Design of an exploratory development plan for the assessment of the activity of drugs for the treatment of chronic inflammatory dermatological diseases

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Design of an exploratory development plan for the assessment of the activity of drugs for the treatment of chronic inflammatory dermatological diseases

Memòria presentada per Roser Vives Vilagut per optar al títol de doctora en Farmacologia per la Universitat Autònoma de Barcelona

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Certifico:

Que la memòria titulada ***"Design of an exploratory development plan for the assessment of the activity of drugs for the treatment of chronic inflammatory dermatological diseases"*** presentada per Roser Vives Vilagut per a optar al grau de doctora s'ha dut a ha terme sota la meva direcció i és conforme per a la seva presentació, lectura i defensa davant el tribunal corresponent.

Per tal que consti i tingui els efectes oportuns, signo el present document a Sabadell, a dinou de Setembre de 2016.

Dra. Caridad Pontes García

MENDO

Es que tu inocencia ignora

que a más de una hora, señora,

las siete y media es un juego.

MAGDALENA

¿Un juego?

MENDO

y un juego vil

que no hay que jugarle a ciegas,

pues juegas cien veces, mil...

y de las mil, ves febril

que o te pasas o no llegas.

y el no llegar da dolor,

pues indica que mal tasas

y eres del otro deudor.

Mas ¡ay de ti si te pasas!

¡Si te pasas es peor!

La venganza de don Mendo. Pedro Muñoz Seca. 1918

AGRAIMENTS

A la Cari, la meva directora de tesis i la meva amiga, perque ha estat al meu costat tot aquest temps i m'ha donat l'empenta final

Al Santi, la Núria i la Laia, que han tingut molta paciència

Als meus pares, per ells vaig estudiar medicina

A totes les companyes i companys del servei de Farmàcia del Taulí, amb qui he compartit aquests tres anys

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Abbreviations

AE: Atopic Eczema

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios

BA: Bioavailability

BSA: Body Surface Area

CDER: Center for Drug Evaluation and Research

CHMP: Committee for Human Medicinal Products

CNS: Central Nervous System

CONSORT: Consolidated Standards of Reporting Trials

CRF: Case Report Form

CRO: Contract Research Organization

CT: Clinical Trial

EASI: Eczema Area and Severity Index

EC: Ethics Committee

EMA: European Medicines Agency

EPAR: European Public Assessment Report

EU: European Union

FDA: Food and Drug Administration

GCP: Good Clinical Practices

GFT: Guía Farmacoterapéutica

GLP: Good Laboratory Practices

ICH: International Conference on Harmonization

IDD: Inflammatory Dermatological Diseases

IGA: Investigator General Assessement

IL: Interleukin

IND: Investigational New Drug

IRB: Institutional Review Board

MTD: Maximum Tolerated Dose

NME: New Molecular Entity

NOAEL: Non Observed Adverse Effects Level

PASI: Psoriasis Area and Severity Index

PDE: Phosphodiesterase

PGA: Physician Global Assessment

PK: Pharmacokinetics

PoC: Proof of Concept

PSI: Psoriasis Severity Index

PSO: Psoriasis

Q&A: Questions and Answers

QoL: Quality of Life

RA: Regulatory Authorities

RA: Regulatory authority

RCM: Reflectance Confocal Microscopy

SASSAD: Six Area, Six Sign Atopic Dermatitis

SCORAD: SCORing Atopic Dermatitis

TCI: Topical Calcineurin Inhibitors

TCS: Topical Corticosteroids

TEWL: Trans Epidermal Water Loss

TNF: Tumor Necrosis Factor

1. Introduction

1.1. Chronic inflammatory dermatological diseases: atopic eczema and psoriasis

Chronic inflammatory dermatological diseases (IDD) are highly prevalent chronic diseases that imply a serious burden to patients.

