should be evaluated for the need of an ERA. FDA regulations specify that an ERA must be submitted as part of investigations for new drug (IND) applications (the equivalent of a CTA in Europe), and for the MAA of a biologic product (named BLA in US; Biologics License Application), unless it qualifies for an ERA exemption, also called categorical exclusion (FDA Center for Biologics Evaluation and Research (CBER) 2015; National Environmental Policy Act 2019). IND applications for the development of an ATMP are ordinarily categorically excluded from the requirement to submit an ERA, unless extraordinary circumstances indicate that the specific action may significantly affect the quality of the environment. Possible exceptions may usually occur for use of virulent organisms or organisms that are ecologically more fit than their wild-type counterparts. The reason to consider a clinical development a categorical exclusion is that a clinical study involves small quantities of a medicinal product and a limited number of patients, not having a significant cumulative effect into the environment. Therefore, the regulatory process is very short, since the trials are usually exempt from an ERA (Rudelsheim and Smets 2012; FDA Center for Biologics Evaluation and Research (CBER) 2015).

The ERA exemption may also be applicable for the MAA in cases where the gene therapies "occur naturally in the environment", meaning that the product includes functional protein-coding sequences from one or more species within a single genus. This definition also includes products that differ from a wild-type substance only in attenuating point mutations or deletions, or that have been killed or inactivated by undergoing a specific manufacturing step designed to eliminate their ability to replicate. Thus, most MAA for GTMP will require an ERA, since they usually include functional protein-coding sequences from a different genus. However, unlike in the EU, genetically-modified human cells are considered substances that "occur naturally in the environment", since these cells are not viable in the environment and are degraded into naturally occurring substances (FDA Center for Biologics Evaluation and Research (CBER) 2015). In fact, the two approved CAR-T therapies in the US were granted with a categorical exclusion (FDA Center for Biologics Evaluation and Research (CBER) 2017a, 2017b). In those cases where the ERA is required, the necessary information is usually collected while conducting trials and not at an earlier stage of development.

Environmental studies during development of ATMPs

The ERA in EU and the US is based on nonclinical and/or clinical data, which mainly includes: description of the biological properties of the product that may pose a hazard, pathogenicity, its genetic stability, replication competence, host range, tissue tropism, the ability of the virus vector to survive after being shed, or the clearance, persistence and latency,

shedding and biodistribution (Anliker et al. 2010). Therefore, during the development of the product it is necessary to generate enough information to address all these issues and conduct a proper ERA (Table 1).

One of the most important factors to analyze consists in the shedding assessment, which is the dissemination of the virus/vector through secretions and/or excreta of the patient, i.e. saliva, sweat, urine, feces, nasopharyngeal fluids, blood, exudates from skin lesions, breast milk and semen. Shedding studies constitute the fundamental studies for an ERA, since they are used to understand the potential risk associated with transmission to third parties and the potential risk to the environment. These studies are usually carried out for oncolytic and virus-based gene therapy products, and not for genetically modified mammalian cells and other products (FDA Center for Biologics Evaluation and Research (CBER) 2014). When evaluating shedding, biological properties of the product such as replication competence, the status of the host including immunocompetence, dose and route of administration, sampling frequency and duration of sampling, and method analysis, are all important considerations for data interpretation (Okeke et al. 2017). The biological properties of the wild-type strain can provide guidance in shedding evaluations, as well as inventories of shedding data from publications on clinical gene therapy trials (Schenk-Braat et al. 2007). The nonclinical shedding assessments can be integrated into the design of other nonclinical studies such as preliminary and pivotal nonclinical studies. Clinical shedding assessments are also non-standalone studies and are integrated into the clinical trial designs. The nonclinical data allows the choice of clinical samples that need to be collected from subjects in a trial (e.g. feces, urine, nasal swabs), the frequency of sample collection and duration of the monitoring period; however, the type of samples required might differ depending on each region and Agency. There are two main guidelines that extensively explain how the design of the shedding studies and its analysis should be conducted; the EMA Guideline on general principles to address virus and vector shedding (ICH considerations) and the FDA Guideline on design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic products. The use of a quantitative polymerase chain reaction PCR (qPCR)-based assay and/or infectivity assays to detect viral/vector genetic material are the usual methods to assess the shedding, having into consideration that these methods should be qualified. Due to the increasing number of GTMPs under development, new ICH recommendations are expected, as well as an harmonization with regards to shedding assessment (ICH M6 2009).

Biodistribution assessments are also another key point for the ERA, as they provide information about the dissemination of the recombinant vector from the site of administration. This fact may influence the routes of shedding of the virus from the recipient, and therefore, the likelihood of transmission to third parties, including vertical transmission. Similarly to shedding assessments, biodistribution is usually part of the pivotal study and there is a minimum panel of tissues to be analyzed, apart from the ones considered necessary depending on the product and route of administration, i.e. blood, injection site(s), gonads, brain, liver, kidneys, lung, heart, and spleen (FDA Center for Biologics Evaluation and Research (CBER) 2018). If vector is detected in gonads, germline transmission studies should be performed (EMEA/273974/20 2006).

Depending on the features of the product and the results of the nonclinical and clinical development, it should be noted that the proposed Summary of Product Characteristics (SmPC) will communicate the risks of shedding and transmission to the prescribing physicians, as well as handling of the product should also adequately described. Some additional environmental considerations for approved ATMPs are summarized in Table 4.

General discussion and conclusions

In the EU, clinical trials with medicinal products that contain or consist of GMOs are subject to both clinical trials and environmental legislations under national competences, where an ERA needs to be submitted at each step of clinical development. In the US, an ERA is necessary for clinical trials only in specific cases, and it is required when the product nears commercialization. In this sense, compared to the European situation, GTMP developers do not need to produce as much information to conduct the ERA at an early stage of development or deal with the administrative burden that it entails. In addition, the lack of harmonization of the GMO requirements across the European Member States implies a challenge to integrate the GMO assessment in the clinical trial process, above all for multinational trials. Both in the EU and the US, there are harmonized and detailed guidelines on the ERA requirements for an MAA, where the assessment is evaluated under a centralized procedure by the EMA committees in the case of EU, and by the FDA in the case of US. While in the US there is the option of categorical exclusion for certain GTMPs, for the same product in EU a full ERA should be submitted in accordance with Annex II to Directive 2001/18/EC (2001) on the deliberate release, subject to a monitoring plan after its authorization. It is recommended to include shedding and biodistribution assessments at an early stage of development along with a full characterization of the product, as it will allow a proper ERA and will guide in the design of clinical studies, as well as facilitate the marketing authorization and post-marketing monitoring requirements. Although EU and US Agencies are actively supporting common scientific approaches on the regulation of ATMPs in order to facilitate their development, this is not the case with regard to environmental legislation that consists of (Reinforced EU/US Collaboration on Medicines 2018; Iglesias-López et al. 2019).

One of the current topics of debate in relation to environmental regulation is the need for a European harmonization that rationalizes regulatory processes and where the same scientific approaches are adopted. The rise of advanced therapies and their clinical use in a context of development or commercialization has highlighted these European differences, which is leading to great efforts for harmonization in a short time. Although there is currently a European repository that gathers the required requirements to carry out clinical trials with ATMPs, a centralized process is needed, such

the one that will be implemented with the new regulation for clinical trials, consisting of a single "on-line" node for the presentation and consultation of applications throughout the union, where the evaluation and supervision is coordinated by the member states with defined and established time-frames. This would allow the presentation of common documents in a single international language (i.e. English), reduce the times of applications and approvals, especially in multi-center trials, as well as reduce the translation burden to the official languages of each member state. This "single portal" would not have to circumvent certain specific national requirements, such as those mentioned for Germany or Belgium, and would still speed up the process. These specific requirements could be described in this portal in this single language, thus facilitating the procedures. On the other hand, it should be noted that in order to be able to present these common documents, first, an harmonization of which products are defined as GMO, which is considered "donor organism", a common terminology, or a homogeneous classification of "deliberate use" or "contained use" is essential. Although consensus documents are being launched for the EEA countries, a single, consensual European document is needed to address all these points of divergence. The coordination of a parallel review between the health authorities in charge of the CTA and the regulatory authorities for the GMOs is not so trivial, since they are different regulatory bodies evaluating different processes although within the same context, i.e. the clinical trial. This coordination could be handled by the Sponsor in order to minimize the time between both authorizations.

One of the proposed solutions that would further optimize these procedures is to adapt the future European portal for clinical trials to integrate the GMOs procedures. During the process a single coordinator and contact is proposed between the Sponsor and the authority responsible for CTA review and the regulatory organism responsible for the GMO. Finally, even more optimized would be the implementation of a specific centralized process for clinical trials with ATMPs consisting of or containing GMOs.

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Methodological Characteristics of Clinical Trials Supporting the Marketing Authorisation of Advanced Therapies in the European Union

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Several advanced therapy medicinal products (ATMPs) have been approved in the European Union (EU). The aim of this study is to analyse the methodological features of the clinical trials (CT) that supported the marketing authorization (MA) of the approved ATMPs in the EU. A systematic review of the characteristics of pivotal CT of ATMPs approved in the EU until January 31st, 2021 was carried out. A total of 17 ATMPs were approved and 23 CT were conducted to support the MA (median, 1, range, 1–3). Of those studies, 8 (34.78%) were non-controlled and 7 (30.43%) used historical controls. Only 7 (30.4%) were placebo or active-controlled studies. Among all CT, 21 (91.3%) were open-label and 13 (56.52%) had a single-arm design. To evaluate the primary endpoint, 18 (78.26%) studies used an intermediate and single variable. The median (IQR) number of patients enrolled in the studies was 75 (22–118). To date, ATMPs' approval in the EU is mainly supported by uncontrolled, single-arm pivotal CT. Although there is a trend toward an adaptive or a life cycle approach, a switch to more robust clinical trial designs is expected to better define the benefit and the therapeutic added value of ATMPs.

Keywords: drug development, drug approval, research design, methods, clinical trials, advanced therapies, cell- and tissue-based therapy, genetic therapy

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INTRODUCTION

Advanced therapy medicinal products (ATMPs) are a medicinal class that includes gene, cell and tissue therapies. The success of ATMP development and the approval of these therapies in the European Union (EU) has been crucial to the growth of clinical research during the last few years in this field, particularly for gene therapy.

Multiple indications are being targeted, most of them being refractory and recurrent stages of a disease that lacks effective therapeutic alternatives, and a significant proportion of them affecting the paediatric population (Alamo et al., 2019). With the introduction of ATMPs that can cover unmet needs and have the potential to cure life-threatening diseases, biological therapies initiated a shift from traditional clinical development pathway to an accelerated and highly product-specific one. The adaptive pathway concept and Priority Medicines scheme (PRIME) were launched in the EU specifically to speed the access of products targeting a significant unmet medical need. Several approved ATMPs were granted a PRIME designation

and accelerated marketing authorisation application assessment during their development, allowing early access to these medicines (Iglesias-Lopez et al., 2021a).

Due to the type of target diseases, the inherent complexity of these products, and their accelerated developments, less comprehensive clinical data might be generated. These characteristics may lead to uncertainties in the benefit/risk profile for the product at the time of marketing authorization (MA). The aim of this study is to further analyse the clinical development of the current approved ATMPs'. Here, we describe the methodological features of the clinical trials that have driven ATMPs to their European approval and we compare the gene therapy trials versus the cell and tissue engineered trials.

METHODS

A systematic review of the pivotal trials' features that supported the MA of the ATMPs approved in the EU was carried out using the following approach:

1) *Search strategy*: Data collection was primarily extracted from European Public Assessment Reports on the European Medicines Agency (EMA) website (www.ema.europa.eu). The search was carried out until January 31st, 2021. In addition, a search for the main clinical trials of the approved ATMPs was conducted using ClinicalTrials.gov database and the related publications.
2) *Eligibility criteria*: Only products classified as ATMPs according to the EMA criteria (European Medicines Agency, 2010; Iglesias-Lopez et al., 2019) and authorised under centralised procedure in the EU have been considered. Combined ATMPs class, i.e., ATMP combined with a medical device, have been grouped according to the main ATMP category: gene therapy medicinal product, somatic cell therapy medicinal products or tissue engineered products. Only those trials identified or referenced as pivotal, and therefore, decisive for the MAA were analysed.
3) *Data extraction and collected variables*: The authors designed specific data extraction forms using Excel 2019 (Microsoft Corporation, Redmond, WA, United States) to collect information. For each ATMP the following variables were collected: type of ATMP, pharmacotherapeutic group, ATC code, therapeutic area (according to MeSH terms), diseases and other circumstances for its use (according to chapter's title from the international version of the ICD-10), number of assessed clinical indications and pivotal clinical trials conducted. For each pivotal clinical trial, the following variables were selected: phase, design, type of randomization, type of control, type of study blinding, number of arms, participating centres, type of hypothesis and primary endpoint, presence and type of health-related quality of life (HRQoL) endpoints, presence of pre-specified analysis, duration of the main phase of the study, pivotal trial ongoing at the time of MAA, overall number of patients that participated in the study (enrolled, on intervention arm or control arm and safety set), age and sex of population, existence or absence of previous treatments, and geographic location of the pivotal trial. To determine if the study was ongoing at the time of the submission, the MAA submission date and the final data collection date for the primary outcome measure of the pivotal clinical trial were reviewed. Standard definitions of analysis set were used to classify among intended to treat (ITT), modified ITT (mITT) and per protocol set (PP) following ICH (E9) and EMA guidelines (ICH, 1998b; European Medicnes Agency, 2007). To assign the type of hypothesis in the case of two variables being used to evaluate the primary endpoint, the most robust variable was selected, i.e., final *versus* surrogate variables.
4) *Statistical analysis*: Statistical analysis for categorical and continuous variables was made using means of proportions, mean, standard deviation (SD), median, quartiles 25 and 75 (Q25, Q75), and range (minimum and maximum). The statistical analysis was performed using SAS® 9.4 (SAS Institute Inc., Cary, NC, United States).

RESULTS

A total of 17 ATMPs have been approved in the EU (**Table 1**) and 23 main trials were conducted to support the MA for these products (median, 1, range, 1–3). The ATMPs trials by disease area, according to ICD-10 classification, included: neoplasms (7), endocrine, nutritional and metabolic diseases (2), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (2), diseases of the eye and adnexa (2), diseases of the nervous system (1), diseases of the musculoskeletal system and connective tissue (3), diseases of the digestive system (1). In addition, there were 6 ATMPs for rare inherited disorders and 6 for neoplasms in which 4 were indicated for haematological malignancies and 2 for solid tumours. The detailed results of this study are presented in **Table 2** by type of ATMP, in **Table 3** for gene therapy studies and in **Table 4** for cell and tissue therapy studies.

Regarding the design of the studies, 13 (56.52%) were Phase 2/3 and Phase 3 trials, 9 (39.13%) were Phase 1/2 or Phase 2 trials, and 1 (4.35%) was a retrospective study. For all types of therapies, 8 (34.78%) trials were non-controlled, 7 (30.44%) where active- or placebo-controlled, and 7 (30.43%) used an historical control as comparator. Differences were observed between gene and non-gene therapies (**Supplementary Table S1** in Supplementary material). Six (42.87%) gene therapy studies were non-controlled and 6 (42.87%) used a historical control, whilst cell and tissue therapies studies were mainly controlled (66.66%). A total of 14 (60.87%) studies were not randomized. Similarly, differences in the existence of randomization between gene and non-gene therapies studies were also observed. Most of the studies for gene products lacked randomisation (85.71%), whereas this was present in 75% of the cell therapies studies and 80% of the tissue therapies studies. A total of 21 (91.30%) were open-label studies; all gene and tissue therapy studies were open-

TABLE 1 | Approved ATMPs in the European Union and therapeutic indication.

Trade name	International non-proprietary name (INN) or common name	Pharmacotherapeutic group/ATC code	Therapeutic area (MeSH)	Chapter's title from the international version of the ICD-10
Gene therapy medicinal products				
Kymriah®	Tisagenlecleucel	Antineoplastic agents/L01XX71	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	Neoplasms
Kymriah®	Tisagenlecleucel	Antineoplastic agents/L01XX71	Lymphoma, Large-B-cell, Diffuse	Neoplasms
Yescarta®	Axicabtagene ciloleucel	Antineoplastic agents/L01XX70	Lymphoma, Large-B-cell, Diffuse	Neoplasms
Tecartus®	Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured	Antineoplastic agents/L01X	Lymphoma, Mantle-Cell	Neoplasms
Imlygic®	Talimogene laherparepvec	Antineoplastic agents/L01XX51	Melanoma	Neoplasms
Glybera®	Alipogene tiparvovec	Lipid modifying agents/C10AX10	Hyperlipo-proteinemia type I	Endocrine, nutritional and metabolic diseases
Strimvelis®	Autologous CD34 $^{+}$ enriched cell fraction that contains CD34 $^{+}$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Immunostimulants/L03	Severe combined immunodeficiency	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
Luxturna®	Voretigene neparvovec	Ophthalmologicals, other ophthalmologicals/S01XA27	Leber congenital amaurosis Retinitis Pigmentosa	Diseases of the eye and adnexa
Zynteglo®	Betibeglogene autotemcel	Other haematological agents/ B06AX02	Beta-Thalassemia	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
Zolgensma®	Onasemnogene abeparvovec	Other drugs for disorders of the musculoskeletal system/M09AX09	Muscular Atrophy Spinal	Diseases of the nervous system
Libmeldy®	Atidarsagene autotemcel	Other nervous system drugs/N07	Leukodystrophy, Metachromatic	Endocrine, nutritional and metabolic diseases
Somatic-cell therapy medicinal products				
Provenge®	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (Sipuleucel-T)	Other immunostimulants/L03AX17	Prostatic Neoplasms	Neoplasms
Zalmoxis®	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	Antineoplastic agents/L01	Hematopoietic Stem Cell Transplantation Graft vs Host disease	Neoplasms Factors influencing health status and contact with health services
Alofisel®	Darvadstrocel	Immunosuppressants/L04	Rectal Fistula	Diseases of the digestive system
Tissue-engineered medicinal products				
Chondrocelect®	Characterised viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins/	Other drugs for disorders of the musculoskeletal system/M09AX02	Cartilage Diseases	Diseases of the musculoskeletal system and connective tissue
MACI®	Matrix-applied characterised autologous cultured chondrocytes	Other drugs for disorders of the musculoskeletal system/M09AX02	Fractures, Cartilage	Diseases of the musculoskeletal system and connective tissue
Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Other drugs for disorders of the musculoskeletal system/M09AX02	Cartilage Diseases	Diseases of the musculoskeletal system and connective tissue
Holoclar®	*Ex vivo* expanded autologous human corneal epithelial cells containing stem cells	Ophthalmologicals/S01XA19	Stem Cell Corneal Diseases	Diseases of the eye and adnexa

label, and this was also the approach for 50% of cell products trials. However, there is a difference in the blinding evaluation of the relevant endpoints between gene and non-gene therapy studies, as such evaluation is mostly absent in the case of gene therapies (85.71%) but is present in the case of cell and tissue engineered therapies (50% for cell therapy studies and 100%

TABLE 2 | Design features of pivotal clinical trials for the approved advanced therapy medicinal products in the European Union.

ATMP clinical development		Gene therapy medicinal products	Somatic cell therapy medicinal products	Tissue engineered therapies	All types of therapies
Number of products	**N**	**10**	**3**	**4**	**17**
Number of indications per product	Mean (SD)	1.10 (0.32)	1 (0)	1 (0)	1.06 (0.24)
Total number of pivotal trials and studies	N	14	4	5	23
—	Mean (SD)	1.27 (0.65)	1.33 (0.58)	1.25 (0.5)	1.28 (0.57)
—	(min, Max)	(1, 3)	(1, 2)	(1, 2)	(1, 3)
Clinical trials	—	—	—	—	—
Phase 1	N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Phase 1/2	N (%)	4 (28.57)	1 (25)	0 (0)	5 (21.74)
Phase 2	N (%)	3 (21.43)	0 (0)	1 (20)	4 (17.39)
Phase 2/3	N (%)	3 (21.43)	0 (0)	0 (0)	3 (13.04)
Phase 3	N (%)	4 (28.57)	3 (75)	3 (60)	10 (43.48)
Observational retrospective studies	N (%)	0 (0)	0 (0)	1 (20)	1 (4.35)
Randomization	—	—	—	—	—
No	N (%)	12 (85.71)	1 (25)	1 (20)	14 (60.87)
Yes 1:1	N (%)	0 (0)	1 (25)	4 (80)	5 (21.74)
Yes ≥2:1	N (%)	2 (14.29)	2 (50)	0 (0)	4 (17.39)
Control	—	—	—	—	—
Not controlled	N (%)	6 (42.87)	0 (0)	2 (40)	8 (34.78)
Placebo controlled	N (%)	0 (0)	2 (50)	0 (0)	2 (8.70)
Active controlled	N (%)	1 (7.14)	1 (25)	3 (60)	5 (21.74)
Historical control	N (%)	6 (42.87)	1 (25)	0 (0)	7 (30.43)
Other	N (%)	1 (7.14)	0 (0)	0 (0)	1 (4.35)
Blinding	—	—	—	—	—
Open label	N (%)	14 (100)	2 (50)	5 (100)	21 (91.30)
Single blind	N (%)	0 (0)	0 (0)	0 (0)	0 (0)
Double blind	N (%)	0 (0)	2 (50)	0 (0)	2 (8.70)
Blinding evaluation	—	—	—	—	—
Yes	N (%)	2 (14.28)	2 (50)	5 (100)	19 (82.61)
No	N (%)	12 (85.71)	2 (50)	0 (0)	4 (17.39)
Multicentric	—	—	—	—	—
No	N (%)	4 (28.57)	0 (0)	0 (0)	4 (17.39)
Yes	N (%)	10 (71.43)	4 (100)	5 (100)	19 (82.60)
Number of arms	—	—	—	—	—
1 arm	N (%)	11 (78.57)	1 (25)	1 (20)	13 (56.52)
2 arms	N (%)	2 (14.29)	3 (75)	3 (60)	8 (34.78)
3 arms	N (%)	1 (7.14)	0 (0)	1 (20)	2 (8.70)
Design	—	—	—	—	—
Parallel groups	N (%)	2 (14.29)	3 (75)	3 (60)	8 (34.78)
Single arm	N (%)	11 (78.57)	1 (25)	1 (20)	13 (56.52)
Other	N (%)	1 (7.14)	0 (0)	1 (20)	2 (8.70)
Main Outcomes	—	—	—	—	—
Final variable	N (%)	2 (14.28)	2 (50)	1 (20)	5 (21.74)
Intermediate variable	N (%)	12 (85.71)	2 (50)	4 (80)	18 (78.26)
Co-primary	N (%)	2 (14.28)	1 (25)	1 (20)	4 (17.39)
Composite variable	N (%)	1 (7.14)	0 (0)	0 (0)	1 (4.35)
Single variable	N (%)	11 (78.57)	3 (75)	4 (80)	18 (78.26)
Type of variable for main outcome	—	—	—	—	—
Qualitative	N (%)	13 (92.85)	3 (75)	1 (20)	17 (73.91)
Quantitative (discrete and continuous)	N (%)	2 (14.28)	1 (25)	4 (80)	7 (30.43)
Health related quality of life	—	—	—	—	—
No	N (%)	7 (50)	2 (50)	1 (20)	10 (43.48)
General questionnaires	N (%)	5 (35.71)	1 (25)	1 (20)	7 (30.43)
Specific questionnaires	N (%)	4 (28.57)	1 (25)	4 (80)	9 (39.13)
Prespecified previous analysis	—	—	—	—	—
Interim analysis	N (%)	11 (78.57	3 (75)	3 (75)	17 (73.91)
Final analysis type (primary analysis)	—	—	—	—	—
ITT	N (%)	10 (71.43)	3 (75)	5 (100)	18 (78.26)
mITT	N (%)	2 (14.28)	0 (0)	0 (0)	2 (8.69)
PP	N (%)	2 (14.28)	0 (0)	0 (0)	2 (8.69)
Hypothesis	—	—	—	—	—
Superiority	N (%)	1 (7.14)	3 (75)	1 (20)	5 (21.74)
Non-inferiority	N (%)	0 (0)	0 (0)	2 (40)	2 (8.7)

(Continued on following page)

TABLE 2 | (*Continued*) Design features of pivotal clinical trials for the approved advanced therapy medicinal products in the European Union.