1.1.1. Atopic Eczema

Atopic eczema (AE) is a common inflammatory skin disease affecting 15-30% of children and 5-10% of adults. The prevalence of this condition has doubled or tripled in industrialized countries over the past three decades.[1,2]

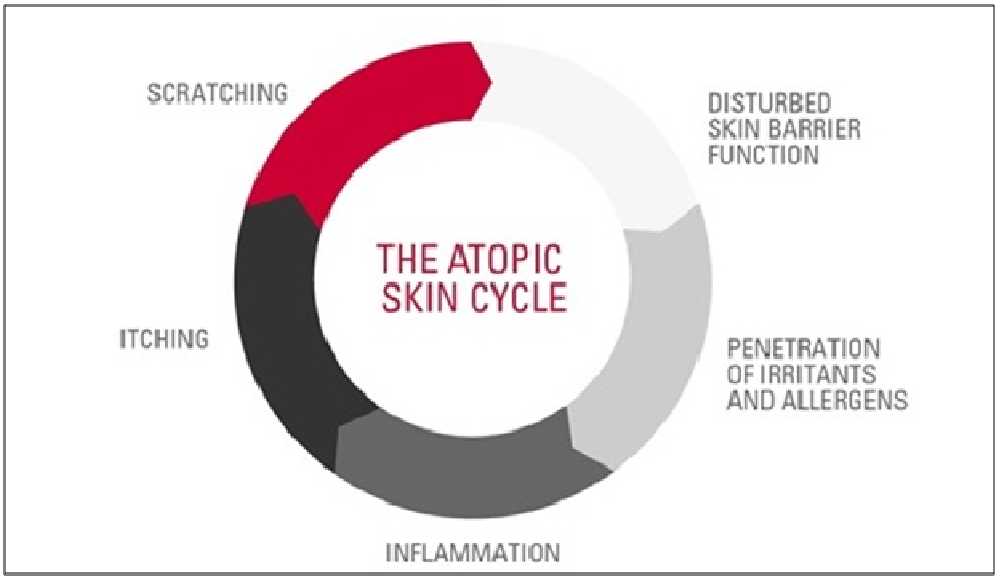
AE is primarily a disease of childhood, with 45% of cases starting as early as 6 months of age and 70% of patients already affected before the age of 5. Most of them will grow out of the disease by adolescence.[1] A late onset of the disease in adults is also possible. The disease is often related with later development of asthma and other allergic diseases.

A higher incidence of AE has been associated with urban and industrial settings, higher economic status and smaller family size. These findings have led to many different hypotheses regarding the mechanism of AE. The etiology is complex involving genetic and environmental factors; however, the initial mechanisms that induce skin inflammation in patients with atopic dermatitis are still unknown. Recently, it has been proved that null mutations in filaggrin gene are associated with the disease.[2] Filaggrin plays a key role in the epidermal-barrier function, thus, mutations in the gene resulting in barrier dysfunction leads to hyper-reactivity to environmental triggers and the induction of

antiIgE antibodies. Early onset atopic dermatitis usually emerges without IgE mediated allergic sensitization and in some children such sensitization never occurs.[2]

The suppression of innate immune system of the skin by the inflammatory *micromillieu* of AE explains the colonization of the skin by *S aureus* in more than 90% of patients. This contributes to allergic sensitization and inflammation, and scratching increases the binding of *S aureus* to the skin and the amount of ceramidase produced by these microorganisms aggravates the defect in the skin barrier.[2]

Figure 1. The Itch-Scratch Cycle



The main clinical characteristics of the disease are barrier dysfunction and chronic inflammation. Thus, long term clinical management should target skin care, reduction of bacterial colonization by means of local application of lotions containing antiseptics and the control of inflammation using corticosteroids or calcineurin inhibitors. Eczematous skin is dry and itchy, leading to scratching, particularly at night, disturbing sleep. This leads to a deterioration of quality of life which is important both in children and in

adults.[3] The skin lesions do not differ from other skin eczemas (such as contact eczema), and are characterized by a red infiltrate with edema, vesicles, oozing and crusting, lichenification, excoriations, papules, and nodules. Typically, patients will present an early onset of itchy eczema localized at typical sites such as the flexures of the elbows and knees. A history of atopia or a familial predisposition to atopic disease will often be present.