ATMP clinical development		Gene therapy medicinal products	Somatic cell therapy medicinal products	Tissue engineered therapies	All types of therapies
Number of products	**N**	**10**	**3**	**4**	**17**
Other	N (%)	13 (92.85)	1 (25)	2 (40)	16 (69.56)
Mean time for the main phase (months)	Mean (SD)	11.5 (9.30)	70.50 (91.22)	24 (9.80)	35.33 (31.08)
Ongoing at the time of the MAA submission (final data for primary outcome measure)	—	—	—	—	—
Yes	N (%)	8 (57.14)	3 (75)	1 (25)	12 (57.14)
No	N (%)	6 (42.86)	1 (25)	3 (75)	10 (47.62)
Population	—	—	—	—	—
Population randomized/enrolled	N	1,065	798	543	2,406
—	Median (Q25 - Q75)	22 (18.75–106.5)	134.5 (27–437)	104 (88.50–131)	75 (22–118)
—	(min, Max)	(5, 437)	(17, 512)	(75, 144)	(5, 512)
Population on intervention arm	N	797	495	254	1,546
—	Median (Q25 - Q75)	21.5 (11.5–93.75)	68.5 (20.25–282.5)	64.5 (53.25–72.75)	41 (16.25–93.75)
—	(min, Max)	(5, 296)	(17, 341)	(52, 73)	(5, 341)
Population on control arm	N	151	416	183	750
—	Median (Q25, Q75)	75.5 (NA)	140 (105–171)	61 (50–72)	88.50 (27.5–140.5)
—	(min, Max)	(10, 141)	(105, 171)	(50–72)	(10, 171)
Population on safety set	N	933	780	439	2,152
—	Median (Q25 -Q75)	22.5 (13.5, 93.75)	128.5 (25.75–430.75)	110 (81.75–137.5)	63.5 (20–118)
—	(min, Max)	(5, 419)	(17, 506)	(75, 144)	(5, 419)
Age of adult population (years)	Mean (SD)	54.29 (9.24)	52.77 (16.67)	37.14 (5.56)	47.84 (18.45)
Age of paediatric population (years)	Mean (SD)	6.15 (8.26)	NA	NA	6.15 (8.26)
Sex	—	—	—	—	—
Female	N (%)	443 (47)	191 (30.31)	231 (42.54)	865 (37.53)
Male	N (%)	498 (53)	630 (76.73)	312 (57.45)	1,440 (62.47)
Location of the pivotal clinical trial	—	—	—	—	—
United States	N (%)	9 (64.28)	1 (25)	0 (0)	10 (43.48)
Europe	N (%)	10 (71.42)	3 (75)	5 (100)	18 (78.26)
Canada	N (%)	5 (35.71)	1 (25)	0 (0)	6 (26.09)
Others	N (%)	7 (50)	3 (75)	0 (0)	10 (43.48)
Previous treatments	—	—	—	—	—
Yes and No	N (%)	1 (7.14)	0 (0)	0 (0)	1 (4.35)
No	N (%)	3 (21.74)	0 (0)	2 (40)	5 (21.74)
Yes	N (%)	10 (65.21)	2 (50)	3 (60)	15 (65.22)

ITT: intended to treat; mITT: modified intended to treat; NA: not applicable; PP: per protocol set; Zynteglo pooled analysis (Studies HGB-204, HGB-205 and LFT-303) was counted as one pivotal study; Holoclar retrospective study was counted as a pivotal study, since it was considered the main study which lead to the Marketing Authorisation of the product; The final analysis type (primary analysis) for TK0008 study of Zalmoxis was not available; The mean time for the main phase excludes Provenge (defined as 'until disease progression or death') and TK0008 study for Zalmoxis; Age of adult population: data not available for TK0008 study for Zalmoxis; Age of paediatric population: data only available for Tecartus, Libmeldy, Kymriah and Strimvelis; Previous treatments: not applicable for Zalmoxis. For the Health related quality of life outcomes, the percentages can exceed 100% given that there might be multiple questioners for the same product (i.e., generic and disease-specific).

tissue engineered therapy studies). A total of 13 (56.52%) studies were single-arm trials and 10 (43.48%) had two or more arms. A difference in the number of arms between gene and non-gene therapy studies was also observed, where single-arm studies comprised 78.57% of total trials for gene therapy products versus the two- or three-arm designs present in 75% of cell therapy studies and 80% of tissue therapy studies. Accordingly, there are some differences in the design between gene and non-gene therapies studies, mainly in the parallel designs for cell and tissue engineered therapy studies versus single-arm designs for gene therapy studies. Of all studies analysed, 19 (82.60%) were multicentric.

Regarding the methodology used in these pivotal studies, 16 (69.56%) of the studies did not use a superiority or non-inferiority hypothesis but an alternative premise, e.g., comparison with historical controls. There is a difference between gene and non-gene therapies studies, where this type of alternative premises was mainly used for gene therapies trials (92.85%), while standard superiority or non-inferiority tests were used more frequently for cell and tissue engineered therapies trials (75 and 60%, respectively). To evaluate the primary objective, 18 (78.26%) of the trials used an intermediate and single main variable, which was mainly qualitative (73.91%). Final and quantitative variables were used in 5 (21.74%) and 7 (30.43%), respectively, which represents a smaller proportion (**Table 5**). Of these confirmatory studies, 18 (78.26%) used the intention-to-treat (ITT) principle in assessing the primary efficacy, 2 (14.28%) gene therapy trials used modified intention-to-treat (mITT) and 2 (14.28%) used per protocol set (PP). A total of 16 (69.56%) analysed studies included HRQoL questionnaires, 9 (39.13%) of

TABLE 3 | Design features of pivotal clinical trials for the approved gene therapy medicinal products in the European Union.

Gene therapies	Glybera®			Imlygic®	Strimvelis®	Yescarta®	Kymriah®		Luxturna®	Zynteglo®		Zolgensma®	Tecartus®	Libmeldy®
CHMP Positive Opinion date	Jun-23-11			Oct-22-15	Apr-01-16	Jun-28-18	Jun-29-18		Set-20-18	Apr-26-19		Mar-26-20	Oct-15-20	Oct-15-20
Authorisation status/type	Withdrawn			Authorised	Authorised	Authorised	Authorised		Authorised	Authorised		Authorised	Authorised	Authorised
Type of authorisation	Under exceptional circumstances			Standard	Standard	Standard	Standard		Standard	Conditional		Conditional	Conditional	Standard
Clinical trial Acronym	CT-AMT-011–01	CT-AMT-011–02	CT-AMT-010–01	Study 005/05	Study AD1115611/ Gene-ADA	ZUMA-1	Study B2202	Study C2201	AAV2-hRPE65v2-301/302	Studies HGB-204, HGB-205 and LFT-303	Studies HGB-207, HGB-212	Study CL-303 (STR1VE)	ZUMA-2	Study 201,222
Phase	II/III	II/III	II/III	III	I/II	I/II	II	II	III	I/II	III	III	II	I/II
Randomization	No	No	No	2:1	No	No	No	No	2:1	No	No	No	No	No
Control	Non-controlled	Non-controlled	Non-controlled	Active control	Historical control	Historical control	Historical control	Historical control	Delayed-intervention control group	Non-controlled	Non-controlled	Historical control	Non-controlled	Historical control
Blinding design	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label	Open label
Blinding evaluation	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No
Multicentric	Single-centre	Dual-centre	Single-centre	Multicentric	Single-centre	Multicentric	Multicentric	Multicentric	Dual-centre	Multicentre	Multicentre	Multicentre	Multicentre	Single-centre
Number of arms	Three	One	One	Two	One	One	One	One	Two	One	One	Two	One	One
Design	Parallel arms (dose range)	Single arm	Single arm	Parallel arms	Single arm	Single arm	Single arm	Single arm	Parallel arms	Single arm	Single arm	Single arm	Single arm	Single arm
Main Outcomes	Intermediate and single variable	Intermediate and single variable	Intermediate and composite variable	Intermediate and single variable	Final and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Final and co-primary variable	Intermediate and single variable	Intermediate and co-primary variable
Type of variable for main outcome	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Quantitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative and Quantitative
Health related quality of life	No	General questionnaire	No	Specific questionnaire	No[a]	No	General questionnaire	General and specific questionnaires	No	No	General and specific questionnaires	No	General questionnaire	Specific questionnaire
Prespecified previous analysis	Interim analysis	Interim analysis	N/A	Interim analysis	None	Interim analysis	Interim analysis	Interim analysis	None	Interim analysis	Interim analysis	Interim analysis	Interim analysis	Interim analysis
Final analysis type (primary efficacy analysis)	ITT	ITT	ITT	ITT	ITT	mITT	PP	PP	ITT	ITT	ITT	ITT	mITT	ITT
Hypothesis	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention	Superiority over an active control	Superiority over historical control group	Intervention compared to historical control	Description of efficacy of intervention	Intervention compared to historical control	Intervention compared non-intervention (natural history)	Description of efficacy of intervention	Description of efficacy of intervention	Superiority versus natural observation study	Description of efficacy of intervention	Superiority versus natural history cohort (or untreated sibling when available)

(Continued on following page)

TABLE 3 | (*Continued*) Design features of pivotal clinical trials for the approved gene therapy medicinal products in the European Union.

Gene therapies	Glybera®		Imlygic®	Strimvelis®	Yescarta®		Kymriah®	Luxturna®	Zynteglo®		Zolgensma®	Tecartus®	Libmeldy®
Mean time for the main phase (months)	3	3	3	12	36	12	3	12	12	12	14	3	24
Ongoing at the time of the MAA submission (final data for primary outcome measure)	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Two studies ongoing	Yes	Yes	No	No
Population	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Population randomised/ enrolled	22	5	18	437	12	111	92	147	31	22	19	22	105	22
Population on intervention arm	14	5	8	296	12	101	75	99	21	22	10	22	92	20
Population on control arm	NA	NA	NA	141	NA	NA	NA	NA	10	NA	NA	NA	NA	NA
Population on safety set	14	5	8	419	12	101	75	99	29	23	14	22	92	20
Age of population (years)	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Mean	45.6	41.8	N/A	63.07	1.7	56.3	12	54	N/A	N/A	N/A	0.31	65	3.6
Sex														
Female	9	1	N/A	250	5	33	32	36	18	15	6	12	15	11
Male	5	4	N/A	187	7	68	43	63	13	7	5	10	77	9
Geographic region	—	—	—	—	—	—	—	—	—	—	—	—	—	—
North America	X	X	—	X	—	X	X	X	X	X	X	X	X	—
Europe	—	—	X	X	X	X	X	X	—	X	X	—	X	X
Others	—	—	—	X	X	X	X	X	—	X	X	—	—	—
Previous treatments	Yes	Yes	Yes	Yes/No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No

ITT: intended to treat; mITT: modified intended to treat; NA: not applicable; N/A: not available; PP: per protocol set.

[a]*Not at the time of the submission. The HRQoL objective applied to the long-term follow-up (4–8 years after gene therapy) only.*

TABLE 4 | Design features of pivotal clinical trials for the approved cell and tissue engineered therapy medicinal products in the European Union.

	Cell therapies				Tissue therapies				
	Provenge®	**Zalmoxis®**		**Alofisel®**	**ChondroCelect®**	**Holoclar®**	**MACI®**	**Spherox®**	
CHMP Positive Opinion date	Jun-12-13	Jun-23-16		Dec-14-17	Jun-25-09	Mar-06-13	Apr-25-13	May-18-17	
Authorisation status	Withdrawn	Withdrawn		Authorised	Withdrawn	Authorised	Withdrawn	Authorised	
Type of authorisation	Standard	Conditional marketing authorisation		Standard	Standard	Conditional	Standard	Standard	
Clinical trial Acronym	9902B (IMPACT)	TK007	TK008	ADMIRE-CD	TIG/ACT/01&EXT′	HLSTM01	SUMMIT	Cod 16 HS 14	Cod 16 HS 13
Phase	III	I/II	III	III	III	Observational retrospective study	III	II	III
Randomization	2:1	No	3:1	1:1	1:1	No	1:1	1:1:1	1:1
Control	Placebo	Historical control[a]	Active treatment	Placebo	Active treatment	Non-controlled	Active treatment	Non-controlled	Active treatment
Blinding	Double-blind	Open-label	Open-label	Double-blind	Open-label	Open-label	Open-label	Open-label	Open-label
Blinding evaluation	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Multicentric	Multicentric	Multicentric	Multicentric	Multicentric	Multicentric	Dual-centre	Multicentric	Multicentric	Multicentric
Number of arms	Two	One	Two	Two	Two	One	Two	Three	Two
Design	Parallel groups	Single arm	Parallel groups	Parallel groups	Parallel groups	Retrospective case-series	Parallel groups	Single arm (three doses)	Parallel groups
Main Outcomes	Final and single variable	Intermediate and single variable	Intermediate and single variable	Final and co-primary variable	Intermediate and co-primary variable	Final and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable
Type of variable for main outcome	Qualitative	Qualitative	Quantitative	Qualitative	Quantitative	Qualitative	Quantitative	Quantitative	Quantitative
Health related quality of life	No	No	General questionnaire	Specific questionnaire	Specific questionnaire	No	General and Specific questionnaire	Specific questionnaire	Specific questionnaire
Prespecified previous analysis	Interim analysis	None	Interim analysis	Interim analysis	None	NA	Interim analysis	Interim analysis	Interim analysis
Final analysis type (primary efficacy analysis)	ITT	ITT	NA	ITT	ITT	ITT	ITT	ITT	ITT
Hypothesis	Superiority over placebo	Description of efficacy of intervention	NA	Superiority over placebo	Non-inferiority vs SOC	Exploratory	Superiority over SOC	Superiority over baseline for the three dose groups	Comparison with baseline and non-inferiority/ superiority with SOC
Duration of the main phase (months)	Until disease progression or death	135	NA	6	36	NA	24	12	24
Ongoing at the time of the MAA submission (primary completion)	No	No	Yes	No	No	NA	Yes	Yes	Yes
Population	—	—	—	—	—	—	—	—	—
Population enrolled	512	57	17	212	118	NA	144	75	102
Population on intervention arm	341	30	17	107	57	104	72	73	52
Population on control arm	171	140	Not known	105	61	NA	72	NA	50
Population on Safety set	506	52	17	205	118	NA	144	75	102

(Continued on following page)

TABLE 4 | (*Continued*) Design features of pivotal clinical trials for the approved cell and tissue engineered therapy medicinal products in the European Union.

	Cell therapies			Tissue therapies				
	Provenge®	**Zalmoxis®**	**Alofisel®**	**ChondroCelect®**	**Holoclar®**	**MACI®**	**Spherox®**	
Age of population	—	—	—	—	—	—	—	—
Mean	71	49	N/A	38.3	33.9	46.8	34	34	37
Sex	—	—	—	—	—	—	—	—	—
Female	NA	30	N/A	161	42	24	51	53	61
Male	512	22	N/A	96	76	80	93	22	41
Geographic region	—	—	—	—	—	—	—	—	—
North America	X	—	—	—	—	—	—	—	—
Europe	—	X	X	X	X	X	X	X	X
Others	—	X	X	X	—	—	—	—	—
Previous treatments	Yes	NA	NA	Yes	Yes	Yes	No	No	No

ITT: intended to treat; NA: not applicable; N/A: not available; SOC: standard of care.

[a]*Upon assessment of the TK007 data and as only limited data from the TK008 study were available, the applicant was asked to perform a comparison of the MM-TK treated patients (TK007 and TK008 combined) with results from suitable historical controls.*

those being disease-specific. No differences were observed in the type of HRQoL questionnaires between gene and non-gene products studies, i.e., generic versus disease-specific variables.

The mean (SD) time for the main phase of the trial was 35.33 (31.08) months, approximately 1 year for the gene therapies and more than 2 years for cell and tissue engineered therapies. A total of 12 (57.14%) studies were ongoing at the time of submission, meaning that the final data collection for primary outcome measuring was not completed. Globally, 17 (73.91%) of the studies had a prespecified interim analysis, with similar proportion among the three types of ATMPs (75–78.57%).

Regarding the overall population size and location of these studies, the median (IQR 25–75) number of patients enrolled in the analysed ATMPs pivotal clinical trials was 75 (22–118). The mean ± SD age of the adult population included in these confirmatory trials was 48 ± 18.45 years old. There is no sufficient data to establish a mean ± SD age for paediatric populations. The sex distribution is higher for males (62.47%) than for women (37.53%). The analysed clinical trials were equally performed in both women and men, but the overall sex distribution was higher for males due to Provenge®'s indication, i.e., treatment of metastatic castration-resistant prostate cancer. The median (IQR 25–75) sample size in the intervention arm was 41 (16–94) patients and 63 (20–118) for the safety set. More than half of participants in these clinical trials had received previous treatments (65.22%). From the 23 pivotal studies analysed, 18 included sites located in the EU (78.26%), and 10 (43.48%) in the United States of America (US) or in other regions, such as Israel, Japan or Australia.

DISCUSSION

Clinical research on ATMPs has increased during the last few years (Alamo et al., 2019). The introduction of ATMPs and the long-term expectancy of their benefit adds a new challenge for the regulatory agencies. In the present study, we aimed to describe the most relevant methodological features of the clinical trials that have driven ATMPs to their approval. The major findings reveal that the pivotal studies of currently approved advanced therapies typically share the following characteristics: 1) they are small, open-label, non-randomised, single-arm studies without control or using historical ones, and 2) intermediate and single variables are used to evaluate the primary efficacy outcome. In addition, this type of designs is more common for gene therapies than for cell and tissue therapies.

Hanna *et al* previously reported the methodological characteristics of clinical trials assessing ATMPs in an early development phase based on clinical trials registries (Hanna et al., 2016). The results showed very similar characteristics to those found in this study such as small sample size, non-randomised trials, single-arm trials, surrogate endpoints, and adaptive designs. Coppens *et al.*, also reported that the level of scientific evidence required for the approval might differ among different regulatory agencies (Coppens et al., 2018). Elsallab *et al.* showed that clinical trials of ATMPs did not meet the same strict standards for clinical evidence that were applied to other biologicals submissions (Elsallab et al., 2020). This previously reported data, together with the results of the present study, highlight the limited clinical evidence upon which the authorisation of most ATMPs is based. Of these approved ATMPs, it was considered that eleven (64.70%) had sufficient data for a full MA, while for the remaining six products, five (29.41%) obtained a conditional approval and one (5.88%) was granted with a MA under exceptional circumstances.

The low disease prevalence, the disease severity and burden, the lack or scarce availability of disease-modifying treatments, the patient population's heterogeneity and the strong presence of paediatric patient populations comprise some of the factors that could contribute to this type of designs.

The type of target diseases has been one of the key factors that might have given more flexibility in terms of level of evidence required for the MA. Our analysis shows that these

TABLE 5 | Primary clinical variables of pivotal clinical trials for the approved ATMPs in the European Union.

Type of product	Product	Type of target disease	Intermediate (I) or final (F) variable	Primary variable description
GTMP	Kymriah (ALL)	Haematological malignancies	I	Overall remission rate, which included CR and CR with incomplete blood count recovery
	Kymriah (DLBCL)	Haematological malignancies	I	Overall response rate defined as the proportion of patients with a BOR of CR or PR, where the BOR was defined as the best disease response recorded from tisagenlecleucel until progression disease or start of new anticancer therapy
	Yescarta	Haematological malignancies	I	Objective response rate, defined as a CR or PR per the revised International Working Group Response Criteria for Malignant Lymphoma as determined by study investigators
	Tecartus	Haematological malignancies	I	Objective response rate, defined as CR or PR using central assessment per Lugano Classification
	Imlygic	Solid tumour	I	Durable response rate was defined as the percentage of participants with a CR or PR maintained continuously for at least 6 months from the time the objective response was first observed and initiating within 12 months of starting therapy as assessed by the Endpoint Assessment Committee
SCTMP	Provenge	Solid tumour	F	Overall survival defined as time from randomization to death due to any cause was analysed for the ITT population
GTMP	Glybera	Inherited monogenic diseases	I	Reduction in fasting plasma triglycerides (median of baseline vs median of week 3–12 post AMT-011) ≥ 40% Achievement of 40% reduction of median fasting triglycerides concentrations 12 weeks after treatment with AMT-011 Reduction in individual median fasting plasma triglyceride levels of ≤10 mmol/L concurrent with a low-fat diet, or 40% reduction, concurrent with a low-fat diet
	Strimvelis	Inherited monogenic diseases	F	Survival at 3 years post-gene therapy
	Luxturna		I	Subject's bilateral performance (no eye patching) on the mobility test, as measured by a change score, 1 year following vector administration as compared to a subject's Baseline bilateral mobility test performance
	Zynteglo	Inherited monogenic diseases	I	The proportion of subjects who meet the definition of transfusion independence (TI). TI is defined as a weighted average Hb ≥ 9 g/dl without any packed red blood cells transfusions for a continuous period of ≥12 months at any time during the study after drug product infusion
	Zolgensma	Inherited monogenic diseases	F/Co-primary	Proportion of patients that achieve functional independent sitting for at least 30 s at the 18 months of age study visit. It is defined by the Bayley Scales of Infant and Toddler Development (Version 3), confirmed by video recording, as a patient who sits up straight with head erect for at least 30 s Survival at 14 months of age
	Libmeldy	Inherited monogenic diseases	I/Co-primary	Total Gross Motor Function Measure score 2 years after treatment was the primary endpoint The co-primary endpoint was the ARSA activity
TEP	Chondrocelect	Condrophaties	I/Co-primary	Histomorphometry on end point biopsies at 12 months post-surgery and overall Histology Assessment on First Subscale of ICRS II Score Change from Baseline in Overall Knee Injury and Osteoarthritis Outcome Score at 12–18 Months
	MACI	Condrophaties	I	Change from Baseline to Week 104 for the Participant's Knee Injury and Osteoarthritis Outcome Score Pain and Function (Sports and Recreational Activities) Scores
	Spherox	Condrophaties	I	Change of overall Knee Injury and Osteoarthritis Outcome Score from baseline to final assessment determined for each dosage group and between the dosage groups Change of overall Knee Injury and Osteoarthritis Outcome Score from baseline to final assessment compared between intervention arm and comparator

(Continued on following page)

TABLE 5 | (*Continued*) Primary clinical variables of pivotal clinical trials for the approved ATMPs in the European Union.

Type of product	Product	Type of target disease	Intermediate (I) or final (F) variable	Primary variable description
SCTMP	Zalmoxis	Adjunctive treatment in haploidentical haematopoietic stem cell transplantation	I	Proportion of patients who achieved immune reconstitution, empirically defined a priori as an absolute $CD3^+$ cell count of 100/μL or more for two consecutive observations (and/or $CD4^+$ cells ≥50/μL and/or $CD8^+$ cells ≥50/μL) Disease-free survival measured from the date of randomization until the date of relapse (or progression), or death from any cause, whichever occurs first
	Alofisel	Complex perianal fistula(s)—Crohn's disease	F/Co-primary	Combined remission of perianal fistulising Crohn's disease and absence of collections >2 cm of the treated fistula confirmed by MRI images, at week 24. Remission was defined as clinical closure of external openings that were draining at baseline despite gentle finger compression
TEP	Holoclar	Limbal stem cell deficiency	F	Composite endpoint of the rate of patients with a successful transplantation at 12 months post-intervention, based on the co-presence of clinical signs

Intermediate variable*: a clinical endpoint such as measure of a function or of a symptom (disease-free survival, angina frequency, exercise tolerance) but is not the ultimate endpoint of the disease, such as survival or the rate of irreversible morbid events (stroke, myocardial infarction).*

Final variable: *describes a valid measure of clinical benefit due to treatment: the impact of treatment on how a patient feels, functions and survives. It is clinically relevant, sensitive (responsive to change) and is both accepted and used by physicians and patients. Clinical endpoints may be a clinical event (e.g. mortality) a composite of several events, a measure of clinical status, or health related quality of life (HRQoL) [*Ref: *EUnetHTA, 2015a, b)*. Guideline on Endpoints used for Relative Effectiveness Assessment of pharmaceuticals: Clinical endpoints. https://www.eunethta.eu/wp-content/uploads/2018/01/Clinical-endpoints.pdf*].*

ARSA, arysulfatase A enzyme; CR, complete response; GTMP, gene therapy medicinal product; ITT, intended to treat; PR, partial response; SCTMP, somatic cell therapy medicinal product; TEP, tissue engineered medicinal product.

designs are more commonly used for the development of gene therapy products, which target orphan diseases such as hematologic cancers or rare inherited monogenic disorders (40 and 60% of approved gene therapies, respectively), usually with unmet medical needs. Gene therapies were mainly authorised after conducting a single open-label study, usually non-randomised and non-controlled or using historical controls, and only few of them being Phase III studies. By contrast, tissue therapies trials consisted of Phase III studies controlled with the standard of care, and two out of three cell therapy trials conducted placebo-controlled studies. The approved tissue therapies primarily cover products for articular cartilage damage or prostate cancer, which are relatively common among the overall population and with several treatments available. Moreover, the target population might have also contributed to these alternative designs for gene therapies products, given that 60% of approved gene therapies target paediatric population, while all of the tissue and cell therapies target adults. The targeted paediatric diseases are life-threatening or with a huge impact on patients' and caregivers' quality-of-life, and randomised, controlled trials could have posed ethical concerns, as well as recruitment issues.