Thus, the diagnosis of AE is mainly clinical, based on anamnesis and the associated features of the patient, the morphology and the characteristic distribution of the skin lesions, and clinical signs.[4] The most widely used diagnostic criteria in clinical practice for atopic dermatitis are the Hanifin and Rajka criteria, which were developed in 1980 and later revised by the American Academy of Dermatology.[5] Another set of diagnostic questions widely used in epidemiological research are those developed by the UK Working Party in 1994.[6]

Table 1. AE diagnostic criteria

Hanifin and Rajka criteria[5]	**UK Working Party**[6]
Major criteria (must have three or more of) • Pruritus • Early age of onset • Typical morphology and distribution: – Flexural lichenification and linearity in adults – Facial and extensor involvement during infancy and childhood • Chronic or chronically – relapsing dermatitis • Personal or family history of atopy (asthma, allergic rhino conjunctivitis, AD) **Minor or less specific criteria (should have 3 or more of)** • Xerosis • Ichthyosis, palmar hyperlinearity, keratosis pilaris • Immediate (type 1) skin test reactivity • Raised serum IgE • Early age of onset • Susceptibility to cutaneous infections (especially Staphylococcus aureus and herpes simplex) or impaired cell-mediated immunity • Tendency toward non-specific hand or foot dermatitis	**Must have** • Pruritus/Itching **Plus three or more of the following** • History of flexural dermatitis (front of elbows, back of knees, front of ankles, neck, around the eyes) or involvement of cheeks and/or extensor surfaces in children aged > 18 months • Visible flexural dermatitis involving the skin creases (or the cheeks and/or extensor surfaces in children aged > 18 months) • History of a dry skin in the past year • History of asthma or hay fever (or atopic disease in a first degree relative in

Several scales are used to grade the disease severity and clinical outcomes; the most commonly used being the SCORAD (SCORing Atopic Dermatitis) index,[7] the Eczema Area and Severity Index (EASI),[8] the Investigator's Global Assessment (IGA) and the Six Area, Six

Sign Atopic Dermatitis (SASSAD)[9] severity score. However, while these scales are widely used in clinical trials, they are rarely used in clinical practice.[4]

SCORAD (**SCORing Atopic Dermatitis**) is a clinical tool used to assess the extent and severity of eczema. To determine extent, the sites affected by eczema are shaded on a drawing of a body. The rule of 9 is used to calculate the affected area (A) as a percentage of the whole body: Head and neck 9%, Upper limbs 9% each, Lower limbs 18% each, Anterior trunk 18%, Back 18%, 1% for genitals. Then, the score for each area is added up. The total area is 'A', which has a possible maximum of 100%. To calculate intensity, a representative area of eczema is selected. In this area, the intensity of different signs (redness, swelling, oozing/crusting, scratch marks, skin thickening/lichenification and dryness assessed in an area where there is no inflammation) is assessed as none (0), mild (1), moderate (2) or severe (3). Scores are added together to give 'B' (maximum 18).

Subjective symptoms i.e., itch and sleeplessness, are each scored by the patient or relative using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). These scores are added to give 'C' (maximum 20).

The SCORAD final score is calculated as A/5 + 7B/2 + C, and the maximum score for SCORAD is 103.

The objective SCORAD is the same score without the subjective assessment of pruritus and insomnia.

The **EASI** (**Eczema Area and Severity Index**) is a validated tool to measure the extent (area affected) and severity of each affected area. For this purpose, the body is divided into 4 regions (head and neck, trunk (including genital area, upper limbs, lower limbs (including buttocks) and an area score (percentage of skin affected by eczema) is recorded for each region as indicated in Table 2:

Table 2. Eczema Area and Severity Index: calculation of area

Area score	Percentage of skin affected by eczema in each region
0	0: no eczema in this region
1	1-9%
2	10-29%
3	30-49%
4	50-69%
5	70-89%
6	90-100%: the entire region is affected by eczema

Then, a severity score is recorded for each of the four regions of the body. The severity score is the sum of the intensity scores for four signs. The four signs are:

- Redness (erythema, inflammation)
- Thickness (induration, papulation, swelling—acute eczema)
- Scratching (excoriation)
- Lichenification (lined skin, prurigo nodules—chronic eczema).