It is noteworthy to mention that different types of historical controls were used to compare the efficacy of the intervention: historical references from retrospective studies and retrospective databases, prospective natural history cohorts' studies, untreated sibling data and within-subject comparison between pre- and post-treatment assessments (Hassan et al., 2012; European Medicines Agency, 2021; Maude et al., 2018; Crump et al., 2017). The current EMA guideline states that orphan products are assessed according to the same standards as those for other products but considering their limitations due to low patient recruitment (European Medicnes Agency, 2006). While the same guideline states that most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials and deviation from such standards is uncommon, in the case of the current approved ATMPs, alternative approaches as historical controls were frequently used, i.e., Strimvelis®, Kymriah®, Luxturna®, Zolgensma® and Libmeldy®.

On the other hand, the line of treatment is another factor that might have justified these types of designs so far. As an example of the approved ATMPs, CAR-T therapies are indicated at least as a third-line therapy for relapsed or refractory cancer patients. The four pivotal studies conducted for these products were non-controlled, open-label, Phase II studies where the intervention arm was compared to a historical control. After the approval of the aforementioned therapies, the EMA has published recommendations on clinical considerations on CAR-T-cell product development (European Medicnes Agency, 2020), where it is stated that randomized controlled trial design should be followed even for those cases of late-stage refractory disease. It will be interesting to see how these recommendations are implemented in the near future.

Another important factor observed in the studied designs is the use of surrogate variables instead of a clinically relevant final endpoint. Intermediate endpoints can be used as a primary

endpoint for MA, especially when there is a high unmet need, when clinical events are rare/delayed in slowly progressive diseases and a very long follow-up is needed for their assessment, and for rare and/or life-threatening diseases with no therapeutic alternative available (EUnetHTA, 2015b; ICH, 1998a). In the case of all approved gene therapies that target cancer diseases, the proportion of patients with objective overall response rate (ORR) was used as the intermediate primary variable, unlike cell therapy trials that used overall survival (OS) as a final endpoint. OS analysis usually requires a large sample size, a long follow-up and should be evaluated in a randomised, control trial to avoid cofounding factors due to the switch-over of control to intervention or subsequent therapies (Gutman et al., 2013; Pazdur, 2008). However, ORR has been the most commonly used surrogate endpoint in support of accelerated/conditional approvals, but also of standard approvals, since it is directly attributable to a drug's effect, providing an accurate assessment in single-arm trials conducted in patients with refractory tumours (Food and Drug Administration, 2018a). On the other hand, for gene therapies targeting inherited monogenic diseases, biomarkers were commonly used to predict changes in the desired clinical endpoints, and at least one of the pivotal studies included HRQoL outcomes. Exceptionally for other products, a novel clinical meaningful endpoint, i.e. Luxturna® (Russell et al., 2017), or survival as a final primary outcome were used, i.e. Zolgensma® (Del Rosario et al., 2020; Cech et al., 2012).

These types of non-robust designs for new drugs in areas of high unmet medical need are mainly justified on the basis of ethical reasons, based on the potential life-saving opportunities or quality of life improvement for patients who may not survive or will progress rapidly until robust clinical data is available. On the other hand, the difficulties of conducting standard clinical developments with orphan drugs are well-recognised, and single small trials using alternative approaches have been the basis for numerous MAA in the recent years (Blin et al., 2020; Micallef and Blin, 2020; Picavet et al., 2013; Pontes et al., 2018). This regulatory flexibility sometimes comes at the cost of having a less comprehensive clinical data, and in consequence, greater uncertainty about the product's benefit-risk balance at the time of MA (Iglesias-Lopez et al., 2021b). In addition, since the introduction of the adaptive pathway concept, the shift towards accelerated clinical developments has also been associated with an intrinsic uncertainty on effectiveness and safety, which can result in promising Phase II results but an unsuccessful Phase III or post-marketing studies (Pharma Intelligence, 2019; Novartis press release, 2021a, b). This highlights the possibility for a patient to receive an early-authorised treatment without meaningful clinical benefits and with exposure to its adverse effects, missing clinical opportunities, and wasting healthcare system resources (Ermisch et al., 2016).

The speeding up access to new drugs is achieved by putting aside traditional Phase III clinical trials in favour of post-marketing evidence generation. This fact is translated into the need to perform long and extensive post-marketing studies, where the costs of evidence generation as well as the costs of therapy are likely to be transferred from the MA holder to healthcare systems (Ermisch et al., 2016; Joppi et al., 2016). It is known, that this post-authorisation commitments can be challenging due to the long-term follow-up, which may lead to delays to complete the studies, and given that patients are more reluctant to participate in a post-marketing trial with all its constraints, if the medicine is already available, above all in those cases where the trial includes randomization (Joint briefing paper, 2015).

Costly treatments with high uncertainties in regard to its benefits, translates to a complex evaluation by the Health Technology Assessment bodies (HTAb), as well as there is industry pressure for corporate pharma and its investors to ensure sustainability in drug development.

Several detailed methodological recommendations for clinical trial designs have been launched to address the shortcomings of carrying out studies in small population (Day et al., 2018; ASTERIX project, 2021; IDEAL project, 2021; Friede et al., 2018) and examples of effective use of a historical control have also been reported (Mulberg et al., 2019). Multi-arm designs and platform designs sharing where a common control is shared have been raised as a potential solution (International Rare Diseases Research Consortium, 2016; Food and Drug Administration, 2018b). Comparator data can also be taken from pragmatic trials, observational studies or registries, but ensuring its quality (EUnetHTA, 2015a). In addition, real world data plays a key role to provide sufficient therapeutic evidence for these type of therapies and efforts are being made for a better use of registries (European Medicines Agency, 2017).

Methodological and clinical guidelines for a specific medical condition is an effective manner of obtaining regulatory guidance and providing a predictable decision-making regulatory framework. Given that ATMPs are innovative and more complex than traditional pharmaceuticals or other biological drugs, some specific requirements related to the study design and methodology, study population, safety, dose selection, as well as preclinical and product controls need to be considered for the development of these therapies. The FDA has launched several guidelines for the development of ATMPs aimed at certain types of conditions based on the acquired experience of the current approved advanced therapies. These guidelines address the point of uncontrolled designs and the need of more robust study designs in order to provide proper evidence of efficacy (Food and Drug Administration, 2020a; Food and Drug Administration, 2020b; Food and Drug Administration, 2021). Although still limited, with the current experience of the approved ATMPs in the EU, the EMA has started to launch new recommendations on the types of study designs and methodologies that can support the MA more robustly (European Medicnes Agency, 2020). This fact might lead to a switch on the current trend used in clinical designs based on uncontrolled pivotal studies or with historical control comparisons to randomised-controlled trials.

The limitations of this study are the small sample size and the fact that further analysis, once more therapies are approved, is required to determine with greater accuracy

the most common clinical design and methodology for ATMPs, as well as to elucidate the potential differences between gene therapy trials versus cell and tissue therapy trials. Another limitation is that approved ATMPs have not been compared to other approved medicines. Nevertheless, this is an exhaustive study that evaluates the pivotal trials for approved ATMPs.

CONCLUSION

The results of our study show that most authorised ATMPs are based on small, open-label, uncontrolled and single-arm pivotal trials using single and intermediate variables to evaluate outcomes. ATMPs are innovative therapies that mainly target orphan diseases and high unmet medical needs. This fact has led to certain methodological. weaknesses in their pivotal clinical trials, which in turn has resulted in limited data to robustly assess the benefit/risk of the product. A gradual shift towards the production of more methodologically sound randomized-controlled trials is expected to better define the benefit and the therapeutic added value of ATMPs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

Conception and design of the study: CI-L, AV, AA, and MO. Acquisition of data: CI-L. Analysis and interpretation of data: CI-L, AV, AA, and MO. Drafting and revising the manuscript: CI-L. Reviewed and edited the manuscript: CI-L, AA, MO, and AV. All authors have approved the final article.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.773712/full#supplementary-material

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Supplementary Material

1 Supplementary Tables

Table S1. Differences by type of advanced therapy (gene therapies versus cell and tissue therapies)

Design and methodology of the pivotal trial	Gene Therapies	Non-Gene Therapies
Mean (SD) number of pivotal clinical trials	1,27 (0,65)	1,14 (0,38)
Phase of the trials		
Phase 1, Phase 1/2, Phase 2 and retrospective trials	7	3
Phase 2/3 and Phase 3[1]	7	6
Type of control		
Non-controlled[2]	13	3
Placebo or active controlled	1	6
Randomisation		
Yes	2	6
No	12	3
Blinding design		
Open	14	7
Single or double	0	2
Blinding evaluation		
Yes	2	7
No	12	2
Multicentre		
Yes	11	9
No	3	0
Number of arms		
1 arm	11	2
≥ 2 arms	3	7
Design		
Parallel	2	6
Other[3]	12	3
Type of objective		
Superiority and non-inferiority	1	6
Other	13	3
Main outcome		
Final variable	2	3
Intermediate variable	12	6
Type of primary variable		
Number of quantitative variables	13	4
Number of qualitative variables	2	5
Health-related quality of life variables		
Yes	9	7
No	7	3

Sample size (n=17): Gene therapies (n= 10), non-gene therapies (n=7). Non-gene therapies comprise both cell and tissue engineered medicinal products. [1] Including 1 retrospective study; [2] Including historical controls and ¨other¨ studies; [3] Including single, crossover and ¨other¨ studies. SD: standard deviation.

Molecular Therapy
Methods & Clinical Development
Review

Current landscape of clinical development and approval of advanced therapies

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Advanced therapy medicinal products (ATMPs) are innovative therapies that mainly target orphan diseases and high unmet medical needs. The uncertainty about the product's benefit-risk balance at the time of approval, the limitations of nonclinical development, and the complex quality aspects of those highly individualized advanced therapies are playing a key role in the clinical development, approval, and post-marketing setting for these therapies. This article reviews the current landscape of clinical development of advanced therapies, its challenges, and some of the efforts several stakeholders are conducting to move forward within this field. Progressive iteration of the science, methodologically sound clinical developments, establishing new standards for ATMPs development with the aim to ensure consistency in clinical development, and the reproducibility of knowledge is required, not only to increase the evidence generation for approval but to set principles to achieve translational success in this field.

INTRODUCTION

Advanced therapy medicinal products (ATMPs) are a medicinal class that includes gene therapy medicinal products, somatic cell therapy medicinal products, and tissue-engineered therapies[1,2,3]. The marketing approval of these therapies in the last years has been crucial to the growth of clinical research in this field.[4] However, due to the current type of target diseases, i.e., orphan and unmet needs, and the inherent complexity of these products, less comprehensive clinical data have justified their approval. Here, we review and discuss the current landscape and challenges for clinical development and approval of advanced therapies, as well as the current efforts and potential future approaches to overcome these obstacles.

LEVEL OF CLINICAL EVIDENCE AT THE TIME OF MARKETING AUTHORIZATION

Until September 31, 2021, 19 advanced therapies were approved in the EU[5,6]. The key therapeutic areas mainly include hematological malignancies, monogenic diseases, and cartilage diseases (Table 1). The clinical development of these approved ATMPs for the authorized clinical indications was based on 25 pivotal trials. Most of these trials consisted of small, open-label, non-randomized, single-arm studies, comparing the efficacy with historical controls, and using intermediate variables to evaluate the primary efficacy outcome (Table 2)[5]. Other studies that analyzed ATMP clinical trials in an early development phase reported similar results.[7] The type of current target diseases including orphan indications,[8] unmet needs,[9] and the presence of pediatric patient populations has justified more flexible clinical designs and methodologies using adaptive pathways and balancing the need for timely patient access through staggered approval (Table 2).[10]

Although controlled randomized clinical trials are the standard for evidence generation in terms of efficacy and safety for regulatory decision-making, the treatment comparison with the standard of care (SOC) or placebo might have not been considered feasible and/or ethical in these cases. This is translated into less comprehensive clinical data at the time of marketing authorization (MA), and therefore, greater uncertainty about the product's benefit-risk balance.[11] For instance, Zalmoxis authorization was mainly based on promising results of an open-label, non-randomized phase I–II study, supported by the preliminary efficacy and safety data from the first 17 patients of an ongoing phase III controlled study. The final results from this controlled study failed to confirm any benefit at post-marketing level and the drug had to be withdrawn.[12] Another recent case is Kymriah, approved based on a phase II open-label and single-arm study and where the randomized post-marketing phase III trial that analyzed the drug against SOC failed to meet the primary efficacy endpoint, i.e., event-free survival.[13,14] Nevertheless, the patient profile for this last study may differ from that included in the pivotal trial that led to its MA. It should be mentioned that although most of the products were approved based on single-arm designs, some of their competitors conducted controlled studies to support the MA for the same indication, e.g., Spinraza,[15] or planned controlled post-marketing trials, e.g., Kymriah or Yescarta.[11] By contrary for cell therapies, it should be noted that even though Zalmoxis and Alofisel were granted with an orphan designation, phase III studies were conducted including a comparator arm.[16,17]

With these types of flexible and expedited developments with the ATMPs, the current landscape of biological therapies has initiated a shift from traditional clinical developments to a highly product-specific one. Elsallab et al. conducted a matched comparison of the regulatory submissions between ATMPs (n = 17) and other biologicals

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Table 1. Approved ATMPs in the EU and therapeutic indication

Trade name	International non-proprietary name or common name	Pharmacotherapeutic group/ATC code	Therapeutic area (MeSH)/type of authorization
Gene therapy medicinal products			
Kymriah (orphan medicine)	tisagenlecleucel	antineoplastic agents/L01XX71	precursor B cell lymphoblastic leukemia-lymphoma lymphoma, large B cell, diffuse/standard approval
Yescarta (orphan medicine)	axicabtagene ciloleucel	antineoplastic agents/L01XX70	lymphoma, large B cell, diffuse/ standard approval
Tecartus (orphan medicine)	autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured	antineoplastic agents/L01X	lymphoma, mantle cell/conditional approval
Imlygic	talimogene laherparepvec	antineoplastic agents/L01XX51	melanoma/standard approval
Glybera (orphan medicine)	alipogene tiparvovec	lipid-modifying agents/C10AX10	hyperlipoproteinemia type I/approval under exceptional circumstances
Strimvelis (orphan medicine)	autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	immunostimulants/L03	severe combined immunodeficiency/ standard approval
Luxturna (orphan medicine)	voretigene neparvovec	ophthalmologicals, other ophthalmologicals/S01XA27	Leber congenital amaurosis retinitis pigmentosa/standard approval
Zynteglo (orphan medicine)	betibeglogene autotemcel	other hematological agents/B06AX02	β-thalassemia/conditional approval
Zolgensma (orphan medicine)	onasemnogene abeparvovec	other drugs for disorders of the musculoskeletal system/M09AX09	muscular atrophy spinal/conditional approval
Libmeldy (orphan medicine)	atidarsagene autotemcel	other nervous system drugs/N07	leukodystrophy, metachromatic/ standard approval
Abecma (orphan medicine)	idecabtagene vicleucel	antineoplastic agents/L01	multiple myeloma/conditional approval
Skysona (orphan medicine)	elivaldogene autotemcel	other nervous system drugs/N07	adrenoleukodystrophy/standard approval
Somatic cell therapy medicinal products			
Provenge	autologous peripheral blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (Sipuleucel-T)	other immunostimulants/L03AX17	prostatic neoplasms/standard approval—withdrawn
Zalmoxis (orphan medicine)	allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low-affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	antineoplastic agents/L01	hematopoietic stem cell transplantation graft versus host disease/conditional approval—withdrawn
Alofisel (orphan medicine)	darvadstrocel	immunosuppressants/L04	rectal fistula/standard approval
Tissue-engineered medicinal products			
Chondrocelect	characterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins	other drugs for disorders of the musculoskeletal system/M09AX02	cartilage diseases/standard approval—withdrawn
MACI	matrix-applied characterized autologous cultured chondrocytes	other drugs for disorders of the musculoskeletal system/M09AX02	fractures, cartilage/standard approval—withdrawn
Spherox	spheroids of human autologous matrix-associated chondrocytes	other drugs for disorders of the musculoskeletal system/M09AX02	cartilage diseases/standard approval
Holoclar (orphan medicine)	*ex vivo* expanded autologous human corneal epithelial cells containing stem cells	ophthalmologicals/S01XA19	stem cell corneal diseases/conditional approval

(n = 17). The results showed that clinical studies for ATMPs did not meet the same strict standards for clinical evidence that were applied to other biological products. The evidence on the design, conduct, and outcome of ATMP clinical studies suffered from more objections when compared with other biologicals. Despite matching for the disease area and orphan status, ATMPs had more non-randomized, non-blinded trials and included significantly lower numbers of patients, raising doubts about the trial outcomes.[18] How this non-robust data can affect the approval of advanced therapies has also been reviewed. Bravery and co-workers tried to answer the question whether ATMPs are more or less likely to be approved than other medicines. The results showed that for all medicine applications combined, there is a 76% success rate (n = 632) compared with 59% for ATMPs (n = 22), but for non-orphan ATMPs the chance of success seems to be lower, at only 50% (n = 10).[19] Other studies also analyzed the evidence submitted to support the ATMPs MA by quantifying the objections raised by regulatory authorities during the assessment. The two more common issues included suitable quality and clinical data demonstrating the efficacy and safety.[20,21] Barkholt et al. identified the "hotspots" in ATMP development analyzing the MA applications (MAAs) (n = 20) and all scientific advice given for ATMPs by the European Medicines Agency (EMA) (from 2009 to 2018). The clinical data package, the clinical results, the target indication, limited safety information and limited safety and efficacy follow-up, and risk management were the most common development issues and objections raised during the MAA procedure.[21] Similar results were obtained by Bravery et al., where 74% of applications (n = 19 ATMP submissions) raised major objections to the clinical data package. This category covers issues such as lack of randomization, issues with the design, conduct of the clinical study, and/or choice of control group. It was found that failed products have more issues in this category (83% of applications; n = 6). The authors found that evidence submitted with the ATMP dossiers are in need of improvement.[19] This point is also highlighted by the fact that those applications that have been granted with an accelerate assessment revert to standard timelines during the MA procedure due to the immaturity of the data and the major issues raised (n = 6 out of 7 EU approved ATMP granted with accelerate assessment; as of September 31st, 2021).[2] Carvalho et al. analyzed and compared the major objections reported in the MAA assessment for approved ATMPs (n = 3) and non-approved ATMPs (n = 4).[22] The most frequent objections for gene therapy medicinal products in terms of clinical efficacy were the lack or insufficient efficacy demonstration, the change or use of novel and non-validated primary endpoints, and efficacy claims based on non-prespecified post-hoc analysis. Regarding safety, the most common objections were the limited safety database and the risks associated with immunogenicity. Most deficiencies were addressed through the submission of additional data either during the MAA review or post-marketing setting.[22]

EFFORTS TO OVERCOME THE CLINICAL CHALLENGES FACED BY ADVANCED THERAPIES

All these reported data support the fact that there is room for improvement in terms of clinical evidence generated to support the drug approval (Figure 1). A more efficient, consistent, and robust clinical development not only may give more chances to achieve MA and led to less objections by the agencies allowing for a quicker product launch, but it also may prevent post-marketing withdrawal anticipating the negative benefit/risk balance. It is recognized that clinical development for diseases that have a high unmet need and/or are orphan can be complex and can leverage the opportunities that regulatory bodies offer to speed up access and get an accelerated approval. However, given all the implications that expedited clinical developments might have—not only to the patients and payers but to the pharmaceutical companies—whenever feasible, the gold standard pivotal randomized clinical trials, clinically relevant endpoints, and longer follow-up should be performed.

When randomized control designs are not feasible, alternative design options should be considered aimed to provide robust evidence. Many efforts have been carried out to launch methodological recommendations to address the shortcomings of conducting studies in small populations. The Small Population Clinical Trials Task Force within The International Rare Diseases Research Consortium investigated the use of non-conventional statistical methods on small population trials with the input of regulatory agencies.[23] Three relevant European Commission-funded projects (i.e., ASTERIX, IDeAl, and InSPiRe) are promoting the development of new or improved statistical methodology for clinical trials for small population groups, as well as defining adequate randomization procedures, investigating adaptive designs, extrapolating dose-response information, among others.[24–26]

On the other hand, several innovative trial designs under the concept of master protocol are starting to change the landscape of clinical research.[27–29] This approach uses a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple sub-studies, allowing for efficient and accelerated drug development. A master protocol provides an opportunity to increase data quality through shared standardized trial procedures and the use of centralized data capture systems.[30] Within this concept there are different innovative typologies, i.e., basket, umbrella, and platform designs, which have been raised as a potential solution to improve clinical evidence robustness. Platform trials allow multiple interventions to be evaluated simultaneously against a common control group within a single master protocol. The treatments are tested for similar indications and with test products entering and leaving the study based on results. The control arm usually consisting of the SOC may change over time if newer drugs replace the SOC.[31] Comparisons between each of the intervention arms and the control arm can be done to determine which is the best intervention option for a given disease. Yescarta and Kymriah are chimeric antigen receptor (CAR) T cell therapies approved for patients with refractory diffuse large B cell lymphoma (DLBCL) on the basis of ZUMA-1 and JULIET trials, respectively.[32,33] In the absence of head-to-head trials, an indirect treatment comparison between both products was carried out. It was concluded that this comparative analysis is not feasible due to the substantial differences between

Table 2. Design features of pivotal clinical trials for the approved advanced therapy medicinal products in the EU

Trade name	Pivotal study	Non-randomized	Non-controlled	Historical control	Intermediate endpoints	Population/no. of patients (enrolled)
Gene therapy medicinal products						
Kymriah (ALL)	Phase II	✓	✓	✓	✓	Children/92
Kymriah (DLBCL)	Phase II	✓	✓	✓	✓	Adults/147
Yescarta	Phase I/II	✓	✓	✓	✓	Adults/111
Tecartus	Phase II	✓	✓			Adults/105
Imlygic	Phase III				✓	Adults/437
Glybera	3 Phase II/III	✓	✓		✓	Adults/45
Strimvelis	Phase I/II	✓	✓	✓		Children/12
Luxturna	Phase III				✓	Children and adults/31
Zynteglo	Phase I/II and Phase III	✓	✓		✓	Children and adults/41
Zolgensma	Phase III	✓	✓	✓		Children/22
Libmeldy	Phase I/II	✓	✓		✓	Children/22
Skysona	Phase II/III	✓		✓		Children/32[a]
Abecma	Phase II	✓	✓	✓	✓	Adults/140
Somatic cell therapy medicinal products						
Provenge	Phase III					Adults/512
Zalmoxis	Phase I/II and Phase III	✓ (Phase I/II)		✓ (Phase I/II)	✓	Adults/71
Alofisel	Phase III					Adults/212
Tissue-engineered medicinal products						
Chondrocelect	Phase III				✓	Adults/138
MACI	Phase III				✓	Adults/144
Spherox	Phase II and Phase III		✓ (Phase II)		✓	Adults/177
Holoclar	Observational retrospective	✓	✓			Adults/104[a]

ALL, refractory B cell acute lymphoblastic leukemia; DLBCL, diffuse large B cell lymphoma.
[a]Number of patients in the intervention arm.

the trials, e.g., timing of leukapheresis and enrollment, use of bridging chemotherapy (90% in JULIET versus 0% in ZUMA-1), different lymphodepleting regimens, different outcome definitions, etc.[34] In addition, as previously mentioned, the comparison of Kymriah against SOC failed to meet the primary efficacy endpoint.[35] To explore the option of a platform trial for these therapies would have allowed the comparisons between each of the intervention arms and the SOC, as well as efficiently sharing the same control group given that is an orphan disease. The same point can be raised in the case of spinal muscular atrophy (SMA), a rare disease. The SOC for SMA has improved over the last decade due to changes in care, as well as the fact that new promising drugs are becoming available, such as Zolgensma, Spinraza, or Evrysdi. The IQWiG, Germany's health technology appraisal institute, has carried out separate benefit assessments comparing these three new drugs, finding that Zolgensma offers no additional benefit compared with Spinraza for treating SMA. IQWiG pointed out that the differences between populations across different studies made indirect comparisons challenging and makes it difficult to understand which of the three products might be suitable in different situations.[36] This type of innovative trials would allow a stratification into multiple subgroups depending on the SMA type and *SMN2* gene copy number, with eligibility for each intervention arm defined by the intervention's mechanism of action. In addition, another advantage of conducting platform trials is the investigation of treatment combinations. For instance, during clinical development of Zolgensma, Spinraza treatment was started on parental request to determine if there was additional benefit from this combination therapy.[37] Finally, it should be noted that master protocols for CAR T cell therapies have already been initiated in the field of ATMP, e.g., phase I proof-of-concept study in relapsed and refractory multiple myeloma and a phase II study in patients with metastatic or unresectable synovial sarcoma or myxoid/round cell liposarcoma.[38,39] Although platform trials are usually focused on oncology, they also have been conducted in other disease settings such as Alzheimer's disease.[40]

Even though still limited, with the current experience of the approved ATMPs, the regulatory agencies are launching recommendations on the types of study designs and methodologies that can support the MA more robustly. This fact might lead to a shift on the current trend clinical designs based on uncontrolled pivotal studies or with historical control comparisons with randomized controlled trials. After the

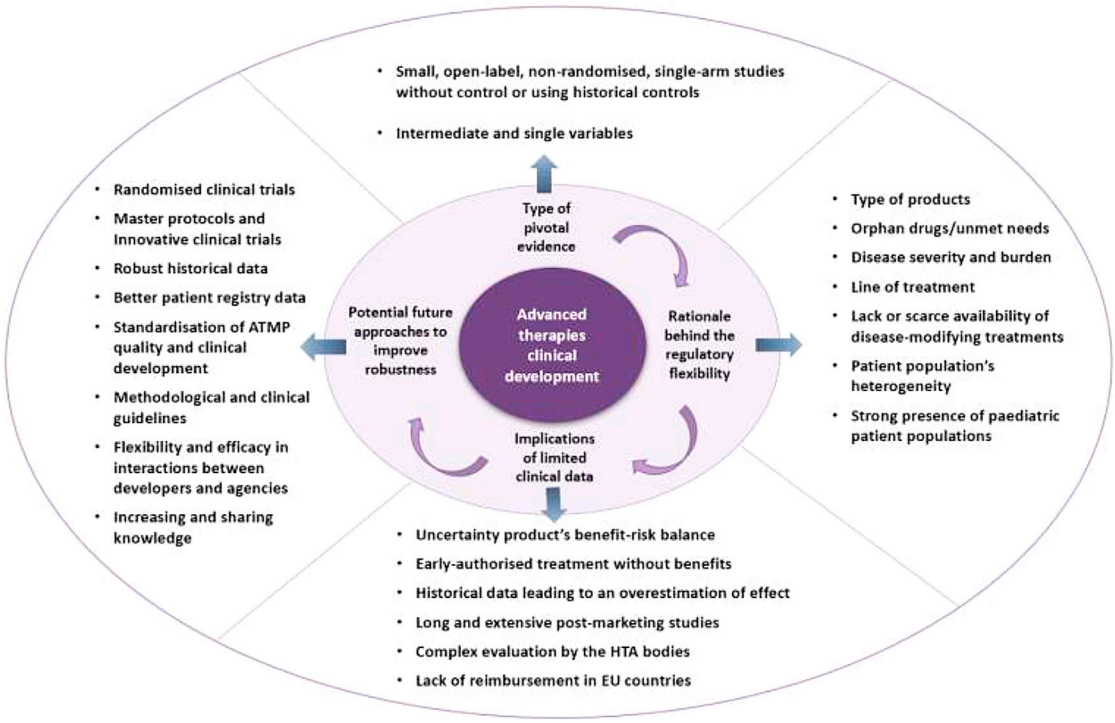

Figure 1. Current landscape of ATMPs clinical development

approval of the CAR T cell products, the EMA has published guidance on the clinical development for CAR T cell products.[41] The recommendations include the performance of confirmatory trials with a randomized controlled design allowing the comparison with a reference product, e.g., high-dose chemotherapy followed by autologous stem cell transplantation. In the guideline, it is recognized that refractory settings are clinically very different from early settings, which in some cases may justify different requirements in terms of level of evidence for MAA. However, it is emphasized that even for those cases where late-stage refractory disease is targeted or where reference therapies are not available, a randomized controlled trial design should be followed, and an uncontrolled single-arm one would be exceptionally accepted.[42] In parallel, the Food and Drug Administration (FDA) has also launched several guidelines for the development of ATMPs aimed at certain types of conditions. For instance, to support the standard approval of a gene therapy for hemophilia, the FDA recommends a non-inferiority clinical trial design, to compare the primary efficacy endpoint with that of current prophylaxis therapies, using within-subject comparison trial.[43] In the case of gene therapies aimed at retinal disorders, inclusion of a randomized, concurrent parallel control group (placebo or active) is recommended whenever possible. Given that for these study designs, the intravitreal injection of the vehicle alone could be feasible but not ethical, other possibilities suggested including alternative dosing regimens or dose levels.[44] The new guidance on gene therapy for neurodegenerative diseases comprises different study design alternatives depending on the indication, study population, or where the disease course is well characterized. For studies involving placebo, FDA recommends add-on designs or randomized, concurrent-controlled, double-blind crossover trials when possible.[45] On the other hand, it is recognized that the typical paradigm of clinical development, i.e., phase I, II, and III, is shifting for advanced therapies and adaptive designs are becoming common. Regulatory agencies are also in consequence releasing new recommendations on innovative designs as well as advice programs to ensure that these adaptive approaches are as solid as possible.[46–48] Finally, analytical tools, such as matching-adjusted indirect comparisons and network meta-analyses, have also been introduced for regulatory submissions and health technology assessments (HTAs) allowing comparisons.[49]

USE OF HISTORICAL CONTROLS

When a randomized clinical trial is not possible, the historical controls can be used to supplement a control arm. Different sources of external control can be used: retrospective data, prospective natural history, external data from completed trials, data from pragmatic trials, observational studies, or registries.[50] The use of historical controls to compare the treatment effect have been highly used so far for the EU approved ATMPs (8 out of 19 approved therapies, as of September 31, 2021), above all in the case of gene therapies (7 out of 12 approved products) (Table 1).

Strimvelis, Kymriah, Luxturna, Zolgensma, Libmeldy, and Skysona target orphan diseases for pediatric population and all of them contextualized the results of the pivotal study with different types

of historical controls. For Strimvelis and Libmeldy, the hypothesis of the study was based on demonstrating superiority over a historical control group, which was considered acceptable given the rarity of the disease. For Strimvelis, while the primary endpoint based on survival was compared with this historical reference, other efficacy endpoints were considered as within-subject, between pre- and post-treatment assessments. The historical control used was based on the outcomes obtained in a multicenter retrospective study (between August 1981 and March 2009) including 106 patients with adenosine deaminase-deficient severe combined immunodeficiency from 16 international centers.[51] The main study for Libmeldy was conducted in a single center, as well as the concurrent natural history cohort. Both natural history cohort (n = 31) or untreated sibling data (n = 11), were used as controls to compare the treatment effect for the co-primary endpoint. It was considered by the assessors that a comparison with a matched sibling appears to have the least variability and the comparison between pre-symptomatic subjects versus their affected siblings is considered the most informative.[52] In the case of Kymriah for relapsed or refractory B cell acute lymphoblastic leukemia (ALL), the single-arm design was planned to test for an improvement in overall remission rate relative to historical control rates from two previous studies performed for the same indication with other products (clofarabine and blinatumomab approved in 2007 and 2015 by the EMA, respectively).[53] Luxturna's trial randomized patients to a control or to intervention arm, given that for most inherited retinal dystrophies, natural history data were limited. The control group became eligible to receive the product 1 year after their baseline evaluations. Nevertheless, a natural history study that consisted of a retrospective medical chart review (from July 2014 to February 2016) was also submitted as a supportive by the applicant to further support the MAA (n = 70).[54] For Zolgensma, two natural history studies were used for comparison; one retrospective and prospective study using data from the Paediatric Neuromuscular Clinical Research database (inclusion of the patients ranged from May 2005 to April 2009), and another prospective, multi-center natural history study (from November 2012 to September 2014) that enrolled 26 SMA infants.[37,55] Similarly, in the case of Skysona, both data from a retrospective natural history study (data collected between 2011 and 2012; n = 137) and a retrospective and prospective data collection study (from 2015 to December 2019; n = 59) were used.[56]

Yescarta, Zalmoxis, Kymriah, and Abecma target adult orphan indications and also used historical controls to compare product's efficacy. For Yescarta, a retrospective, patient-level, pooled analysis from two randomized phase III clinical and retrospective databases was conducted to support the results from the pivotal study (SCHOLAR-1),[57] and for Kymriah, the pivotal efficacy results were compared with three historical datasets (SCHOLAR-1, the pooled CORAL extensions, and the open-label, randomized PIX301 trial). For Zalmoxis, at the time of approval, there was neither approved therapy nor widely accepted SOC. Therefore, the treatment effect could only be compared versus historical control data from either a large retrospective survey (between January 1995 and December 2004) or single-center experiences.[16,58] For additional comparisons with historical control data from patients, the European Blood and Marrow Transplant society patient database was used to better define the product's clinical benefit.[16] For Abecma, the results were compared with a matched real-world historical control that consisted of a non-interventional, retrospective study (n = 190) as well as reported literature.[59]

The relevance of historical data is sometimes questioned and could lead to an overestimation of effect. The limitations of historical controls are well known; comparability of the population, potential changes in SOC, lack of standardized diagnostic criteria or equivalent outcome measures, and variability in follow-up procedures.[60–62] The standardization and quality of the data collection, the selection of an applicable approach to account for biases, to plan for an extensive sensitivity analyses to demonstrate the robustness of the results, or the use quantifiable and objective outcomes are some of the measures that would improve the quality of the historical controls.[63] The case of Abecma is an example of the historical control limitations. The real-world evidence study was found to be inconclusive by the FDA to provide context or comparison for the outcome of the pivotal study. The missing data, differences in follow-up and response assessment, population heterogeneity, and bias in endpoint assessment, hampered the comparison.[64,65] When similarity can be proven between arms, the use of a historical control replacing the concurrent control arm can be the alternative source of data in a context of life-threatening disease with no treatment available. In other scenarios, a clear justification for a non-randomized trial is needed and an early dialogue with regulatory agencies at the design stage is highly encouraged to avoid potential problems during the clinical development plan and final authorization. According to recent FDA recommendations, the use of historical controls is discouraged but it might be considered appropriate only under very exceptional circumstances where: the product targets a rare and serious neurodegenerative disease for which there is an unmet medical need, the disease course is well documented, highly predictable and can be objectively measured and verified, the study population and the historical controls are suitably comparable, and the expected treatment effect is large and self-evident.[45]

It is known that registries provide an important source of information on diseases, patients, SOC, or outcomes of treatments, in particular for rare diseases or patients treated with ATMPs. In this sense, there have been some proposals to overcome the current challenges in using registries data such as interoperability and patient privacy improvement, standardization of data and terminology, better reporting of clinical trial outcomes, and other measures to maximize registry use in drug and therapeutic development to support evidence-based clinical decision-making.[66] EMA's initiative for patient registries, launched in September 2015, is focused on supporting a systematic and standardized approach to their use for regulatory purposes.[67] The need for individual patient data is a key factor to conduct better historical comparison. For instance, for Kymriah in refractory ALL indication, external control was used for comparison with data pooled from the three main Kymriah trials, despite confounding patient populations and matching on few variables.[33,68] For Kymriah and

Yescarta in DLBCL indication, the treatment effect was compared with SCHOLAR-1 sponsored by Kite Pharma (MA holder of Yescarta).[57] The acceptance of comparison between Yescarta pivotal results and the SCHOLAR-1 study was attributed to the availability of individual patient data, enabling the company to match patients in both trials.[68,69] However, for Kymriah given that only published data of SCHOLAR-1 was available for comparisons, the data from the pooled CORAL extensions study was accepted by the agency as a more suitable comparator than SCHOLAR-1 due to similarities in the populations enrolled and the objective response rate results obtained.[33,57,68]

USE OF SURROGATE ENDPOINTS

Another important factor observed in the pivotal studies of the approved ATMPs is the use of surrogate variables instead of a clinically relevant final endpoint. Results from surrogate endpoints are common in accelerated approvals and allow for clinical trials with shorter follow-up periods and smaller sample sizes.[70,71] It has been reported that the pivotal trial evidence supporting MA for products granted conditional MA or accelerated assessment was based dominantly on non-validated surrogate endpoints.[72] This point can be translated into lower likelihood identifying safety issues (especially if they are rare) and long-term observations of safety adverse events. It has been reviewed that surrogate endpoints might lead to erroneous, or even harmful conclusions, since they might fail to fully capture the complete risk-benefit profile.[73] On the other hand, this type of endpoints is ethically preferable, especially when clinical events are rare/delayed in slowly progressive diseases or when there is a high unmet need, as well as practically preferable since the short-term assessment helps to avoid non-compliance and missing data, increasing effectiveness and reliability of the study.[73–75] The acceptability of the surrogate endpoints needs to be based on their biological plausibility and empirical evidence, and should be validated with evidence that goes beyond showing a statistical association between the surrogate and clinical endpoints.[73,74,76]

In the case of all approved gene therapies that target cancer diseases, the proportion of patients with objective overall response rate (ORR) was used as the intermediate primary variable. In these cases, ORR was an acceptable endpoint given that the studies that support the MA consist of phase II exploratory trials and given that an accelerated approval was granted. According to the most recent version of the EMA guideline on anticancer drugs, for confirmatory trials the overall survival, progression-/event-/disease-free survival would be considered as adequate primary endpoints. However, selected patient-reported outcomes, such as symptom control, could also constitute clinically relevant and valid primary endpoints, provided high data quality are ensured.[77] In addition, and if available, the use of validated biomarkers should be considered to allow a clinical trial to identify and differentiate between drug responders and non-responders.

Although surrogate variables are not always ideal, it is not trivial to select either a final and/or surrogate primary efficacy endpoint for an ATMP, which can accurately predict or correlate with clinical benefit in the studied indication. For instance, in the case of Luxturna, the applicant had to develop a novel clinical meaningful endpoint to assess the drug effect through a mobility test.[54] For Zolgensma, although the survival endpoint was used as a final co-primary outcome, survival with no motor milestone achievement would have not probably been considered as clinically meaningful outcome in the treatment of SMA. Moreover, performance and socialization at school age around 5–6 years was suggested by the experts as long-term data to be captured relating to efficacy.[37,78] For those patients with lipoprotein lipase (LPL) deficiency, the most severe associated complication is pancreatitis. The hypothesis that Glybera could improve chylomicron particle metabolism and then reduce the pancreatitis in these patients could not be substantiated by clinical data at the time of MA.[79]

With increasing pressure for an early access to therapies, the use of surrogates is likely to increase. The key guidelines of the European network for HTA, which have been adopted by many European HTA agencies, state a preference for using final patient-relevant outcomes, but the need for surrogate endpoints is also recognized.[48,80] Therefore, it is recommended to use surrogate variables only to those that have been validated appropriately, to avoid uncertainty on coverage decisions on health technologies, as well as to ensure less objections during the MAA assessment.[81] It has been reported that only few HTAs have provided specific methodological guidance on the statistical methods that should be used for the validation and assessment of acceptability of surrogate endpoints, and there is still lack of methodological consensus around the level of evidence necessary for the validation of these endpoints. In consequence, efforts on better harmonization are currently being conducted to minimize different access for patients across different jurisdictions.[80,82] On the other hand, to guide the developers, the FDA has recently published a list of accepted surrogate endpoints that were the basis of approval of a medicinal or a biological products under both the accelerated and standard pathways.[83] Finally, the validation of a surrogate endpoint is not a straightforward process, given that the association between surrogate and final outcome usually is demonstrated by randomized controlled trials, or epidemiological/observational studies. Therefore, as discussed by Ciani et al., extension of follow-up studies, as well as the natural history studies combined with analyses on baseline data, emerging large data networks, or previous conducted trials on the disease might help to identify adequate surrogate variables.[81]

LIMITATIONS OF NONCLINICAL DEVELOPMENT

Properly designed nonclinical studies can reduce the clinical uncertainty and support a positive risk-benefit ratio. However, the traditional and standardized approaches for nonclinical toxicity testing are often not appropriate for evaluating the safety of gene and cell therapy products, and several challenges are also associated with the nonclinical development of ATMPs.[84–86] General nonclinical studies and toxicity studies may be unable to detect the effects relevant for human efficacy and safety. Some examples include Glybera, the proof-of-concept demonstrated reduction in plasma triglycerides related to LPL activity of treated animals, and this was used as the

primary pharmacodynamic measure to show activity. However, the applicant failed to adequately demonstrate pharmacokinetic and pharmacodynamic properties of the product in the clinical setting, since LPL plasma activity could not be consistently demonstrated, and no sustained TG decrease could be observed.[79] Associated CAR T cell toxicities, such as cytokine release syndrome, neurological toxicity, on target/off tumor events were not fully anticipated by nonclinical studies either.[86,87] For Zolgensma, the different cardiovascular safety profile observed in the preclinical and clinical stage was attributed to a difference in transduceability at individual cardiomyocyte levels between mice and humans.[37] Finally, adeno-associated virus (AAV)-related toxicities are currently being discussed by the agencies.[88] Dorsal root ganglion pathology has been observed in nonhuman primates but it is still unclear if it is translated to the clinical setting in human beings.[37,89] Similarly, although AAV integration associated with hepatocellular carcinoma (HCC) was observed in neonatal mice, there has been minimal evidence of HCC occurring in patients receiving gene therapies.[89]

An iterative approach was suggested to be informative, for example, when early clinical experience identifies unexpected adverse reactions then additional preclinical studies may provide a mechanistic basis for mitigation measures.[86,90] On the other hand, the need for standards to enable cross-comparisons of, and confidence in, testing results, or ensure techniques that are consistently implemented for the nonclinical studies so that data can be compared, would allow to increase and share knowledge in the field, e.g., biodistribution studies.[91] Finally, a risk-based approach during product development to design a tailor-made ATMP development program is usually recommended to determine the extent of quality, nonclinical and clinical data necessary for an MA and to justify any deviation from the requirements, i.e., as defined in annex I, part IV of Directive (2001)/83/EC.[92,93]

INTERPLAY BETWEEN CLINICAL EVIDENCE AND PRODUCT QUALITY

Not only does the limited clinical evidence at the MAA stage impact the approval decision, but the quality development and lack of quality standards for these products is a key challenge.[94] Several factors limit the achievement of consistent data and adequate interpretation of clinical results across studies: the uniqueness of each product, the heterogeneity of this novel group of products, the variability in the pipeline of clinical development and approaches chosen, the divergent manufacturing strategies, and the different tests/assays applied during clinical development and its validation.[75,95]

The quality of manufacturing can affect the clinical outcome, and issues within the quality module of MAA dossier might be directly related with the acceptability of the clinical package. Issues are mostly related to validation of the analytical methods, design and control of the manufacturing process, and comparability.[18] The comparability of manufacturing processes remains one of the major issues and was raised during assessment of the majority of the approved products.[96] When a process change is required, for instance, to increase production volume for a phase III trial or commercialization, questions of comparability between processes during the MAA review and how this can affect the clinical safety and efficacy outcomes are common. This point can imply the requirement of generating additional clinical data or impair the validity of previously generated data, as was the case for Kymriah or Zolgensma.[37,96] Not only the comparability between manufacturing processes, but batch to batch inconsistency, which might contribute to the heterogeneity of clinical response, has been observed for some approved therapies.[37] The inadequate comparability assessments, coupled with the difficulty of potency assays, can also impact key clinical aspects, such as the consistency of doses administered during the clinical development.[37,97] For cell therapies, the mechanisms to study cell activity are complex and poorly understood and the cell counts may vary over time, which makes it difficult to establish standard, effective doses, and routes of administration in clinical trials. This might lead to inconsistent trial results that are hard to interpret and replicate across studies.[91] For some approved gene therapies, uncertainties with regard to control of the effective dose, without a stable reference standard to control the potency of the product have been also observed.[37]

Standardization of manufacturing may be difficult given proprietary platforms, but some common processes, such as common operational steps, product characterization, design and validation of processes, and testing could be achieved to improve some of these issues.[98] Previous experience available in humans with similar products and with similar standards that allow performing a comparison with valid pooling data would help to improve the current translation challenges in the ATMP field, e.g., AAV-based gene therapies, CAR T cell therapies, autologous cultured chondrocytes, or mesenchymal adult stem cells. For instance, it has been stated that longitudinal investigations of anti-CAR immune responses through the same validated assays would be particularly important in understanding how immunogenicity can lead to treatment failure. For the three approved CAR T cell therapies, there were huge differences in the reported percentages of patients with pre-existing antibodies and it was suggested that this fact could reflect the different assays used for detection.[99] Similarly, pre-existing immunity and immunogenicity toward the vector or transgene are the largest challenge for AAV-based gene therapies given that it can interfere with therapeutic efficacy if not identified and managed optimally.[100] Common ways to test tissue engineering product integrity, including tensile strength and suture retention, to ensure that these products meet safety thresholds for use in clinical environments, has also been raised.[91]

The quality requirements are not reduced due to accelerated access routes, and it is under debate that greater standardization and harmonization across regulatory authorities could reduce the burden on companies to ensure compliance at every phase of the development and commercialization process.[101,102] Several organizations are working to assemble and define standards and the convergence of common requirements.[101,103–105] Although it should be recognized how challenging standardization is given the diversity in the cell and gene therapy space and its rapid progress, the standard needs have already been identified.[91,98] Examples from a quality standpoint include: (1) create

management systems for processing and handling cells, establish cell collection requirements that ensure consistency, safety, and comparability in the final products, (2) identify potential commonalities across manufacturing processes and create broadly applicable guidelines, or (3) establish guidelines to harmonize manufacturers' characterization, design, and validation processes to lower barriers. From nonclinical and clinical standpoint, it has been proposed: (1) to establish consensus on which biodistribution approaches are most applicable, (2) to implement a standard approach to pre-existing immunity assay development, selection, and evaluation to enhance patient safety and quality of clinical trial data, or (3) initiate cell counting methods/technologies, optimal timing for dose assessment, and qualify routes of administration and dose preparation methods to select safe and effective doses, among others.[91]

IMPACT AT THE POST-MARKETING SETTING AND MARKET ACCESS

Pre-registration randomized clinical trials are not always representative of patient populations in the routine practice due to the strict patient inclusion and exclusion criteria, and the strict intervention protocols.[35,106–109] Therefore, the generation of evidence throughout the medicine's life cycle is essential to gain more information about its effectiveness and safety in a more diverse clinical setting, to improve healthcare quality, and to provide information to either complement initial evidence or to verify whether the MA should be maintained as granted, varied, suspended, or revoked. In the case of ATMPs, real-world evidence plays a major role and is essential to confirm the benefit-risk profile given the imprecise clinical data available at the time of MA. This point might be translated into the need to perform long and extensive post-marketing studies.[110,111]