The average intensity of each sign in each body region is assessed as: none (0), mild (1), moderate (2) and severe (3). Severity score and area score for each region are then multiplied and weighed differently for each region, as follows:

- Head and neck: severity score x area score x 0.1 (in children 0–7 years, x 0.2)

- Trunk: severity score x area score x 0.3
- Upper limbs: severity score x area score x 0.2
- Lower limbs: severity score x area score x 0.4 (in children 0–7 years, x 0.3)

The final EASI score is the sum of the scores for each region. The minimum EASI score is 0 and the maximum EASI score is 72. The score is assessed completely by the dermatologist. A modified EASI score can also be used by adding to the score a patient assessment of itching.

The **Investigator Global Assessment (IGA)** allows investigators to assess overall disease severity at one given time point, and it usually consists of a 6-point severity scale from clear to very severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease and 5 = very severe disease).

IGA uses clinical characteristics of erythema, infiltration, papulation, oozing and crusting as guidelines for the overall severity assessment. IGA has not been validated as an outcome measure, however, it has been used to validate other outcome scales as one "gold standard." IGA appears to correlate well with the EASI and is considered an instrument with reasonable face validity. Potential weaknesses of IGA include lack of responsiveness and discrimination for disease severity and lack of subjective symptoms.[10]

Table 3 lists some other severity and clinical outcome assessment tools used in AD

Table 3. Atopic Eczema Severity of disease scales

Severity scoring of atopic dermatitis (SCORAD)
Eczema Area and Severity Index (EASI)
Investigators' Global Assessment (IGA)
Six Area, Six Sign Atopic Dermatitis (SASSAD)
Investigators' Global Atopic Dermatitis Assessment (IGADA)
Costa et al
Leiciester Sign Score (LSS)
Visual Analogue Scale (VAS) pruritus
Total Severity Score (TSS)
Physicians Global Assessment (PGA)
Intensity Item Score Aggregate (IISA)
Atopic Dermatitis Severity Index (ADSI)
Investigators' Static Global Assessment (ISGA)
Nottingham Eczema Severity Score (NESS)
Investigators' Global Assessment Score (IGAS)
Dry skin are and severity index (DASI)
Atopic Dermatitis Area and Severity Index (ADASI)
Total body severity assessment (TBSA)

Modified from Rehal et al [10]

The first approach to management of this condition should be skin directed, aimed to repair and maintain the skin barrier with moisturizing agents, administering topical anti-inflammatory agents, controlling itching to comfort the patient and also to avoid perpetuation of inflammation by scratching, and the management of infectious triggers. To reach the objectives of the treatment, education of patients and families is a critical factor.[3]

The maintenance of skin care helps in reducing the frequency and severity of flares and reduces the quantity and potency of pharmacologic interventions.[3]

Flares of dermatitis seen in AE are unlikely to respond to moisturization alone. When flares appear, the first line of treatment includes anti-inflammatory treatment with topical corticosteroids (TCS), which are the most commonly used medications. When used appropriately for short periods they are effective and safe. However, they have potential risks when used for long periods and/or high doses, such as skin atrophy, striae, telangiectasia and systemic absorption resulting in adrenal suppression.[11] The risk of systemic reactions is higher in children due to their higher ratio of total body surface area to body weight. In addition, cutaneous adverse reactions appear after prolonged treatment and depend on the type of TCS, the vehicle and the area of the body. These effects are clinically apparent and well known, and have led to a "steroid phobia phenomenon" and undertreatment of the skin disease.[11]

Alternatives to TCS have traditionally been sought in order to obtain safer treatments with similar efficacy. Currently, the most recognized alternative includes the use of topically applied immunosuppressant drugs, in particular calcineurin inhibitors (TCI) like tacrolimus and pimecrolimus. These drugs are both effective in reducing inflammation and pruritus associated with AE flares, and have a different safety profile as compared to TCS. While they do not cause the typical chronic dose-dependent AEs related to TCS, they present poorer local tolerability, with frequent burning and stinging at the application site. A major drawback for these treatments, however, is the concern of a potential increased cancer risk, which is included as a black box warning in the US product labeling. Such concern refers to the observation that some laboratory animals exposed to high doses of these products developed malignancies, and a few case reports of adult patients

using TCI who developed lymphoma and skin cancers have been reported. Whether there is an actual relationship is a matter of debate, since the background incidence of these rare events in the general population is difficult to quantify, and the study of the risk attributable to drug exposure is methodologically challenging. Because of that, the relationship of TCIs with malignancies is unclear up to date.[12]

Different studies have shown the effectiveness of proactive treatment with low doses of topical anti-inflammatory agents to reduce AE flares, as soon as initial symptoms appear, although the long term safety of these long term intermittent exposures has not been fully evaluated.[13,14]

Oral therapy is generally reserved for severe and non-responsive cases. The oral immunosuppressive agents cyclosporine and azathioprine have been both described as effective, but careful monitoring is required with both agents since side-effects may occur (e.g. dose-dependent nausea and hematological toxicity with azathioprine, and nephrotoxicity with cyclosporine).[15,16]

New efficacious anti-inflammatory agents that may be safe by both topical and oral route and appropriate for children are needed, since none of the currently available alternatives provides an ideal treatment with appropriate risk/benefit profile for patients with AE, especially for those with severe and chronic forms of disease.

1.1.2. Psoriasis

Psoriasis (PSO) is a common inflammatory disease of the skin mainly affecting adults. Different epidemiological studies have described prevalence rates between 1 and 2% in most countries in Europe.[17]

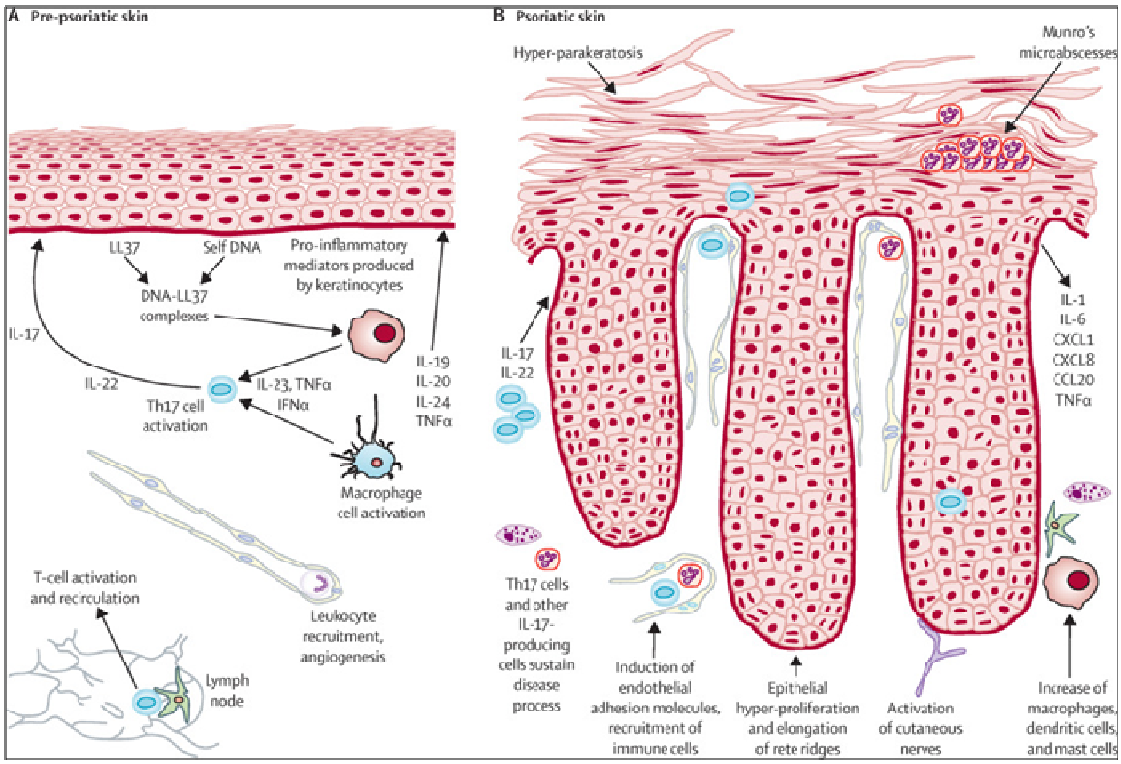
Psoriasis has several different clinical presentations with different clinical features, courses, severities and treatment approaches, and some patients may present with more than one of these variants along time.[18,19] However, about 90% of psoriasis cases present chronic plaque psoriasis, characterized by red patches of thickened skin (called plaques) covered with silver scales, typically localized in knees, elbows, lower back and scalp; nails may have a typical and characteristic involvement in many patients.