It has been reported that post-authorization studies for the approved ATMPs consist both in interventional studies (some of them ongoing at the time of MA) and observational studies. The profile of the planned interventional trials to further assess effectiveness resemble pre-market trials in terms of design, i.e., using single-arm designs, reduced sample sizes, and are focused on a narrow study population.[11] In some cases, generation of evidence post-launch can be particularly challenging, especially when it requires long-term follow-up, since participants may be lost during the trial due to different causes (i.e., cure of the disease, depression, among others) or may be reluctant to participate when the pharmaceutical is already launched. The latter is more evident when the study is randomized.[112] On the other hand, the burden that the clinical post-marketing requirements imply, along with the extensive manufacturing commitments, could hamper market access. This was the case for Glybera, where the extremely limited use of the product and the costs of post-marketing requirements, including maintaining the commercial manufacturing capabilities, led to its withdrawal after two years on the European market.[113,114]

The insufficient evidence available on comparative clinical effectiveness or clinical benefits hinder the determination of appropriate pricing and payment schemes. The decision on price and reimbursement requires an exhaustive study of the evidence generated during product development, the relative effectiveness and safety, the patient-reported outcomes (including quality of life), and the cost-effectiveness and budget impact to finally assess its place in therapy. At this stage, HTA bodies (HTAb) have an important role. The scientific evidence of the product and its potential contribution in the therapeutic management of the disease is deeply studied in EU countries, but the recommendations from the HTAb may differ among them, above all for orphan drugs.[115] HTAb-specific requirements can be related to the acceptability of the endpoints used, the control arm, the inclusion and exclusion criteria, and, at the end, the generalization of the results obtained in clinical practice.[76] When the product clinical data are limited, to determine all the aforementioned is complex and usually translates to long negotiations between the MA holder and the health authorities. This negotiation may be one of the reasons for the time elapse between MA and final drug prescription and this represents a major concern for healthcare systems, patients, and industry. The difficulty of accessing the market once the product is authorized highlights the differences in the answers that a regulatory agency and a healthcare system are seeking in clinical trials.[116]

Finally, there is industry pressure for corporate pharma and its investors to ensure the return of drug development investment. With a high expected value, but with immature evidence and high prices requested, the complexity of negotiations between industry and payers is becoming common, and sometimes the non-reimbursement has been justified. Managed entry agreements have been a solution to this challenge. Commercial arrangements have been frequently used in European countries either financial (discounts and rebates) or outcome-based to finally release a product into the market. Provenge, MACI, and ChondroCelect were withdrawn because of poor commercial performance and lack of reimbursement in EU countries.[2,95,114] The limited use of the product, the costs of post-marketing requirements, including clinical trials and maintaining commercial manufacturing capabilities, are other factors that contributed to ATMP withdrawal.[113,114]

To avoid costly corrections in late clinical development and a weak market access value dossier (a document that provides evidence-based messages in communicating product value), a comprehensive risk assessment must be carried out before committing to a particular pivotal trial design. The development strategy for an ATMP should also include parallel EMA-HTAb advice regarding optimization of evidence generation of in the EU, to discuss different design options during clinical development, their applicability with respect to efficiency and risk of bias, and the potential post-launch generation of evidence. The same approach is recommended through FDA interactions in the case of the United States, such as special protocols assessments.[2] These discussions, along with the potential implementation of the advice, could reduce the risk of benefit-risk uncertainty and production of data that would be inadequate to support the company's future reimbursement request.[117,118] In addition, the company's retrospective analysis from the drug pipeline development and failures during different phases of clinical trials will have led them to improve its research and development workflow in terms of

learning, strategy, costs, and performance.[119,120] For instance, Alofisel (sponsored by TiGenix) set a model of iterative strategy that enabled MA through improving late clinical development with the lessons learnt from the previous autologous cell therapy, sponsored by Cellerix.[121]

CONCLUSIONS

ATMPs are innovative therapies that mainly target orphan diseases and high unmet medical needs. The level of generated clinical evidence and the quality aspects of advanced therapies playing a key role in the development, approval, and post-marketing setting for these therapies. This article describes the current landscape of clinical development of advanced therapies, its challenges, and some of the potential solutions that are currently under discussion. Most authorized ATMPs are based on adaptive, small, open-label, uncontrolled, and single-arm pivotal trials. Flexibility on conventional regulatory requirements has been widely implemented by regulators, especially for low prevalence, life-threatening, or seriously debilitating diseases. Progressive iteration of the science, establishing new standards for ATMP development with the aim to ensure consistency in clinical development, and the reproducibility of knowledge is required not only to increase the generation of evidence for approval but to set principles to achieve translational success in this field. Although there is a trend toward an adaptive approach to licensing or a life-cycle approach, after the experience with the approvals of ATMPs so far, regulators and global working groups are developing and releasing new recommendations to promote an approach to clinical development that is methodologically sound and thus significantly more relevant. It remains to be seen how clinical development of ATMPs will evolve, but it is recommended that the industry stakeholders should strive to understand and try to apply the recommendations of relevant parties to better succeed in market access.

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AUTHOR CONTRIBUTIONS

Acquisition of data, analysis and interpretation of data, C.I.-L.; drafting and revising the manuscript, C.I.-L.; reviewed and edited the manuscript, C.I.-L., A.A., M.O., and A.V. All authors have approved the final article.

DECLARATION OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The findings and conclusions in this article should not be construed to represent any agency determination or policy.

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REVIEW

Regulatory and clinical development to support the approval of advanced therapies medicinal products in Japan

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ABSTRACT

Introduction: A new category of products, i.e. regenerative medicine products (RPs), has been defined for advanced therapies medicinal products in Japan, as well as a legislative and regulatory framework to promote their clinical development.

Areas covered: This review analyses the most relevant features of the regulatory strategies and clinical development that led RPs to their approval in Japan.

Expert opinion: As of 31st September 2021, a total of 14 RPs were approved for 16 indications. From a regulatory standpoint, the available designations allow attractive benefit packages that promote the development of innovative products in Japan and is one of the key points to consider when the global regulatory strategy for the product is being developed. RPs regulations in Japan allow adaptive licensing and constitute shortcut through the clinical development to the approval. RPs have been mainly approved so far based on small studies with inconclusive and limited evidence of efficacy and safety, prioritizing the unmet medical needs of the target diseases, and therefore, the early access for patients. This review also compares the regulatory and clinical development for the current approved RPs in Japan with the development trends in the European Union and United States of America.

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Japan; clinical development; drug approval; cell- and tissue-based therapy; gene therapy; adaptive pathways; accelerate approval; orphan drug designation; Sakigake designation

1. Introduction

Advanced therapy medicinal products (ATMPs) are a group of innovative and complex biological products for human use that comprise gene, cell- and tissue-engineered therapies. The discovery of induced pluripotent stem cells in 2006 and the approval of the two first autologous cell products in Japan, human autologous epidermal cell sheet (JACE) and human autologous tissue for transplantation (JACC), set a precedent and constituted a major breakthrough in stem cell and ATMP research [1]. With the introduction of this type of therapies, the regulations for the human use of ATMPs were established in several regions and are evolving in accordance with the acquired scientific knowledge and clinical experience. In Japan, a new product category was defined for advanced therapies, i.e. regenerative medicine products (RPs), and new laws were implemented in 2014 to provide a legislative framework for these treatments, promote their timely development and bring these innovative products to patients [2].

The key regulatory procedures and considerations for the development of RPs in Japan are depicted in Figure 1 and summarized as follows:

(1) *Legal framework and regulatory classification* – Since 2014, advanced therapies are regulated as RPs under the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act) when a marketing authorization (MA) is sought. The Act on the Safety of Regenerative Medicine (RM Act), which falls outside of the scope of this paper, covers clinical research with these products, performed in medical institutions for academic purposes. The Japanese Pharmaceuticals and Devices Agency (PMDA) conducts the scientific reviews of the applications for regenerative medicines, and the Ministry of Health, Labor and Welfare (MHLW) approves the MA or withdraws products in case of safety concerns. Within the PMDA, the Office of Cellular and Tissue-based Products (OCTP) is responsible for regulating regenerative therapies [2].

RPs include two main categories of products: gene products (*in vivo* and *ex vivo*), and cellular medicinal products [3]. Gene therapies must be intended for the treatment of disease in humans (or animals) and carry or deliver transgenes to be expressed in human (or animal) cells. This category includes products derived from plasmid vectors, products derived from viral vectors and gene expression treatment products. Vaccines or siRNAs, antisense RNAs oligonucleotides, aptamers, and nucleic acid derivatives that are chemically synthetized will be excluded of this category, although the use of non-viral vectors designed to express the siRNAs or antisense RNAs might be considered a gene therapy [4,5]. On the other hand, the cell therapies are intended for either: the reconstruction, repair, or formation of the structure or function of the human or animal body (i.

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Article highlights

- More than half of approved regenerative products target orphan indications.
- The number of products under development granted with Sakigake designation is increasing.
- The overall marketing authorization application review period in Japan for the currently approved products is shorter than in the EU and higher than in the US.
- In Japan the approval of regenerative products is mainly granted with non-confirmatory evidence under the ground of prioritizing the unmet medical needs of the target diseases.
- Clinical development that supported the product approval in Japan for regenerative products was based on small exploratory Phase I/II, uncontrolled, single-arm trials.
- Products granted with a standard approval did not have a substantially more robust clinical development than the ones approved under the conditional and term-limited approval pathway.

This box summarizes key points contained in the article.

tissue-engineered products), or the treatment or prevention of human or animal diseases (i.e. cellular therapy products). To be classified as a cellular medicinal product, the cells must be processed and/or intended for non-homologous use. Cell/tissue processing is defined as the propagation of a cell or tissue, any pharmaceutical or chemical treatment to activate the cells or tissue that alters the biological features, the combination with a noncellular component and/or manipulation by genetic engineering. A list of manipulations that are not considered processing is also provided in the PMD Act, e.g. disintegration of tissue or treatment with antibiotics. In addition, the term ¨processing¨ includes cells for non-homologous use. Therefore, the cells or tissues (whether processed or not) that are not used to maintain the original function-(s) in the same anatomical or histological environment, are considered regenerative products [5]. Whether the products are processed or not is judged on a case-by-case basis, and consultation with the MHLW/PMDA is recommended in case of uncertainty. Finally, it should be noted that there is a clear differentiation between cell-based products considered as RPs, and cell-based therapies covered by other legal frameworks such as the blood system or transplant laws, e.g. hematopoietic stem cell transplantation [2,4,6].

(2) *Scientific advice* – Apart from a wide range of consultation procedures, the PMDA also offers specific scientific advice procedures for RPs: i) advice on pre-exploratory clinical study, ii) at end of this exploratory clinical study and for clinical study design after the conditional limited-term MA, and iii) advice and certification on the qualification of manufacturing material. Differently to the European Medicines Agency (EMA), the PMDA does not differentiate between consultations for orphan products and regular ones [7].

(3) *Orphan drug designation* – Products with an orphan drug designation (ODD) benefit from a 10-year market exclusivity period and from other financial incentives, but with the particularity that in Japan these products are also automatically granted a Priority Review for the marketing authorization application (MAA). The eligibility criteria to obtain the orphan status are: i) the target indication must affect less than 50,000 patients in Japan or consist of an intractable disease with unknown mechanisms for which standard therapy has not yet been established, ii) the product must be indicated for the treatment of serious diseases with high medical needs (if there is available treatment, the new product must be expected to achieve substantially higher efficacy or safety), and iii) there is medical plausibility for the use of the product for the target disease and an appropriate development plan [8,9].

(4) *Environmental risk assessments (ERA)* – Genetically modified organisms (GMOs), referred to as living modified organisms (LMO) in Japan, are regulated under the Cartagena Act. The ERA needs to be submitted during the clinical development phases in parallel with the clinical trial applications and for the MAA, unless a claim of categorical exclusion applies. The framework contemplates two possible ways in which a LMO can come into contact with the environment: 'Type 1 use,' which refers to any intentional introduction into the

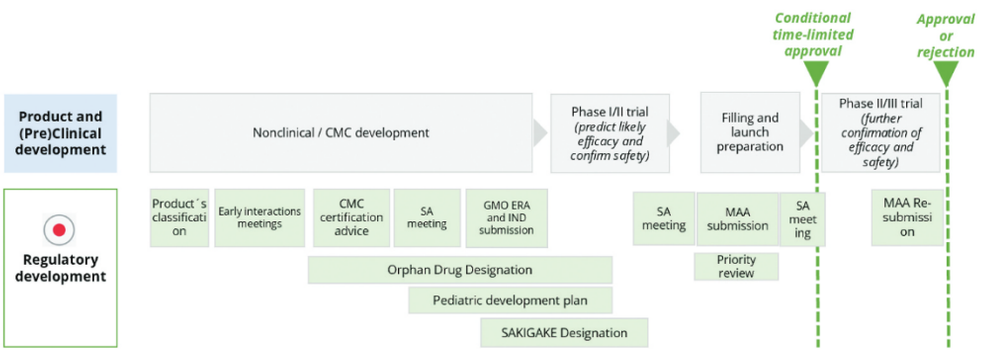

Figure 1. Overview of Japan regulatory steps for advanced therapies during development.

CMC: Controls Manufacturing Chemical; GMO: genetically modified organism; IND: investigational new drug application; MAA: marketing authorization application; SA: scientific advice or consultation.

environment, and 'Type II use,' which entails the use of LMOs under a 'closed containment' environment. The ERA for the MAA is submitted to the PMDA and reviewed by the MHLW and the Ministry of Environment. The assessment report can be submitted separately to the MAA dossier, with the content being similar to what is required for an ERA in the European Union (EU) [10,11].

(5) *Expedited development programs and fast track approval processes* – More focused on product development and similar to the concept of breakthrough and regenerative medicine advanced therapy (RMAT) designations in the United States of America (US) or Priority Medicines scheme (PRIME) designation in the EU, the Sakigake designation was introduced in Japan in 2015 to enhance the early access of innovative medical products. The benefits of the Sakigake include: continuous support and guidance from the agencies during clinical development so as to optimize and speed up the drug development plans and evaluation, *de facto* review of the application before the submission, rolling submission and a target review application period of 6 months, the extension of the re-examination period once an approval is granted, and potential pricing concessions [12,13]. The key feature of this designation is that in order to be eligible, the sponsor must develop the product first in Japan with the aim to launch the product in the Japanese market first or at least not later than in other regions. In addition, the product should represent an innovation (e.g. new mechanism of action), be intended to treat a serious disease or a disease with chronic debilitating conditions and target conditions with an unmet medical need, as well as a mechanism of action that demonstrates promising effectiveness during early-phase clinical studies and non-clinical studies [12,14,15]. An option to expedite the MAA assessment includes the Priority Review designation, which grants an accelerated MAA review lasting 9 months instead of the 12 months that the standard procedure requires. Similarly to the US designation, the eligibility criteria for the priority review include: i) that there are no available therapies, or the product shows clinical superiority compared with the existing products (including quality of life of patients), and ii) the product must be indicated for severe diseases or have an orphan designation [12]. Therefore, Priority review status is usually granted to orphan drugs and to Sakigake -designated drugs for therapeutic areas of significant medical need.

(6) *Type of marketing authorization* – RPs might be authorized through a standard MA, conditional MA or under a conditional and time-limited MA. The latter was instituted in 2017, and is a MA designed exclusively for RPs. With this type of authorization, the sponsor needs to demonstrate the product´s quality and safety, but the efficacy can be supported with limited data (i.e. from early-phase phase I/II, with a small patient number, using surrogate endpoints and accepting wider significance levels than those used in conventional trials). This first conditional MA must be followed by a re-application and a second approval procedure within a period of 5 to 7 years from the initial MA, where additional safety and efficacy data from post-marketing clinical studies (PMS) is submitted to confirm the positive benefit-risk profile. This second MAA review can lead to a standard approval if the data confirms the efficacy and safety of the product, or to the product´s withdrawal from the market. It is recommended to obtain the Agency´s advice at an early clinical stage to discuss the design of the trial and the data needed to be considered for obtaining the standard or conditional limited-term approval [14,16,17].

Therefore, considering the particular characteristics of the regulatory framework for the development of RPs in Japan, it is interesting to analyse the clinical development that have supported the current RPs approval in the Japanese market. The aim of this review is to analyse the regulatory and clinical developmental strategies that supported the MA for the current approved RPs in Japan. In addition, this development of ATMPs in Japan is compared with the development trends in the EU and the US.

2. Methods

A systematic review of the pivotal trials' features that supported the MA of the RPs approved in Japan was carried out until September 31st, 2021. Data collection was primarily extracted from the 'Review reports for Regenerative Medical Products' on the PMDA website (www.pmda.go.jp) and the related publications. Data was collected on the features of regulatory and clinical development for the approved RPs, excluding experimental research that falls under the RM Act. For each RP the following variables were collected: type of RP, number of approved clinical indications and their diseases area according to ICD-11 classification, pivotal clinical trials conducted and supportive clinical studies, ODD, expedited program or expedited review designation (Sakigake or Priority review, respectively), timing and type of MA, timing for re-examination period, and post-marketing data required. For each pivotal clinical trial, the following variables were selected: phase, design, type of randomization, type of control, type of study blinding, number of arms, centers participating, type of hypothesis and primary endpoint, duration of the main phase of the study, overall number of patients that participated in the study (enrolled, on intervention arm or control arm and safety set), and age and sex of population. Statistical analysis for categorical and continuous variables was made by means of proportions, mean, standard deviation (SD), median, quartiles 25 and 75 (Q25, Q75) and range (min, max). A specific data extraction form was designed using Excel 2019 (Microsoft Corporation, Redmond, WA, USA) to collect information and to perform the statistical analysis. Data was only collected and analyzed for those approved products with an available PMDA report as of September 31st, 2021. For axicabtagene ciloleucel, the PMDA summary report was not publicly available and data collection was done through

publications, and thus its analysis excludes some variables. Human autologous oral mucosa-derived epithelial cell sheet was excluded from the clinical analysis since the report was also not publicly available. One indication was counted for beperminogene perplasmid, i.e. chronic arterial occlusive disease (which includes arteriosclerosis obliterans and Buerger's disease).

3. Results

3.1. Regulatory development for approved advanced therapies in *Japan*

A total of 14 RPs were approved in Japan for 16 indications. Of these products, 9 were developed specifically in Japan and 5 products were developed in the EU and the US and later or simultaneously applied to the Japanese market. Two of those products developed in Japan also submitted foreign data from a global program to support the MA, beperminogene perplasmid and human allogenic bone marrow-derived mesenchymal stem cells. Overall, a total of 6 (42.85%) products consists of gene therapies and 8 (57.14%) were cell therapies (6 autologous and 2 allogenic). For the products specifically developed in Japan, 7 (77.78%) were cell therapies. Table 1 summarizes the regulatory procedures adopted for the approved RPs that were specifically developed in Japan, and Table 2 summarizes the regulatory development for those products with the main development in regions other than Japan, such as EU and/or US.

Ten out of 14 (71.4%) approved therapies were granted an ODD and 3 products (21.4%) obtained the Sakigake designation. Overall, the mean (SD) time required from submission of the MAA to its final approval was 13.38 (10.27) months (median, 9, IQR, 8–14.5, range, 4–36). For those therapies with an ODD (and therefore with a Priority Review designation), the mean (SD) time required from the submission of the MAA to its final approval was 9.57 (3.36) months (median, 9, IQR, 8–11, range, 4–15). For the 3 products with a Sakigake designation, the MAA procedure lasted 4 months, less than 6 months for one of them and 15 months, the latter being substantially delayed due to the applicant's time to provide responses. A total of 12 out of 16 (75%) indications received a standard approval, whereas 4 (25%) received a conditional and time-limited one. For those therapies granted a standard approval, the mean (SD) time required from submission of the MAA to its final approval was 15.77 (11.38) months (median, 11, IQR, 8.25–14, range, 8–36), while for those products granted with a conditional and time-limited approval was 8 (4.55) months (median, 7, IQR, 4.25–12.75, range, 4–14). The timing for re-examination period, was set at 5 years under conditional and time-limited approval and exceptionally extended for teserpaturev, human autologous bone marrow-derived mesenchymal stem cells, and human autologous skeletal myoblast-derived cell sheet due to the potential recruitment issues in the post-marketing study.

3.2. Clinical development that supported the marketing authorization of regenerative therapies in *Japan*

RPs by disease area according to ICD-11 classification included: neoplasms (4), diseases of the musculoskeletal system and connective tissue (1), diseases of the eye and adnexa (2), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (1), diseases of the skin (1), diseases of the circulatory system (2), diseases of anal canal (1) and diseases of the nervous system (2). A total of 14 main trials were conducted to support the MA for these therapies specifically developed in Japan (median, 1, range, 1 to 3). The characteristics of clinical trials that support the MA for those products are included in Table 3, except for human autologous oral mucosa-derived epithelial cell sheet.

Of these studies, a total of 3 (21.42%) were Phase III, 1 (7.14%) was a Phase II/III and 10 (71.42%) were Phase I/II or II. All the RPs, except for beperminogene perplasmid, were approved based on a small, open-label, non-randomized, uncontrolled, single-arm clinical trial conducted in Japan, independently of whether they were granted a standard or conditional and term-limited approval. Regarding the methodology used in these pivotal studies, all the studies (except for beperminogene perplasmid) provided a description of the efficacy and safety of the intervention (92.85%), 3 (21.43%) of the studies also used historical references to provide context for interpreting the results and 2 studies (14.28%) used literature references to set up the efficacy threshold. To evaluate the primary objective, 11 (78.57%) of the trials used intermediate variables, which were mainly qualitative (85.71%). The mean (SD) time for the main phase of the trial (i.e. to evaluate the primary outcome) was 5.32 (4.29) months. The median (IQR 25–75) number of patients enrolled and treated was 15 (5–22) and 13 (6–17), respectively. It is noteworthy to mention that based on the limited number of patients included in these studies (including Phase III trials), the efficacy could not be evaluated or concluded in most cases. Finally, the mean (SD) age of the adult population included in these confirmatory trials was 45.32 (12.78) years old. There was an imbalance in the sex distribution, there being more males (n = 99, 66%) than females (n = 51, 34%), for those analyzed trials where the sex of the enrolled participants was reported.

Axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, darvadstrocel and onasemnogene abeparvovec were not specifically developed in Japan but were approved in the three key regions: US and/or EU and Japan. Foreign data was used to support the MA of tisagenlecleucel and onasemnogene abeparvovec, along with data from the Japanese cohorts in these studies (n = 15 for tisagenlecleucel and n = 3 for onasemnogene abeparvovec). The approval of axicabtagene ciloleucel was based on data from the global pivotal trial (ZUMA-1) and the results of a phase 2, open-label, single-arm study conducted in Japan to assess efficacy and safety in 16 patients. For lisocabtagene maraleucel, the safety and efficacy data was based on a US Phase 1 trial and a Japan-

Table 1. Product classification and regulatory procedures for the approved regenerative medicine products.

Products with specific development in Japan

Nonproprietary name	Teserpaturev	Human (autologous) oral mucosal-derived epithelial cell sheet	Human (autologous)s corneallimbus-derived corneal epithelial cell sheet	Beperminogene perplasmid	Human (autologous) bone marrow-derived mesenchymal stem cells	Human (allogenic) bone marrow-derived mesenchymal stem cells	Human (autologous) skeletal myoblast-derived cell sheet	Human autologous tissue for transplantation	Human autologous epidermal cell sheet		
Product brand name	Delytact	Ocural	Nepic	Collategen	Stemirac	Temcell	HeartSheet	JACC	JACE		
Type of therapy and Classification	Gene expression therapy products (excluding those listed in the preceding item 2)	Human somatic stem cell-processed products	Human cellular/ tissue-based products. Human somatic stem cell-processed products	Gene Therapy Product. Plasmid vector product.	Human cellular/tissue-based products. Human somatic stem cell-processed products	Human cellular/ tissue-based products. Human somatic stem cell-processed products	Human cellular/tissue-based products. Human somatic stem cell processed products	Human autologous tissue for transplantation*	Human cellular/tissue-based products. Human somatic stem cell processed products*		
Product´s description	Genetically engineered herpes simplex virus type 1	Human (autologous) oral mucosa-derived epithelial cell sheet	Human (autologous) corneal limbus-derived corneal epithelial cell sheet	Plasmid DNA encoding the gene of human hepatocyte growth factor	Human (autologous) bone marrow-derived mesenchymal stem cell	Human (allogeneic) bone marrow-derived mesenchymal stem cell	Human (autologous) skeletal myoblast-derived cell sheet	Human (autologous) chondrocytes in a three-dimensional environment using atelocollagen gel	Human (autologous) epidermis-derived cell sheet		
Date of MAA application	28 Dec 2020	Not known	20 Mar 2019	22 Jan 2018	29 Jun 2018	26 Sep 2014	30 Nov 2014	24 Aug 2009	20 Mar 2018	29 Jan 2016	06 Nov 2004
Date of Committee positive opinion	24 May 2021	11 Jun 2021	26 Feb 2020	26 Mar 2019	28 Dec 2018	18 Sep 2015	18 Sep 2015	27 Jul 2012	28 Dec 2018	29 Sep 2016	29 Nov 2007
Type of authorization	Conditional/ Time limited approval	Standard approval	Standard approval	Conditional/Time-limitedApproval	Conditional/Time-limitedApproval	Standard approval	Conditional/Time-limitedApproval	Standard approval	Standard approval	Standard approval	Standard approval
Re-examination period	7 years	Not known	10 years	5 years	7–8 years	10 years	5–8 years	7 years	10 years	10 years	10 years
Orphan Drug designation	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No
ODD	10 Jul 2017	Not known	25 Mar 2015	N/A	N/A	12 Dec 2013	N/A	N/A	18 Mar 2011	25 Nov 2014	N/A
SAKIGAKE Designation	Yes	No	No	No	Yes	No	No	No	No	No	No
Priority review	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes

It has been assumed that the products with an ODD were granted with a Priority Review designation. *JACC and JACE were originally approved as medical devices. Under the PMD Act (effective from 2014), these products were transferred from the medical device category to the regenerative medicine product category.

Table 2. Product classification and regulatory procedures for the approved regenerative medicine products with a global development.

	Products with global development				
Nonproprietary name	Darvadstrocel	Lisocabtagene maraleucel	Axicabtagene ciloleucel	Onasemnogene abeparvovec	Tisagenlecleucel
Product brand name	Alofisel	Breyanzi	Yescarta	Zolgensma	Kymriah
Type of therapy and Classification	Human somatic stem cell-processed products	Human cellular/tissue-based products. Human somatic cell processed product	Human cellular/tissue-based products. Human somatic cell processed product	Gene therapy products, Viral vector products	Human cellular/tissue-based products. Human somatic cell processed product
Product´s description	Cell suspension of expanded allogenic adipose-derived stem cells	Autologous CAR-T cells	Autologous CAR-T cells	scAAV9 vector containing human survival motor neuron gene (SMN1)	Autologous CAR-T cells
Date of MAA application	Not known	22 June 2020	Not known	01 Nov 2018	23 Apr 2018
Date of Committee positive opinion	27 Sep 2021	05 March 2021	Jan 2021*	06 Feb 2020	20 Feb 2019
Type of authorization	Standard approval	Standard approval	Standard approval	Standard approval	Standard approval
Re-examination period	Not known	10 years	Not known	10 years	10 years
Orphan Drug designation	Yes	Yes	Yes	Yes	Yes
ODD	Not known	Oct 2018	Oct 2018	Oct 2018	25 May 2016
SAKIGAKE Designation	No	No	No	Yes	No
Priority review	-	Yes	Yes	Yes	Yes

It has been assumed that the products with an ODD were granted with a Priority Review designation. *Date of Japanese Ministry of Health, Labor and Welfare granting the MA approval. CAR-T: chimeric antigen receptor T cell product; scAAV: self-complementary Adeno-Associated Virus.

included global Phase 2 study. The approval of darvadstrocel was supported by data from two clinical trials, a Phase 3, multicenter, open-label, uncontrolled study conducted in Japan that assessed the efficacy for 24 and 52 weeks, and safety for 156 weeks in 22 patients, and a pivotal study conducted in Europe and Israel.

From the 10 indications targeted with the products specifically developed in Japan, 4 (36.36%) of them had to perform use-results surveys (i.e. post-marketing surveillance system unique to Japan to collect information on treatment outcomes in real-world clinical practice) in all treated patients until the end of the reevaluation period as the only post-marketing requirement. For 2 (18.18%) indications an open-label, uncontrolled study to further assess efficacy and safety had to be conducted, and for the other 4 (36.36%) indications a prospective clinical study to compare the treatment with a control group in order to evaluate the efficacy and safety was agreed (Table S1). For onasemnogene abeparvovec, lisocabtagene maraleucel and tisagenlecleucel only use-results surveys in all Japanese treated patients were required.

4. Discussion

Clinical research on ATMPs has increased during the last few years and Japan is among the countries investing in this emerging technology [18]. Nagai *et al*., described and compared the expedited review processes for advanced therapies in the US, the EU, and Japan, emphasizing how the regulatory agencies have elaborated regulatory frameworks for innovative products and have influenced each other [8]. Kurauchi *et al*., compared several aspects of the clinical and non-clinical development of ATMPs between Japan and the EU [19]. In the present study, we provide an overview of the current picture, describing the most relevant features of the regulatory and clinical development that has driven RPs to their approval in Japan. Several RPs have already reached the Japanese market, but the regulatory and clinical development that supported their MA has not been systematically analyzed to our knowledge for all of them.

The main characteristics of the RPs approved in Japan and the ATMPs approved in the EU and the US are shown in Tables 4 and 5. In the EU, the US and Japan, ATMPs are regulated as biological products for human use with a specific framework for advanced therapies. Like in the US, the Japanese classification of RPs comprises two main categories: cell and gene therapy products, and in the three regions, the processing of cells is a mandatory criterion to consider a cell-based product as an advanced therapy [20]. More than half of the approved RPs target orphan indications, in line with our previously reported results for the approved advanced therapies in the EU and the US [21]. For the three regions, in order to obtain the orphan status, the medical plausibility needs to be demonstrated. The defined cutoff for the disease prevalence is different in each region, and the criterion of targeting a serious disease or unmet need and/or the clinical benefit demonstration is applicable to both the EU and Japan.

The Sakigake designation not only speeds up drug development but also the MAA assessment. The attractive benefit package that this designation constitutes,

Table 3. Clinical development of the approved regenerative medicine products developed in Japan.

Non-proprietary name	Teserpaturev	Human (autologous)s corneallimbus-derived corneal epithelial cell sheet	Beperminogene perplasmid			Human (autologous) bone marrow-derived mesenchymal stem cells	Human (allogenic) bone marrow-derived mesenchymal stem cells		Human (autologous) skeletal myoblast-derived cell sheet	Human autologous tissue for transplantation	Human (autologous) epidermal cell sheet			
Product Brand name	Delytact	Nepic		Collategen		Stemirac	Temcell		HeartSheet	JACC	JACE			
Clinical trial Acronym	Study GD01	EYE-01 M	ASO phase III	TAO open-label	Advanced medical care B clinical research study	Study STR01-03	JR031-201	JR-031–301	M-51073-21 (pivotal study)	J-TEC002	J-TEC-EB	J-TEC-01-01	3SI-GCMN001	J-TEC003
Indications	Malignant glioblastoma	Limbal stem cell deficiency	Critical limb ischemia of arteriosclerosis obliterans (ASO)	Buerger's disease	ASO and Buerger's disease	Neurological symptoms and functional disorders associated with spinal cord injury	Corticosteroid-refractory acute graft versus host disease (GVHD) following hematopoietic stem cell transplantation		Severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies	Symptoms of traumatic cartilage defect or osteochondritis dissecans (excluding gonarthrosis) of the knee*	Dystrophic Epidermolysis Bullosa and Junctional Epidermolysis Bullosa		Giant Congenital Melanocytic Nevus	Serious and Extensive Burns
Phase	II	III	III	II	II	II	I/II	II/III	I/II	I/II	II	III	I/II	I/II
Randomization	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Control	Uncontrolled	Uncontrolled	Placebo-controlled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled	Uncontrolled
Blinding	Open-label	Open-label	Double-blind	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label
Number of centers		5 centers	57 centers	8 sites	5 sites	1 center	12 centers	18 centers	3 centers	5 centers	4 centers	1 center	4 centers	2 centers
Number of arms	One	One	Two arms	One	One	One	One	One	One	One	One	One	One	One
Design	Single arm	Single arm	Parallel groups	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm
Main Outcomes	Final and single variable	Intermediate and single variable	Intermediate and composite variable	Intermediate and single variable	Intermediate and composite	Final and single variable	Intermediate/final variables and co-primary	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable	Intermediate and single variable
Type of variable for main outcome	Quantitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative	Quantitative	Qualitative	Qualitative	Qualitative	Qualitative	Qualitative
Type of objective	Comparison against a reference threshold of 15%, where a statistical significance with the one-sided significance level of 5% was required to demonstrate the efficacy	Description of efficacy of intervention (efficacy threshold for the primary endpoint set as 15% based on literature)	Intervention compared to placebo	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention. Historical reference used to provide context for interpreting the results	Description of efficacy of intervention	Intervention compared to historical reference	Description of efficacy of intervention. Historical reference used to provide context for interpreting the results	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention	Description of efficacy of intervention
Duration of the main phase (months)	12	13	3	3	3	7	6	1	6,5	12	3	1	3	1
Population														
Population enrolled or randomized	19	12	46	11	6	17	na	25	7	33	4	3	8	2

(*Continued*)

Table 3. (Continued).

Non-proprietary name	Teserpaturev	Human (autologous)s corneallimbus-derived corneal epithelial cell sheet	Beperminogene perplasmid			Human (autologous) bone marrow-derived mesenchymal stem cells	Human (allogenic) bone marrow-derived mesenchymal stem cells		Human (autologous) skeletal myoblast-derived cell sheet	Human autologous tissue for transplantation	Human (autologous) epidermal cell sheet			
Product Brand name	Delytact	Nepic		Collategen		Stemirac	Temcell		HeartSheet	JACC	JACE			
Population on intervention arm	13	10	29	10	6	13	14	25	7	32	4	3	8	2
Population on control arm	NA	NA	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Population on Safety set	16	10	41	10	6	13	14	25	7	33	4	3	8	2
Age of population														
Mean (SD) or reported age range	53 (na)	51.1 (22.65)	71.9 (7.6)	na	na	47 (14,71)	46,43 (16,35)	5 to 66	56,28 (13,22)	31,75 (9,61)	29,25 (20,37)	44,33 (18,77)	34 (16,97)	33,5 (0,71)
Sex:														
Female	3	3	6	na	na	1	9	10	0	10	2	2	4	1
Male	10	7	21	na	na	12	5	15	7	14	2	1	4	1

NA: not applicable; na: not available.

Table 4. Comparison of regulatory development to support approval of RPs in Japan, and ATMPs in the EU and the US.

	Japan	EU	US
Number of approved products	14	19[a]	14[b]
Number of approved indications	16[c]	20[d]	15[e]
Number of approved gene therapies	6 /14	12 /19	8 /14
Number of approved cells therapies[d]	8 /14	7 /19	6 /14
Number of products with ODD designation	10 /14	15 /19	10 /14
Number of products with Expedited development Designation[2]	3 /14	8 /19	11 /14
Number of products with Expedited MAA[3]	10 /14	9 /19	9 /14
Mean (SD) time to MA approval[3] (months)	13.4 (10.3)[h]	15.2 (6.0)[g]	10 (2.8)[f]
Mean (SD) time to MA approval of products with accelerated review[3] (months)	9.6 (3.3)	11.0 (2.9)	7.6 (2.0)[f]
Number of approved products with conditional and time-limited approval[4]	4 (28.6%)	7 (36.8%)	1 (7.14%)

[a]approved ATMPs in the EU (until 31 December 2021): Glybera®, Imlygic®, Kymriah®, Yescarta®, Tecartus®, Strimvelis®, Luxturna®, Zynteglo®, Zolgensma®, Libmeldy®, Abecma®, Skysona®, Provenge®, Zalmoxis®, Alofisel®, ChondroCelect®, Holoclar®, MACI®, Spherox®.
[b]Approved ATMPs in the US (until 31 December 2021): Abecma®, Stratagraft®, Rethymic®, Breyanzi®, Tecartus®, Gintuit®, Kymriah®, Imlygic®, LaViv®, Luxturna®, MACI®, Provenge®, Yescarta®, Zolgensma®.
[c]13 RPS have one indication, and 1 RP have three different indications; [d] 14 ATMPs have one indication, and 1 ATMP have two different indications; [e] 8 ATMPs have one indication, and 1 ATMPs have two different indications; [f] excluding Rethymic®, considered an outlier; [g] excluding Spherox®, considered an outlier.[h] 9.36 (3.32) considering JACC and one indication of JACE that might be considered as an outliers.
[d]Includes tissue-engineered products; [2]It includes any of those designations: PRIME (EU), Fastrack designation (US), breakthrough designation (US), RMAT (US) and Sakigake designation (Japan); [3]Include priority review for Japan and US and Accelerated Assessment for EU. The mean time required from submission of the MAA to its final approval (CHMP positive opinion in the case of EU); [4] It includes a conditional and time-limited approval (Japan), as well as a conditional approval and an approval under exceptional circumstances (EU), and accelerated approval (US).
MA: marketing authorization; ODD: orphan drug designation.

Table 5. Comparison of clinical development to support approval of RPs in Japan, and ATMPs in the EU.

	Japan	EU*
Number of products analysed	8[a]	17
Number of pivotal clinical trials	14	23
Mean (min-max) number of pivotal clinical trials	1–3	1-3
Phase of trials		
Phase I, Phase I/II, Phase II and retrospective trials	10 /14	10 /23
Phase II/III, Phase III	4 /14	13 /23
Type of control		
Non-controlled	13 /14	16 /23
Placebo or active-controlled	1 /14	7 /23
Type of objective		
Superiority or non-inferiority study	1 /14	7 /23
Other	13 /14	16 /23
Main outcome		
Intermediate variable	11 /14	18 /23
Final variable	3 /14	5 /23

*Based on data from previous analysis [23]. [a]Only products with a development specific in Japan were considered.

promotes the development of innovative products and is one of the key points to consider when the global strategy for the product launch is being developed. A low percentage of approved products were granted this designation, similarly to the percentage of approved products in the EU that obtained a PRIME designation [21]. However, there are at least 9 RPs with this designation, some of them still in development, and the number of approved products with this designation is expected to increase in the near future [22]. On the other hand, the three regions have an expedited MAA assessment, called 'priority review' in Japan and the US and 'accelerated assessment' in the EU. The eligibility criteria for the priority review in Japan are similar to the US, although three additional months are required for the MAA review under this designation. It should be mentioned that another appealing regulatory tactic in Japan is to automatically obtain a Priority Review for having an ODD, where the developers can benefit from both an expedited review and market exclusivity.

The overall MAA review period in Japan for the currently approved products is shorter than in the EU (15.2 ± 6 months) and higher than in the US (10 ± 2.8 months) [21]. Regarding the types of MA, the conditional and term-limited approval system has similarities with the accelerated approval in the US and the conditional approval in the EU. These three types of approvals require that exploratory clinical trials predict a reasonable likelihood of clinical benefit by using a surrogate endpoint, in those cases where comprehensive clinical data may not be readily obtained.

The clinical development that supported the MA for RPs is mainly based on small exploratory Phase I/II, uncontrolled, single-arm trials. Similarly to the adaptive licensing in the EU, the concept behind the conditional and term-limited approval pathway entails that a product can be approved based on the limited available safety, and efficacy data and a low number of treated patients. However, in the case of the analyzed RPs, it seems that those products developed in Japan and granted standard approval did not have a substantially more robust clinical development (Table S2). Even though in the EU and the US the type of trial designs to support the MA with advanced therapies has a similar trend (i.e. open-label, non-randomized, single-arm studies without control or using historical ones) [23], it seems that more robust confirmatory evidence support the clinical benefit. In the EU and US, the approval was based on the assessment of more patients and more conclusive efficacy, comparison with different types of historical controls and supportive studies, whereas in Japan the approval is mainly granted with non-confirmatory evidence under the ground of prioritizing the unmet medical needs of the target diseases. Similar results have been reported by Coppens *et al*., where the level of scientific clinical evidence for approval in the US, the EU and Japan was analyzed, concluding that in Japan non-significant trends of efficacy and uncertain safety were sufficient for approval [24]. Considering that the methodology used for these studies

was mainly descriptive and using surrogate variables, had a low sample size and presented data with a wide variation in cases and responses, it can be inferred that determining the efficacy can be a particularly challenging endeavor. In addition, it also should be noted that the timing assessments did not exceed 52 weeks, averaging approximately 5 months. These short-term investigations allow the assessment of acute adverse events, long-term safety and effectiveness being evaluated in the post-marketing setting along with the efficacy. Finally, the lower number of subjects could be compensated using the results of clinical studies from other countries with the proper clinical extrapolation [25].

Examples of products that might have had more solid data but were approved based on their potential benefit for diseases with high unmet needs include human autologous tissue for transplantation (JACC), beperminogene perplasmid (Collatagen), human autologous epidermal cell sheet (JACE) and human autologous bone marrow-derived mesenchymal stem cells (Stemirac). The efficacy of human autologous tissue for transplantation, a product for cartilage damage, was investigated in a non-controlled trial with 24 evaluable cases and 12 months of clinical data. Given the prevalence of this target indication and the availability of standard treatments, the design of the trial was questioned, as even in a non-blinded manner, a control could have been included. A re-analysis of efficacy had to be performed and the product was approved on the basis that it represented a new treatment option for patients with a rare disease, narrowing the indication to patients who are unlikely to be adequately responsive to conventional therapies and who have a relatively large cartilage defect area. On the other hand, given that the trial did not support cartilage regeneration, the indication consists of 'alleviation of clinical symptoms' [26]. For a similar product approved in the EU, i.e. characterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins (ChondroCelect), a non-inferiority trial with the standard of care as the comparator was conducted with 118 patients (57 treated and 61 in the control arm), with 36 months of follow up data and morphological assessment using tissue sections and biopsies that supported the 'repair of cartilage defect' indication.

For the only product investigated on a controlled trial, beperminogene perplasmid, a conditional time-limited approval was granted, since the efficacy could not be adequately established. A final clinical endpoint (limb salvage) was not used, the thresholds for the chosen primary endpoints did not have an established criterion (ulcer size or improvement in pain at rest), there were differences in efficacy among studies in different regions, and there were also some deficiencies with the blinding that compromised the integrity of the study and the reliability of the results [27].

For human autologous epidermal cell sheet (JACE), the submission was based on the results of the percentage of epithelialization 4 weeks after grafting in 2 patients, and the approval was justified on the absence of standard therapy, the seriousness of disease and it is potential contribution to a higher survival rate [28]. Specialists in stem cells and spinal cord injuries flagged the fact that human autologous bone marrow-derived mesenchymal stem cells' (Stemirac) approval was based on poorly designed clinical trial that could not reveal efficacy, as well as the potential safety concerns associated with the infusion of stem cells into the blood. Moreover, the mechanism of action of the product was strongly questioned (i.e. mesenchymal stem cell differentiation into neurons) [29,30]. While human autologous tissue for transplantation (JACC) and human (autologous) epidermal cell sheet (JACE) obtained a standard approval, the limitations of beperminogene perplasmid's (Collategen) and human autologous bone marrow-derived mesenchymal stem cells' (Stemirac) development were justified with the type of approval, conditional and time limited.

As discussed in our previous publication [23,31], limited data at the time of approval has consequences and implications for the patient, the healthcare system and for reimbursement, and implies that substantial post-marketing risk management activities need to be conducted. The post-marketing conditions in Japan include follow-up for all patients treated. In addition, under the conditional and time-limited approval scheme, it is required to demonstrate efficacy within the granted time period and the applicant is subject to a post-marketing study (PMS) as a condition for approval. Four products were granted this type of approval requiring a PMS, where the treatment is compared with a control group, there is a reasonable sample size and the primary and secondary endpoints are focused on efficacy and include final variables. While it could have been questioned why these controlled and more solid studies were not conducted at pre-marketing stage, the Japanese framework for RP allow this staggered approval, which implies uncertain benefit-risk balance at the time of MA.

Finally, the conditional and time-limited approval scheme constitutes a separate drug approval pathway for RPs unique to the Japanese market. Within this scheme, an approval can be granted based on inconclusive efficacy and limited safety, relying on robust Phase III studies conducted in the post-MA setting. This high regulatory flexibility, the extremely abbreviated clinical development required to obtain approval and the benefits of the available designations, can be seen attractive incentives for the future development of RPs. On the other hand, it should be noted that no product has yet been granted a standard authorization after a re-application under this conditional and time-limited framework. However, while under this framework these products could obtain full approval based on controlled studies and sound data, drugs that were directly granted a standard authorization obtained their MA through smaller and uncontrolled trials. Therefore, when choosing a regulatory strategy for approval in Japan, the opportunity cost of pursuing the conditional and time limited approval must be considered, as this scheme can provide faster market access but might require more comprehensive and burdensome PMS than a direct standard approval. It should also be noted that Japan's eight-year experience with RPs may not be enough to accurately evaluate whether or not Japan's model is successful and if further monitoring is needed.

4.1. Limitations of the current study

The limitations of this study are its small sample size and the fact that further analysis is required, once more therapies are approved, to determine with greater accuracy the most common clinical trial design and methodology for RP approval in Japan. Nevertheless, this is an exhaustive study that evaluates the regulatory development and pivotal clinical trials for the approved RPs in Japan with the available information.

5. Conclusion

Severely debilitating or life-threatening targeted diseases, most of them with lack of available alternative treatments, or rare diseases have had an impact on the decision-making for the approval of regenerative therapies in Japan so far. RPs regulations, including adaptive licensing, promote early patient access, enabling shortcuts to speed up clinical development and thus shortening the time to approval. Under this scheme, study designs might lead to limitations in the interpretation of efficacy and safety outcomes, but these are accepted based on the severity of targeted diseases and the poor prognosis of patients with no treatment options. When developing the regulatory strategy for Japan, key levers must be considered at the early stages of clinical development: opportunity to pursue ODD, Sakigake designation and the possibility of obtaining a conditional time limited approval instead of a standard authorization. Given the limited experience with Japan's model, it will be interesting to see its pros and cons in the future.

6. Expert opinion

Japan has made considerable efforts to enhance the adoption of RPs, particularly since the discovery of induced pluripotent cells. Flexible regulatory framework is promoting the development of innovative products with designations that include attractive benefit packages and MA granted based on Phase 1 and 2 clinical trials if safety is confirmed, efficacy can be assumed and there is a planned post-marketing study.

So far, the introduction of these therapies is being granted with inconclusive evidence of efficacy and safety, prioritizing the unmet medical needs of the target diseases. Although similar approach is being applied in the US and the EU through accelerate and adaptive pathways and in favor of post-marketing evidence generation, more robust developments and higher sample sizes seem to be needed for the approval of the same type of products. Similarly, most of those RPs not specifically developed in Japan, were authorized with a standard approval based on data from Phase 2 international trials that include Japanese cohorts and small Japanese trials. No Phase 3 clinical trial results were required. These products were previously approved in the EU and US, probably due to a later clinical development and regulatory requirements in Japan (such as GMO procedures).

Currently, RPs are mainly focused on orphan diseases, which have the additional benefits of an orphan regenerative medical product designation, i.e. financially support during drug development, market exclusivity and priority review. However, in the near future, we expect that the RPs will cover higher prevalence indications rather than orphan conditions, which, in turn, will increase the number of RP submissions for approval. Ideally, these changes should evolve in parallel with the regulatory model. While Sakigake is an attractive alternative designation, the regulatory strategy plan for product development should consider the parallel international development in Japan, which so far has not been the case for most of the approved products. When orphan or Sakigake designations are not possible to obtain, the Priority review might be a good option to accelerate market access. However, a comparison with the existing products is required (in case a SoC is available), which might change the type of clinical trial designs.

As outlined in this manuscript, a future re-assessment once more treatments are approved would determine more accurately the most common clinical trial designs and methods for RP approval in Japan. Given the limited experience with this approval model, it remains to be analyzed its pros and cons in the future and how many products might withdraw from the market and their reasons. It would be interesting to assess the differences between standard approvals and conditional and time limited ones, given that so far, the former did not seem to have a substantially more robust clinical development than the latter. Timely publication of evaluation reports in English is essential, not only for transparency purposes but also to increase regulatory knowledge in the field and for pharmaceutical companies as a reference for product development.