The severity of the disease is also variable, with milder patients presenting a single plaque, and most severe patients with >90% of the skin surface affected.

Arthritis accompanies the skin manifestations in 5% - 30% of patients, regardless of the affected skin extension.[20] Psoriasis represents a great burden for patients, affecting substantially their physical and psychological well-being. Actually, the impairment of the quality of life in psoriatic patients is considered equal or even worse than that observed in patients with cancer or heart disease.[18, 20]

The key pathophysiological feature of psoriasis is chronic skin inflammation leading to keratinocyte proliferation.[19]

Figure 2. Immune pathogenesis of psoriasis



Reproduced from Boehncke et al[18]

Genome association studies have identified at least 10 psoriasis-susceptibility *loci* that involve functioning of the immune system. Polymorphisms in the IL-12/IL-13 receptor, the p40 subunit of IL- 12 and IL-23, and the p19 subunit of IL-23 have been shown to play a critical role in the disease process and have thus provided targets for medical therapy.[19] A number of triggering factors have been also identified, including skin injuries, infections, hypocalcaemia, pregnancy, psychogenic stress, different drugs, alcohol, tobacco and obesity.[19]

The diagnosis of most clinical presentations of psoriasis generally relies in clinical features, although atypical presentations may require more careful clinical examination. In contrast with atopic eczema, no diagnostic criteria exist for plaque psoriasis.

The assessment of the severity of the skin manifestations of psoriasis is based on the clinical examination of a number of clinical signs by a trained observer. The current gold standard for assessment of psoriasis is the **Psoriasis Area and Severity Index (PASI)**,[21] a score that rates the common signs of psoriasis skin lesions (redness, thickness and scaling) and grades them on a 0-4 scale (0 = clear; 1–4 = increasing severity) and weights them by the extension of the areas involved (head, upper extremities, trunk, lower extremities). The limitations of PASI are that it has poor sensitivity to change for relatively small areas of involvement and it is not a measure widely used in routine clinical practice and thus, physicians are not trained in it. It is also not a useful measure when measuring one index lesion. In such situations, target lesion assessments of the main signs (redness, thickness and scaliness) can be performed.

In this sense, the **Physician Global Assessment (PGA)** is a key measure in clinical trials and is recommended to complement a PASI measure. This assessment can be done for extensive disease or for localized lesions and it can be performed static (measure of the severity at one time point) or dynamic (change or improvement from baseline), the later being less used as it assumes that the evaluator remembers the severity of the lesion at baseline.

Other frequent measures include the **Total Severity Sign Score (TSSS)**, (sum of the scores for signs - redness/erythema, scale/crusting, thickening/elevation - and symptoms - pruritus) and the **Psoriasis Severity Index (PSI)**, both consisting on the sum of ordinal scores assigned to each of a variable number of signs and symptoms.[22]

Table 4 lists some other severity and clinical outcome assessment tools used in PSO