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Declaration of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The findings and conclusions in this article should not be construed to represent any agency determination or policy. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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List of abbreviations

ATMPs	Advanced therapy medicinal products
EMA	European Medicines Agency
ERA	Environmental risk assessments
EU	European Union
GMOs	Genetically modified organisms
ICD-11	International Classification of Diseases 11th Revision
IQR	Interquartile range
LMO	Living modified organisms
MA	Marketing authorisation
MAA	Marketing authorisation application
MHLW	Ministry of Health, Labour and Welfare
OCTP	Office of Cellular and Tissue-based Products
ODD	Orphan drug designation
PMD Act	Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act
PMDA	Japanese Pharmaceuticals and Devices Agency
PMS	Post-marketing clinical studies
PRIME	Priority Medicines scheme
RM Act	Act on the Safety of Regenerative Medicine
RMAT	Regenerative medicine advanced therapy
RNAs	Ribonucleic acids
RPs	Regenerative medicine products
SD	Standard deviation
siRNAs	Small interfering RNA
US	United States of America

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Health Policy Analysis

Financing and Reimbursement of Approved Advanced Therapies in Several European Countries

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ABSTRACT

Objectives: The uncertainty in the cost-benefit of advanced therapy medicinal products (ATMPs) is a current challenge for their reimbursement in health systems. This study aimed to provide a comparative analysis of the National Health Authorities (NHAs) reimbursement recommendations issued in different European countries.

Methods: The NHA reimbursement recommendations for the approved ATMPs were compared among 8 European Union (EU) Countries (EU8: Ireland, England/Wales, Scotland, The Netherlands, France, Germany, Spain, and Italy). The search was carried out until December 31, 2021.

Results: A total of 19 approved ATMPs and 76 appraisal reports were analyzed. The majority of the ATMPs were reimbursed, although with uncertainty in added therapeutic value. No relationship between the type of the European Medicines Agency approval and reimbursement was found. Managed entry agreements, such as payment by results, were necessary to ensure market access. The main issue during the evaluation was to base the cost-effectiveness analyses on assumptions because of the limited long-term data. The estimated incremental cost-effectiveness ratio among countries reveals high variability. Overall, the median time to NHA recommendation for the EU8 is in the range of 9 to 17 months.

Conclusions: Transparent, harmonized, and systematic assessments across the EU NHAs in terms of cost-effectiveness, added therapeutic value, and grade of innovativeness are needed. This could lead to a more aligned access, increasing the EU market attractiveness and raising public fairness in terms of patient access and pricing.

Keywords: added therapeutic value, advanced medicinal products, financing government, health technology assessment, market access.

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Introduction

Advanced therapy medicinal products (ATMPs) are innovative drugs, based on genes, cells, and tissues, offering potentially curative treatment options for a range of diseases. ATMPs are associated with high costs and, for some of them, uncertain efficacy claims, which is being a current setback for the market access of these drugs.[1] This is accentuated by the fact that an increased number of ATMPs are expected to enter the market in the coming decade, covering indications with higher prevalence rather than orphan diseases.[2,3] Once the European Commission (EC) approves an ATMP, the access to treatment depends on the inclusion of the product in the public healthcare funding. Each European Member State has its own authority over the market access of new products and its reimbursement agreements, which are conditioned by the respective healthcare resources. With this purpose, the National Health Authorities (NHAs) of European Member States perform a relative efficacy and safety assessment, giving recommendations on whether a product should be considered for reimbursement and under what conditions, if necessary.[4] These NHAs appraisals usually consider several criteria to make their recommendations, such as the burden and severity of the target indication, the relative effectiveness and safety of the new product compared with the standard of care (SoC) or best supportive care, the cost and economical effectiveness, as well as ethical, social, and patient aspects.[5]

The aim of our research was (1) to provide a comparative analysis of NHAs recommendations issued by 8 different European countries, (2) to analyze if there was any relationship between the type of the European Medicines Agency (EMA) approval (conditional approval or under exceptional conditions vs standard approval) that could affect the reimbursement decision, and (3) to provide insights of the key considerations that played a role in the NHA reimbursement recommendations.

Methods

An analysis of NHAs reports of authorized ATMPs in 8 European Union (EU) countries (EU8) has been conducted using the following approach:

Search Strategy

Data collection was primarily extracted from available NHAs reports, such as health technology assessments (HTAs) and other official national reports of the EU8, that is, Ireland, England/Wales, Scotland, The Netherlands, France, Germany, Spain, and Italy. The inclusion of countries was according to the largest European countries and HTA report availability written in a language understood by the researchers. The search was carried out until December 31, 2021. In addition, a search for related publications was performed for pricing (ie, gray literature: open search and non–peer review journals).

Eligibility Criteria

Only products classified as ATMPs according to the EMA criteria[6,7] and authorized under centralized procedure in the EU have been considered for the analysis.

Data Extraction and Collected Variables

The authors designed specific data extraction forms using Excel 2019 (Microsoft Corporation, Redmond, WA) to collect information. A review of NHAs reports of approved ATMPs published by national bodies in each country was conducted. The national bodies and the type of HTA reports analyzed for each country are reported in Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014.

For each ATMP/indication and NHA body, the following variables were collected: type of EMA approval, reimbursement recommendation, financing conditions, drug comparator used for the cost-effectiveness analysis and incremental cost-effectiveness ratio (ICER), reported price of the product (notified price or applicants requested price), date of publication of technology appraisal guidance, and the date of recommendation implementation. Only reports describing the initial assessments were included, excluding resubmissions. For the ICERs, the base case accepted by the agency after corrections was chosen. Time from EMA approval to NHA recommendation in their appraisal reports and time from EMA approval to implementation (ie, product available to the patients) were analyzed.

It was assessed if there was any relationship between the type of EMA approval (conditional approval or under exceptional conditions vs standard approval) that could affect the reimbursement decision, given that less comprehensive data might be available.

The key considerations that played a role in or might have influenced the NHA reimbursement recommendation or final decision were collected for those products with an available NHA assessment report (in which these considerations could be extracted). After identification of all HTA reports of authorized ATMPs, considerations that had an influence on reimbursement were extracted—a consideration was defined as follows: "a value judgement of the HTA-body during the assessment." These key considerations were classified according to the 5 European Network for Health Technology Assessement HTA Core Model® (version 3) domains and the HTA Core Model for Rapid Relative Effectiveness Assessments domains (version 4.2).[8,9] A review was conducted for the published reports of approved ATMPs to compare the aforementioned variables of the ATMP assessments across the 8 NHA bodies. The items or considerations included in the NHAs reports that might have had an influence on the reimbursement final decision were classified according to the prespecified domains. In addition, these considerations were classified according to the ATMP type: gene therapies (chimeric antigen receptor T cell [CAR-T] products), gene therapies that consist of viral vector–delivered or cell-based therapies and cell- and tissue-engineered products. Data extraction and analysis were conducted by one author, and a second author validated it. Inconsistencies were discussed until consensus was reached.

Statistical Analysis

A descriptive statistical analysis was performed using means, median, and range (minimum and maximum). The relationship between the type of EMA approval and the reimbursement decision was assessed by a chi-square statistic test with Yates correction. A P value $< .05$ was considered statistically significant.

Results

The analyzed products and the type of approval granted by the EMA are listed in Table 1. A total of 19 approved ATMPs were included for 20 indications, 7 of those were authorized under conditional or exceptional circumstances. In addition, 7 ATMPs were withdrawn from the market. A total of 76 NHAs appraisal reports or summaries among the analyzed countries were available and analyzed.

Recommendations of Reimbursement and Type of Reimbursement Schemes

The majority of the ATMPs were initially reimbursed in most EU8, except in the case of Ireland (Table 2). Germany reimbursed all the 13 ATMPs for 14 indications, as well as The Netherlands (6 ATMPs were reimbursed except for 1 indication of 1 product). England and Wales agreed for the reimbursement of 11 out of 12 assessed ATMPs, similar to France with 10 out of 14 and Italy with 7 out of 8 products. Ireland did not reimburse any of the 5 assessed ATMPs at an initial stage but did it later after reassessment with CAR-T products.

England and Wales, Scotland, The Netherlands, France, and Spain narrowed the authorized indication for the reimbursement of some ATMPs. Germany did not restrict any ATMP to specific conditions within the authorized indication.

Most countries established some types of reimbursement schemes, but the specific type of schemes is divergent among the EU8. Managed entry agreements (MEAs) or patient access schemes are regularly used in Scotland and England, determining specific conditions for reimbursement, usually in a confidential manner. Payment based on outcomes are more frequently used in The Netherlands, Spain, and Italy where financing is linked to the achievement of certain clinical outcomes. This risk-sharing reimbursement approach might allow discounts and rebates.

The type of EMA approval did not have an influence on the reimbursement decision (chi-square 0.4742; $P = .492$).

Determination of a Product's Added Therapeutic Value

The determination of a product's added therapeutic value (ATV) has different implications in terms of recommendations, reimbursement negotiations, and granting the drug innovativeness status. In Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014, these implications are further discussed by country. There is not a harmonized or defined standard for ATV classification, and the assessment criteria is different in each country. In France, Italy, and Germany, the ATV is assessed

Table 1. Analyzed ATMP approved in the European Union.

Type of ATMP	Brand name	INN	Pharmacotherapeutic group	Orphan drug designation	Type of authorization and current status
GTMP	Glybera®	Alipogen tiparvovec	Lipid modifying agents	Yes	Exceptional circumstances. Withdrawn
	Imlygic®	Talimogene laherparepvec	Antineoplastic agent	No	Standard
	Kymriah® (DLBCL)	Tisagenlecleucel	Antineoplastic agent	Yes	Standard
	Kymriah® (ALL)	Tisagenlecleucel	Antineoplastic agent	Yes	Standard
	Yescarta®	Axicabtagene ciloleucel	Antineoplastic agent	Yes	Standard
	Tecartus®	Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor and cultured	Antineoplastic agent	Yes	Conditional
	Strimvelis®	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Immunostimulants	Yes	Standard
	Luxturna®	Voretigene neparvovec	Ophthalmologicals	Yes	Standard
	Zynteglo®	Betibeglogene autotemcel	Other hematological agents	Yes	Conditional. Withdrawn
	Zolgensma®	Onasemnogene abeparvovec	Other drugs for disorders of the musculoskeletal system	Yes	Conditional
	Libmeldy®	Atidarsagene autotemcel	Other nervous system drugs	Yes	Standard
	Abecma®	Idecabtagene vicleucel	Antineoplastic agent	Yes	Conditional
	Skysona®	Elivaldogene autotemcel	Other nervous system drugs	Yes	Standard. Withdrawn
SCTMP	Provenge®	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (Sipuleucel-T)	Other immunostimulants	No	Standard. Withdrawn
	Zalmoxis®	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	Antineoplastic agents	Yes	Conditional. Withdrawn
	Alofisel®	Darvadstrocel	Immunosuppressants	Yes	Standard
TEP	Chondrocelect®	Characterized viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	Other drugs for disorders of the musculoskeletal system	No	Standard. Withdrawn
	MACI®	Matrix-applied characterized autologous cultured chondrocytes	Other drugs for disorders of the musculoskeletal system	No	Standard. Withdrawn
	Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Other drugs for disorders of the musculoskeletal system	No	Standard
	Holoclar®	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	Ophthalmologicals	Yes	Conditional

ADA indicates adenosine deaminase; ALL, B-cell acute lymphoblastic leukemia; ATMP, advanced therapy medicinal product; cDNA, complementary DNA; DLBCL, diffuse large B-cell lymphoma; GTMP, gene therapy medicinal product; INN, international nonproprietary name; SCTMP, somatic-cell therapy medicinal product; TEP, tissue-engineered medicinal product.

Table 2. Overview of initial reimbursement recommendations and financing conditions of approved advanced therapy medicinal products in the Europe Union (December 2021).

Product/indication		Scotland	Ireland	England and Wales	The Netherlands	Italy	Spain	France	Germany
GTMP	Glybera®							‡	*
	Imlygic®			MEA†			‡		*
	Kymriah® (DLBCL)	MEA/OEP*	*ODM§	MEA*	‡	PBO*	PBO†	*	*
	Kymriah® (ALL)	MEA/OEP*	*ODM§	MEA*	OEP*	PBO*	PBO†	*	*
	Yescarta®	MEA/OEP*	‡	MEA*	MEA*	PBO*	PBO†	*	*
	Tecartus®	MEA/OEP*		MEA*				*	*
	Strimvelis®			*		PBO*			
	Luxturna®	MEA/OEP†	‡	MEA*	PBO/OEP*	*	PBO*	*	*
	Zynteglo®				PBO/OEP*			†	*
	Zolgensma®	MEA/OEP†	‡	MEA†	PBO†	†		†	*
	Libmeldy®							†	*
	Abecma®								
SCTMP	Provenge®								*
	Zalmoxis®					*		‡	*
	Alofisel®	OEP‡	‡	‡		‡	PBO†	†	*
TEP	Chondrocelect®			†	†			‡	
	MACI®			MEA†					
	Spherox®			†				‡	
	Holoclar®	OEP†		†		PBO*	‡	†	*
Available reports/ indication	20	8	6	13	7	9	7	14	14

ALL indicates B-cell acute lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; GTMP, gene therapy medicinal product; MEA, managed entry agreement; ODM, Oncology Drug Management System; OEP, ultraorphan or end-of-life process; PBO, payment based on outcomes; SCTMP, somatic-cell therapy medicinal product; TEP, tissue-engineered medicinal product.
*Positive recommendation.
†Positive recommendation with restricted indication.
‡Negative recommendation.
§Initial negative recommendation and finally, reimbursement following confidential price negotiations on July 2021.

as a separate parameter according to several ranks and scales, whereas in Scotland, Ireland, and Spain, there is no publicly defined ATV classification, and it seems to be a part of their clinical effectiveness assessment. The Netherlands uses a binary categorical classification system, classifying whether a product has ATV or not, which is called "established medical science and medical practice."[10]

Table 3 compares the ATV assigned per product in France, Italy, Germany, and The Netherlands. In Italy, of the 6 indications (5 ATMPs) in which innovativeness was assessed, 4 indications obtained the innovative status, and 2 were denied. For those products, the ATV was graded as "important" for 4 indications, as "moderate" for 1, and as "low" for 1. In Germany, of the 14 indications (13 ATMPs) approved, 3 were classified as having the "added benefit not proven," 7 were classified as "hint for a non-quantifiable additional benefit" because the scientific data does not permit quantification, 1 product was classified as "hint for a considerable additional benefit," and 2 products were not subject to the scope of the benefit assessment. From the 7 available HTA reports in The Netherlands, 5 assessed indications were considered "substitutable" or with similar therapeutic value, 1 was considered to be equal as SoC, and 1 was concluded to provide insufficient evidence of its intended effects. In France, most ATMPs had a minor or moderate ATV. Overall, there is a benefit found in these drugs, but there are differences in how the magnitude of this benefit is considered among countries (Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014).

Special Funding Process That Affects Reimbursement Decision

Most countries have special funding processes regarding the reimbursement decisions related to orphan drugs, drugs that are targeted to treat patients in their last months of life (also called end-of-life medicine), the disease severity, or to cover an unmet medical need. In Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014, the considerations for special funding processes are further discussed by country.

Of the 7 ATMPs assessed in Scotland, all were submitted under the orphan or end-of-life processes. In England and Wales, 3 ATMPs (Kymriah® in diffuse large B-cell lymphoma indication, Yescarta®, and Tecartus®) met the criteria for life-extending treatments, but Kymriah® in acute lymphocytic leukemia indication did not. From 13 analyzed drugs, 4 were assessed under the Highly Specialized Technology procedure (Strimvelis®, Luxturna®, Zolgensma®, and Libmeldy®). In The Netherlands, 3 ATMPs were reported to have an orphan drug agreement. In Germany, 3 of the 7 analyzed and approved drugs obtained an orphan drug agreement to guarantee patient access.

Table 3. Product ATV and innovativeness status.

Product/indication		Italy	France	Germany	The Netherlands
GTMP	Glybera®		Insufficient clinical benefit	No added benefit proven	
	Imlygic®			No added benefit proven	
	Kymriah® (DLBCL)	INV/important added value	CAV IV: minor added value	Nonquantifiable added benefit	Does not comply with established medical science and medical practice: insufficient evidence of the intended effects*
	Kymriah® (ALL)	INV/ important added value	CAV III: moderate added value	Nonquantifiable added benefit	Meets the statutory criterion of "established medical science and medical practice"
	Yescarta®	INV/important added value	CAV III: moderate added value	Nonquantifiable added benefit	Meets the statutory criterion of "established medical science and medical practice"
	Tecartus®		CAV III: moderate added value	Nonquantifiable added benefit	
	Luxturna®	INV/important added value	CAV II: substantial added value	Hint for a considerable additional benefit	Meets the "current state of science and practice" criterion, but with great uncertainties on long-term effects and the cost-effectiveness
	Zynteglo®		CAV III: moderate added value	Nonquantifiable added benefit	Meets the "current state of science and practice" criterion, but with great uncertainties on long-term effects and the cost-effectiveness
	Zolgensma®	INV/important added value	CAV III: moderate added value	No added benefit proven	Meets the "current state of science and practice" criterion but the scientific data does not permit quantification of added value with the comparator
	Libmeldy®		CAV III: moderate added value	Nonquantifiable added benefit	
SCTMP	Zalmoxis®	Non-INV/moderate added value	-	Nonquantifiable added benefit	
	Provenge®			Nonquantifiable added benefit	
	Alofisel®	Non-INV/minor added value	CAV IV: minor added value	Nonquantifiable added benefit	
TEP	Holoclar®	Unknown	CAV IV: minor added value	†	
	ChondroCelect®		Insufficient clinical benefit		Therapeutic value equal to comparator

Italy: the 5 categories of ATV are as follows: maximum (the drug has proven larger efficacy than any possible existing alternatives to the point of cure or significantly alter its natural history), important (the drug has a proven larger efficacy measured on clinically relevant endpoints, decreases the risk of invalidating or fatal complications, avoids highly dangerous clinical procedures or has more favorable risk/benefit ratio than any available alternatives), moderate (the drug has a larger efficacy than any available alternatives, but it is only moderate or only proven in some subsets of patients, with limited impact on the quality of life), poor (the drug has either a limited improvement of efficacy or has been proven on endpoints which are not clinically relevant, minor advantages, eg, more acceptable administration route), absent (the drug has no relevant benefit when compared with other available treatments).
France: the CAV categories are: major (CAV level I), substantial (CAV level II), moderate (CAV level III), minor (CAV level IV) or no improvement (CAV level V), with the latter level corresponding to no therapeutic progress.
Germany: the 6 categories of ATV are as follows: major, considerable, minor, and nonquantifiable added benefit; no added benefit proven; the benefit of the drug under assessment is less than the benefit of the appropriate comparator therapy.
The Netherlands: "established medical science and medical practice": product leads to relevant (added) value for the patient in comparison with the standard or usual treatment; "net benefit" of the intervention being assessed is a relevant and sufficiently large benefit in comparison with all existing care.
ALL indicates B-cell acute lymphocytic leukemia; ATV, added therapeutic value; CAV, clinical added value; DLBCL, diffuse large B-cell lymphoma; GTMP, gene therapy medicinal product; INV, innovative status granted; Non-INV, innovative status not granted; SCTMP, somatic-cell therapy medicinal product; TEP, tissue-engineered medicinal product.
*In a reassessment performed in January 2022, it was concluded that Kymriah meets the legal criterion of "established medical science and medical practice" in patients with r/r DLBCL.
†Ex vivo expanded autologous human corneal epithelial cells containing stem cells are therefore not included in the scope of the benefit assessment according to Section 35a Social Code Book V.

Table 4. Time (months) from EC approval to the NHA recommendation and product market access.

Type of ATMPs		EC approval date	HTA recommendation	HTA recommendation	Implementation	HTA recommendation	Implementation
			Scotland	Ireland		England and Wales	
GTMP	Glybera®	October 25, 2012					
	Imlygic®	December 16, 2015	16	2		9	12
	Strimvelis®	May 26, 2016				20	23
	Kymriah® (DLBCL)	August 22, 2018	12	12	34‡	6	8
	Kymriah® (ALL)	August 22, 2018	5	18	34‡	3	5
	Yescarta®	August 23, 2018	13			5	7
	Luxturna®	November 22, 2018	14	21		10	13
	Zynteglo®	May 29, 2019					
	Tecartus®	14-December 14, 2020	7			2	4
	Zolgensma®	May 18, 2020	9	10		13	16
	Libmeldy®	December 17,2020					
SCTMP	Provenge®	September 6, 2013					
	Zalmoxis®	August 18, 2016					
	Alofisel®	March 23, 2018	15	18		9	
TEP	Holoclar®	February 17, 2015	66			30	33
	Spherox®	July 10, 2017				7	10
	Median, months		13	15	34	9	11
	Range Max, months		66	21	-	30	33
	Range Min, months		5	2	-	2	4

Note. NHA recommendation: time (months) from EC approval to the date of publication of technology appraisal recommendation. Implementation: time (months) from EC approval to date of implementation of NHA recommendation. When information is not publicly available, there is a blank gap. There is no information published for Abecma® and Skysona® as of December 31, 2021. MACI® and Holoclar® were evaluated via the medical procedure in Germany and not as a medicine, which undergoes the benefit assessment procedure.

ALL indicates B-cell acute lymphocytic leukemia; ANSM, National Agency for the Safety of Medicines and Health Products; ATU, Authorization of Use; DLBCL, diffuse large B-cell lymphoma; EC, European Commission; GTMP, gene therapy medicinal product; HTA, Health Technology Assessment; Max, maximum; Min, minimum; NHA, National Health Authority; SCTMP, somatic-cell therapy medicinal product; TEP, tissue-engineered medicinal product.

*Cohort temporary ATU granted in France.

†Received nominative ATUs in France from June 2019 and a cohort ATU granted by the ANSM on May 15, 2020 in the marketing authorization indication.

‡Finally, reimbursement following confidential price negotiations on July 2021.

§Early access scheme.

Time to Market Access

The time from EC approval to the national NHA recommendation on financing decision and product market access is summarized in Table 4. Overall, the median time to NHA recommendation for the EU8 is in the range of 9 to 17 months, the time to implementation being the same as the time to NHA recommendation in Germany and +2 or +3 months in England. For the other countries that were analyzed, the time to implementation could not be determined due to limited data.

In France, products can be reimbursed before central authorization via the Temporary Authorization of Use (ATU) on a named patient basis (nominal ATU) or for all patients for a given indication (cohort ATU).[11,12] From 10 analyzed products in France, 4 received ATU; 3 products received cohort ATU (Kymriah®, Yescarta®, and Luxturna®) and 1 received nominative ATU and a cohort ATU later in the marketing authorization indication (Zolgensma®). This allowed that once the Committee for Medicinal Products for Human Use opinion was positive the patients could already have access to the medicine without the need of waiting for EC Decision and the HTA full evaluation period. During the ATU validity, the company can set a free price before the negotiation, but subsequently, the ASMR category will be a driver for price negotiation. The data generated during this period are used in addition to the clinical data from pivotal trials to inform the subsequent HTA and reimbursement determination at the time of marketing authorisation.[12,13]

In Scotland, the "interim acceptance decision" was introduced in 2018, which also allows that the SMC should have the option to accept a medicine for use, which is subject to ongoing evaluation and future reassessment for those drugs with a conditional marketing authorization by the EMA or Medicines and Healthcare

Table 4. Continued

HTA recommendation	Implementation	HTA recommendation	HTA recommendation	Implementation	HTA recommendation	HTA recommendation	Implementation
The Netherlands		Italy	Spain		France	Germany	
						27	30
			26			11	11
6		15	4	4	6*	24	24
3		15	4	4	6*	24	24
6	20	21	10	10	6*	8	8
14			29	29	6*	10	10
25					9	11	11
					4	7	8
11		13			7†	17	17
					10§	10	10
						18	18
					30	22	22
			17	17	11	7	7
			18		23	-	-
					35		
8.5	20	15	17	10	9	11	11
25	-	21	29	29	35	27	30
3	-	13	4	4	4	7	7

products Regulatory Agency early access to medicines scheme or innovative licensing and access pathway.[14] Tecartus® and Holoclar® were accepted in the interim for use in National Healht Sevice Scotland.

Comparators Used for the Cost-Effectiveness Analysis, Notified Prices, and ICER

The ICER thresholds varied depending on the country (Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014). Appendix Table 1 in Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014 shows the comparators used to determine the cost-effectiveness analysis of the analyzed ATMPs. The comparators used in the analyzed countries consist of similar SoC or best supportive care. This information was not available for Spain for any product. Most of the therapies are above the set thresholds ranging from €45 000 per quality-adjusted life-year (QALY) to less than €100 000 per QALY (Table 5). The estimated ICER for each product in each country and between countries reveals high variability. The notified prices are aligned across all the EU8 (Table 6).

Key Considerations That Influenced the Reimbursement Decision

The key considerations that might have influenced the reimbursement decision are summarized in Appendix Table 2 in Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014 according to ATMP product. A total of 33 reports were analyzed from Scotland, Ireland, England, and The Netherlands NHA bodies: 3 CAR-Ts for 4 indications (14 reports in total), 5 viral vector gene therapies (13 reports in total), and 3 cell therapies (6 reports in total). Several factors within European Network for Health Technology Assessement domains were considered (Supplemental Material found at https://doi.org/10.1016/j.jval.2022.12.014).

Discussion

Although the majority of the ATMPs were reimbursed in most EU8, the decisions are heterogeneous among these European countries based on how HTA agencies interpret evidence and the associated uncertainties. Whereas most of the approved ATMPs were reimbursed in Germany, none of them were initially financed in Ireland, mainly because of the high uncertainty of efficacy evaluation. Although Germany had the highest approval rate, this was mostly achieved with an unquantifiable benefit. Nevertheless, this is not only the case for ATMP and is common and depends on how the appraisal is conducted. For other countries, there is a substantial tendency to issue a positive recommendation but restricting the approved indication. The type of EMA approval does not seem to have an influence on the

Table 5. Reported ICER for the approved ATMPs in the European Union

Type of ATMPs	Scotland	Ireland	England and Wales	The Netherlands	Italy	France
Imlygic®			• £23 900/QALY vs dacarbazine • £24 100/QALY vs BSC			
Kymriah® (ALL)	£25 238/QALY vs salvage chemotherapy	• €75 748/QALY-€116 506/QALY vs blinatumomab • €75 990/QALY-€107 163/QALY vs FLA-IDA	• £44 299/QALY vs blinatumomab • £74 322 per QALY vs salvage chemotherapy	Estimated added costs vs blinatumomab ranging €1.8-€2.1 million and €1.8 million allogenic bone marrow transplant*	€32 543 80/QALY vs salvage chemotherapy	• €90 029/QALY vs salvage chemotherapy as reference and blinatumomab over a lifetime horizon • €189 822/QALY vs rescue chemotherapy baseline and blinatumomab over a 10-year time horizon
Kymriah® (DLBCL)	• £44 330-48 116/QALY vs [R-] Gem-Ox; • £44 151-47 903/QALY vs [R-] GDP	• €1 035 700/QALY vs SCHOLAR-1 • €734 534/QALY vs CORAL extension studies	£42 991-£55 403/QALY (with the discount agreed)		€60 680 63/QALY vs salvage chemotherapy	€294 381/QALY over 10 years
Yescarta®	£49 136/QALY	€87 957/QALY	£50 000/QALY vs salvage chemotherapy	€46 048/QALY-€600 262/QALY vs SoC*	€54 699/QALY vs BSC	€97 015/QALY (€84 766/QALY before the technical exchange)
Tecartus®	£49 711/QALY vs SoC		£46 898-£72 920/QALY			€111 649/QALY
Strimvelis®			£494 255-£170 668 incremental costs when compared with an HSCT from a MUD and a haploidentical donor respectively			
Luxturna®	£89 871/QALY vs BSC	€189 037/QALY vs BSC (a discount rate of 4% on costs and outcomes is applied)	£60 908-£86 118/QALY (do not include the company's commercial arrangement)			€191 811/QALY vs BSC over a time horizon of 85 years (lifetime)
Zynteglo®				€90 000 per QALY		€ 151 003/QALY vs better supportive care (transfusions + iron chelators), a price of −15% results in an RDCR of 106 175 €/QALY
Zolgensma®	£59 996-£74 000/QALY vs BSC	€298 469/QALY vs Nusinersen €387 717/QALY vs BSC	ICERs cannot be reported	€263 389/QALY vs Nusinersen	€51 690/QALY vs Nusinersen	from €576 000/QALY-€2.6 million/QALY over a time horizon of 10 years and €212 226/QALY-€1.5 million/QALY over a lifetime time horizon depending on the data source chosen
Alofisel®	£20 930/QALY darvastrocel vs surgical examination ± seton placement plus curettage	€109 058-€248 548/QALY	£23 176/QALY			
Chondrocelect®			£14 000/QALY			

continued on next page

Table 5. Continued

Type of ATMPs	Scotland	Ireland	England and Wales	The Netherlands	Italy	France
Spherox®			• £4360/QALY vs microfracture • Lower than £20 000/QALY vs BSC			
Holoclar®	£3483/QALY vs BSC		• £42 139/QALY vs conjunctival limbal allograft from a living related donor • £30 415/QALY vs keratolimbal allograft £6948/QALY vs BSC			

Note. ICER is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance. The indicated costs of the table are per patient and QALY gained.
ALL indicates B-cell acute lymphocytic leukemia; ATMP, advanced therapy medicinal product; BSC, best supportive care; DLBCL, diffuse large B-cell lymphoma; FLA-IDA, fludarabine, cytarabine and idarubicin; GDP, gross domestic product; HSCT, hematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; MUD, matched unrelated donor; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; RDCR, ratio différentiel coût-résultat; SoC, standard of care.
*No cost-effectiveness analysis was not carried out. For Yescarta®, comments on cost-utility analysis from NICE were considered. No economic analysis was performed; Information for Glyebra®, Libmeldy®, Abecma®, Provenge®, Zalmoxis®, and MACI® is not available.

reimbursement decision, probably because of the type of indications targeted, that is, rare, last lines of treatment (in which there is an unmet need), or serious conditions. Our results showed that the potential benefit of these therapies was acknowledged, but overall, the high degree of uncertainty associated with the magnitude of clinical efficacy and safety hampered the decision and made the evaluation complex. Some studies have confirmed that single-arm study, short-duration, and indirect comparison were reported as a major efficacy uncertainty, and it is suggested that the access to these therapies is lower in the EU than in the United States.[15] We found that considerations that might have influenced the decision could go beyond the 3 common core domains (clinical effectiveness, safety, and cost-effectiveness) and include items related to the "health problem and current use of technology" and "patient and social aspects" domains, because most therapies are targeting orphan or end-of-life conditions. Other studies have suggested that the incorporation of additional "social value judgements" (beyond clinical benefit assessment) and economic evaluations could help explain heterogeneity in coverage recommendations and decision making.[16] Budget impact, gross domestic product, involvement of patient advocacy groups, equity considerations, and different economic evaluations performed among European countries could also contribute to this heterogeneity.

In terms of the type of reimbursement scheme applied, the trends are divergent among the EU8—different in each country with different special funding processes but with an extended use of MEAs. It has been recognized that a single payment model is unlikely in the case of ATMPs.[17] The use of MEAs, which are mainly negotiated when there is uncertainty regarding the drug clinical benefit, allows the introduction of new products with potential benefit, but it is not seen as a solution to address high prices and uncertainties associated with the ATMPs.[18,19] The introduction of the 2 initial CAR-T products, Kymriah® and Yescarta®, constituted the first examples of national reimbursement schemes involving outcomes-based, staged payments for innovative therapies in Germany, Italy, and Spain.[12,13,20] Nevertheless, the implementation of these agreements is not always easy, because the burden of monitoring this process is challenging, and can differ among countries. Different agreements arise for the same treatment in different jurisdictions, making it challenging for the sponsor and inefficient in terms of sharing of outcomes data across jurisdictions, which could facilitate more robust evidence for reappraisal.[21] In those countries where payment by results are not used, a continuous reassessment could be an approach to manage the decision uncertainties associated with these therapies (eg, based on cohort data from a combination of follow-up from the pivotal trials and real-world evidence).[12,13] Broad principles for innovative payment models for high-cost innovative medicines have already been addressed by the EC.[22] On the industry side, a concrete list of recommendations has been proposed, which includes payment models that distribute costs over time.[23] It is still uncertain how, with the expansion of ATMPs to high-prevalent diseases, patients will have rapid access to innovation while keeping health systems financially sustainable. Value-based pricing methodologies are suggested to be an option to cope with the specific challenges of ATMPs.[24]

For the NHAs, the ATV of a new drug compared with the best available treatment options is one of the key points to make their recommendation on reimbursement. Although no major significant differences have been found when the ATV for approved ATMPs has been compared among countries, a comparable and unified criterion was not used. Other studies have reported low rates of agreement on the ATV of ATMP and non-ATMP drugs compared with the SoC among Germany, Italy, and France.[25,26] The main reasons for the inconsistency were found to be related to a different appreciation of the subgroup analysis of efficacy data, the appropriateness of comparators, the surrogate endpoints, methodological differences, and the benefit/risk criteria that were used.[26] A study has already been performed with the aim to investigate the feasibility of a harmonized EU approach concerning the assessment of the ATV of medicines in the EU.[27] In this report, it is suggested that the ATV should be measured on an ordinal scale, as well as by a multidisciplinary team of trained experts independent from the committees in charge of determining the reimbursement and product price. A harmonized definition of ATV would clarify the expected benefits of a new drug, set rewards for higher therapeutic added value and promote the innovation.[27] In contrast, it is also under discussion how the ATV of ATMPs, in particular, should be assessed.

Table 6. Notified prices reported for the approved ATMPs in the European Union.

Type of ATMPs	Scotland	Ireland	England and Wales	The Netherlands	Italy	Spain	Germany
Glybera®							€1 321 139 (26 vials per patient)
Imlygic®			£1670 per vial				Annual therapy costs €72 287 80-€289 151 20
Kymriah® (ALL)	£282 000 per infusion	Total cost including rebate is €301 762; VAT is not applicable	£282 000 per infusion (company submission). Commercial arrangement	The total cost of €320 000 per patient and per treatment	€320 000 (excluding VAT)	€320 000 (excluding VAT)	Annual therapy costs €282 419 28-€283 244 95
Kymriah® (DLBCL)	£282 000 per infusion	Total cost including rebate is €301 762; VAT is not applicable	£282 000 per infusion (company submission). Commercial arrangement		€320 000 (excluding VAT)	€327 000 (excluding VAT)	Annual therapy costs per patient €283 062 13-€291 815 14
Yescarta®	£282 451 per infusion	The total cost including rebate and VAT is €384 225	Price submitted as commercial in confidence	€327 000 per infusion (including conditioning chemotherapy)	€327 000 (excluding VAT)		2 single infusion bag €389 130
Tecartus®	£316 118 per infusion		Price submitted as commercial in confidence				1 single infusion bag €360 000
Strimvelis®			£505 000 (excluding VAT; company's evidence submission)		€594 000	€355 000 per vial	
Luxturna®	£658 946 (in each eye)	€690 000 (for 2 single-use packs, 1 for each eye)	£613 410 per patient (excluding VAT; company submission); commercial arrangement	€690 000 (for 2 single-use packs, 1 for each eye)			€321 000 (for both eyes)
Zynteglo®							€1 929 926 88-€1 936 134 22
Zolgensma®	£1 795 000 single infusion	Price to wholesaler €1 945 000, €2 285 375 (including 23% VAT)	£1 795 000 (excluding VAT; company submission). Commercial arrangement		€2 155 124 65 (excluding VAT)	€1 945 000	€2 314 550
Libmeldy®			£2 875 000 (excluding VAT; company submission)				€2 875 000
Provenge®							Annual therapy costs per €79 952 58
Zalmoxis®					€149 000	€60 000	Annual therapy costs per patient: €189 474 78-€757 899 12
Alofisel®		The cost per patient per year to the HSE (incorporating VAT and mandatory 5.5% rebate) is €70 500	£13 500 per vial. One course of treatment (4 vials) costs £54 000 (company submission). Commercial arrangement				€71 400 00
Chondrocelect®			£16 000 (company submission)				
MACI®			£16 226 per implant (price excluding VAT). Negotiated discounts				

continued on next page

Table 6. Continued

Type of ATMPs	Scotland	Ireland	England and Wales	The Netherlands	Italy	Spain	Germany
Spherox®			£10 000 per culture per patient, including cell costs and transportation				
Holoclar®	£80 000 (1 treatment per limbal stem cell transplant)		£80 000 excluding VAT for 1 eye. Commercial arrangement		€95 000		

Note. No information for Abecma® is available yet.
ALL indicates B-cell acute lymphocytic leukemia; ATMP, advanced therapy medicinal product; DLBCL, diffuse large B-cell lymphoma; HSE, health service executive; VAT, value-added tax.

The challenges of the standard value and price assessment methods in the evaluation of ATMPs have already been analyzed, and new elements to define their value have been proposed. These new elements are more focused on societal perspective and not only on comparative clinical benefit and economical aspects, for example, value of hope, real option value, and scientific spillovers.[28,49] It has been reported that the assessments of additional values beyond QALY are often based on "deliberative decision making," which is criticized for the lack of a clear framework and transparency, as well as potential risks of double counting of additional values that are already included as part of HTA reports.[29] It is important to mention that in January 2018, the EC proposed a new regulation with the aim to promote more alignment in terms of HTA assessments, which was approved in December 2021. This regulation aims to replace the current system of cooperation between Member States on HTAs with a permanent framework for joint work, allowing a harmonized approach to clinical assessment of new medicines across EU Member States. With this new regulation that will be mandatory from 2025, transparency and more alignment in terms of pricing is also foreseen. Above all, it is fairly defined in a consistent way among the EU Member States to reflect the added value that the product can bring to patients.[30]

Drugs to treat orphan conditions, end-of-life medicines, and the disease severity and unmet medical needs are factors that have an influence in terms of a higher price, which is the critical feature of ATMPs that restrain the market access. It is generally recognized that drugs in these categories are unlikely to meet the preexisting cost-effectiveness threshold,[31] as well as a higher degree of uncertainty in evidence and assessment outcomes being accepted.[32] These type of applications are increasing access to drugs for end-of-life and rare conditions in Scotland, whereas they might not otherwise have been accepted.[33] It was also suggested that, in England, medicines for rare diseases not evaluated under the Highly Specialized Technology framework or with an appropriate modifier in the appraisal process are subject to disadvantages.[34] Cost-effectiveness analysis and ICER are variable among EU8, because most of ATMPs are above ICER thresholds set by the different countries, with a notified price range comprising between €2 00 000 and €2 million. Moreover, concerns in addition to the price are the additional costs of treating and managing these patients, which are the clinical infrastructure and skills of the clinical staff. The pre-evaluation of the organizational impact of ATMPs and the need for healthcare centers with the necessary resources are suggested requirements to be adopted in preparation for the launch and delivery of these therapies.[12,35] Gene therapies for orphan hereditary diseases comprise a unique group of products, usually administered at an early age and expected to last for the patient's entire life. The economic burden at long-term of these type of diseases with the current SoC might be underestimated and some studies suggest that efforts are needed to reduce costs through improved drugs.[36] Similar analyses have been performed with CAR-T products.[37] For this group of products, these increased ICERs and prices have been justified and the "willingness to pay" levels were exceeded on the assumption of improving long-term clinical outcomes and patient and caregiver quality of life. With these type of drugs, long-term payment with risk-sharing models and a price without the premium addition have been proposed to help with the affordability, patient access, and the given uncertainty on effect durability.[38] The partnership and joint assessments across several countries to make the medicines more accessible to patients have already been applied for some approved ATMPs, as was the case of Zolgensma® and Zynteglo® through the Beneluxa Initiative,[39,40] which led to a successful reimbursement recommendation and an aligned agreement on the price. Other cross-country collaborations aim to negotiate affordable and sustainable prices for new and innovative drugs.[41] In contrast, it should be noted that the gross domestic product, as well as the purchasing power of the population is not homogeneous among the different European countries. Therefore, it would also be necessary to adjust the prices for each country according to its gross domestic product.[42]

Additionally, the lack of transparency of the information on the NHA decision-making process and pricing (because the "real" prices are often unknown because of agreed confidential discounts) has been extensively discussed. The need for a more harmonized, systematic, and reproducible assessment process has already been discussed at the EC level.[43] Transparency and more alignment in terms of pricing is also foreseen, and above all it is fairly defined in a consistent way among the EU Member States to reflect the added value that the product can bring to patients.

The limitation of this study is the small sample size given the limited number of ATMPs approved. In addition, for the latest approved products, the public reports are not yet available given that the evaluations are still ongoing, which also reduces the sample size. Although 8 EU countries were evaluated, the lack of publicly available information and the lack of transparency for some countries led to believe that the study could not cover these 8 EU countries for some of the analyzed points. The conclusions cannot be generalized to other than the EU countries analyzed. The weight of each consideration that influenced the reimbursement decision could not be assigned for each domain, given that is not publicly available.

To sum up, transparent, harmonized, and systematic assessments of ATMPs across the EU NHAs is needed. Robust evidence on the clinical efficacy and safety of ATMPs and the reduction of their costs are key elements for their financing and reimbursement.

Supplemental Material

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SHORT REPORT

Regulatory Policies

Temporary derogation from European environmental legislation for clinical trials of genetically modified organisms for coronavirus disease 2019

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ABSTRACT

Attempts to streamline environmental procedures for those products containing or consisting of genetically modified organisms (GMOs) among the European Union (EU) Member States are ongoing but still need to be further developed. These procedures can be complex, resource-intensive and time-consuming. Some candidate vaccines currently under development for COVID-19 include genetically modified viruses, which may be considered GMOs. Given the public health emergency caused by the COVID-19 outbreak, on July 15, 2020, the European Parliament approved a temporary derogation of the European environmental requirements to facilitate that those clinical trials with GMOs intended to treat or prevent COVID-19 can start as soon as possible in Europe. This measure has been very controversial, since it could entail risks to human health and the environment, and could be seen as unfair for other products targeting unmet medical needs. With the adoption of this measure, the bottlenecks and obstacles for the development of innovative GMO-based medicines in the EU that the environmental legislation entails have become even more evident.

Environmental legislation in the European Union

Biological therapies comprise a wide range of product types, including advanced therapies and vaccines. Gene therapy medicinal products (GTMPs) are cutting-edge therapies and promise to treat indications ranging from rare genetic diseases to cancers. GTMPs treat disease by replacing, inactivating or introducing a recombinant nucleic acid sequence into the body, typically using a viral vector or through other carrier molecules. On the other hand, vaccines are a heterogeneous class of biological medicinal products aimed at the treatment or prophylaxis of infectious diseases and include not only classic vaccines consisting of attenuated or inactivated micro-organisms but also antigens produced through recombinant DNA technology, chimeric micro-organisms and live recombinant viral vectored vaccines. When a biological entity is capable of replication or of transferring altered genetic material, as is the case with many GTMPs and some vaccines, it is also considered a genetically modified organism (GMO).

The clinical use of these therapies might pose a risk since these products may enter the environment by unintended dispersal or via excretion by the patient. This dissemination could potentially spread the GMO further, and it could undergo genetic or phenotypic changes, infect, reproduce, remain latent, compete with existing species or transfer its genetic material to other species, impacting human health and the environment. As a result, medicinal products consisting of or containing a GMO are regulated by environmental and human drug legislation in the European Union (EU), and all potential risks must be evaluated by conducting an environmental risk assessment (ERA) during the product's development. To conduct a clinical trial with a product based on a GMO, the sponsor needs to obtain not only authorization from the ethics committees and competent national health authorities (NHAs) where the study is going to take place but also an additional authorization to "release" or administer the GMO-containing medicinal product in that trial. To obtain this authorization, an ERA must be assessed and endorsed by the government authorities of each Member State in charge of GMO evaluations and responsible for the environment in each country.

In recent years, especially with the increased development of advanced therapies, the lack of harmonization among the European countries and the burden these environmental procedures entail for the sponsor have become notably evident. Although there is a common European framework in place, the environmental EU directives have been implemented differently across European countries. This fact has resulted in a resource-intensive process, above all for multicenter studies, as sponsors of clinical trials need to submit multiple requests for environmental authorizations to multiple competent authorities in different Member States, each with different requirements and ERA procedures that vary greatly from one Member State to another. The

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result is the generation of delays in clinical development, an increase in logistical hurdles at country level and higher costs [1]. The European Commission recognized in 2018 the handicaps of these procedures in the EU and initiated several dialogues with the NHAs with the aim to unify the interpretation of the GMO framework. As a result, common position documents for genetically modified human cells and for products containing adeno-associated viruses were recently endorsed by most NHAs. Nevertheless, this approach is still not enough, and this procedure remains substantially burdensome.

Temporary changes in environmental legislation due to the coronavirus disease 2019 pandemic

Coronavirus disease 2019 (COVID-19) has rapidly developed into a worldwide pandemic with a significant health impact, and clinical trials that aim to discover an effective vaccine are ongoing. Potential vaccines currently under development include genetically modified viruses, which are classified as GMOs [2,3]. Given the public health emergency caused by the COVID-19 outbreak, on July 15, 2020, the European Parliament and the EU Council granted a temporary derogation from the environmental requirements to allow clinical trials with GMOs intended to treat or prevent COVID-19 to start as soon as possible, without the delays generated by the different national implementations of environmental Directives 2001/18/EC and 2009/41/EC and their diverse requirements [4,5]. Although these two directives aim to ensure the protection of human health and the environment through the assessment of the risks posed by the deliberate release or contained use of GMOs, it has been decided that the protection of public health—through accelerating the deployment of a COVID-19 vaccine—prevails in this unprecedented situation.

Pivotal trials with promising candidates will be conducted in several countries, and without this measure, European clinical trials could fall behind those of the US or China, delaying early access to these product candidates. The derogation will apply as long as COVID-19 is regarded as a public emergency, but sponsors should implement appropriate measures to minimize the foreseeable negative environmental impact resulting from the release of the investigational medicinal product into the environment. Compliance with Good Manufacturing Practices and an ERA of the product will still be mandatory before marketing authorization is granted.

This temporary derogation has been very controversial. On the one hand, some expert groups have pointed out that this measure could be irresponsible since the development of vaccines based on GMO viruses might involve risks to human health and the environment, and these risks are not necessarily covered by the general safety protocols aimed at protecting participants [6]. On the other hand, supporters of the measure argue that a clinical study with only small quantities of an investigational product and a limited number of patients should not have a significant cumulative effect on the environment. The same argument can be found in US environmental regulations [7], whereby most investigational products are categorically excluded from the requirement to submit an ERA, but this principle has not been applied in the EU thus far, and massive trials including thousands of participants are expected for phase 3 studies with these vaccine candidates. One of the potential measures that could have been taken is to shorten the period to get the authorization for COVID-19 clinical trials, as was suggested by the Netherlands, which is the second Member State with the highest number of experimental GMO medicinal products approved under deliberate release [8]. However, this proposal does not solve the time-consuming process of preparing and submitting multiple applications with different requirements to several EU Member States.

Finally, this temporary derogation could also be seen as unfair to other products and/or disease areas. There are promising advanced therapies and vaccines under development consisting of GMOs, targeting severe orphan indications for pediatric populations to highly prevalent diseases such as HIV and cancer, the latter being one of the top 10 causes of death in the EU and the second leading cause of death globally [9]. These products still have to deal with the intricacies of these environmental procedures and the delays this implies for the starting of clinical studies in the EU, ultimately postponing patients' early access to these products.

Conclusions

Attempts to streamline environmental procedures among EU Member States have so far been unsuccessful. With the temporary derogation from the environmental requirements for products intended to treat or prevent COVID-19, the bottleneck the environmental legislation represents in the EU for the development of innovative GMO-based medicines has become even more evident. Further efforts are needed to centralize or rationalize this procedure, with the main objective of enabling patients to benefit from innovative medicines for a variety of diseases as soon as possible.

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Author Contributions

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