Table 4. Severity and clinical outcomes assessment tools in PSO

BSA	Estimation of involved body surface area, several scores are used
Signs	Evaluation of the plaque characteristics erythema, scaling, and induration. Erythema and scaling are easily influenced by external factors
PASI	The affected area and lesion characteristics are entered in a formula that results in a score from 0 to 72. The PASI is most often used in clinical trials
PGA	The PGA is a 5, 6, or 7-point ordinal rating ranging from ‘‘clear’’ to ‘‘very severe psoriasis’’
PaGA	The PaGA is an ordinal rating ranging from ‘‘clear’’ to ‘‘very severe psoriasis’’ assessed by the patient
SAPASI	The SAPASI is a structured PASI-like instrument designed for patient self-assessments of severity
PASS	The affected area and plaque characteristics are entered in a formula that results in a score from 0 to 140. Infiltration is given more weight than erythema and scaling.
LS-PGA	The LS-PGA integrates ranges of involved BSA and the overall plaque morphology in which infiltration is given more weight
SPASI	The SPASI equals the sum of the average redness, thickness, and scaling of all the psoriasis lesions multiplied by the percentage of body surface area involved
PEASI	The PLASI is derived from the PASI but uses actual BSA percentages instead of an area score
PLASI	The PLASI is derived from the PASI but uses six BSA groupings with finer partitioning for smaller extents of BSA

The choice of treatment approaches in psoriatic patients should aim a balanced benefit risk ratio, and thus are generally made depending on disease extension and severity. In general, the body surface area (BSA) affected will determine the general treatment strategy, so that topical only treatments are chosen for localized, mild to moderate disease (i.e. ≤ 10% of BSA affected), and systemic drugs are reserved for more severe cases and those with systemic involvement (arthritis). Whichever the case, the objective is to achieve a rapid control of the disease and the maintenance of the remission.[23]

Topical treatments include corticosteroids, vitamin D analogues, topical retinoids, tar-based preparations and dithranol. There is no sequence in which these treatments should

be used first, but the first two are the most commonly prescribed and used because they have better cosmetic acceptability, and thus compliance.

Topical corticosteroids (TCS) are available in different potencies: mild, moderate, potent and very potent, and still are the mainstay of topical treatment. Lower potency corticosteroids are suitable for children and for application to sensitive skin sites (face, axillae), whereas hyperkeratotic areas (such as chronic lesions or those affecting palms and soles) may require high-potency corticosteroids. Long term therapies with TCS are limited by local side effects, including skin atrophy, striae, telangiectasia, purpura, rosacea, acneiform dermatoses and rebound erythema. Intermittent TCS therapies and combined therapeutic schemes with other topical agents are also used to overcome these therapeutic limitations of TCS.

Vitamin D derivatives include calcitriol (the naturally occurring active metabolite of vitamin D) and two synthetic analogues (calcipotriol and tacalcitol). All have been proven as effective psoriasis treatments when applied topically. These compounds have frequent mild acute local side effects (itching, stinging, irritation), but these rarely are severe, and thus they are deemed as adequate agents for long term maintenance therapy.

Among retinoids, tazarotene is the only one used for the treatment of psoriasis. Its use is limited because of poor local tolerability at the application site (erythema, irritation and burning), and also because of a potential teratogenic risk secondary to systemic absorption, which contraindicates tazarotene use in pregnant women and requires precaution in fertile women.[24]

Coal tar and dithranol have been long used for the treatment of psoriasis. However they are cosmetically poorly accepted (odor, skin staining), and its irritation potential limit their use. New formulations of these products try to overcome these limitations.[23]

When topical therapies are insufficient, other treatments are available, such as oral photosensitizing agents coupled with phototherapy. Also, oral immunosuppressant therapies (mainly cyclosporine and methotrexate) may be used, but care must be taken for the nephrotoxicity risk of cyclosporine and with long term treatments with methotrexate due to its hepatotoxicity.[15,25] More recently, the oral PDE4 inhibitor apremilast has been approved for the treatment of psoriasis needing systemic treatment. Parenterally administered biological therapies currently include anti-TNF-alfa agents and IL-12/IL-23 inhibitors; more recently anti IL-17A agents have been commercialized. Due to their safety profile (mainly allergic reactions and increased risks of infections), the uncertainties on long term safety data regarding malignancies, their cost and the concerns on loss of long term efficacy due to immunogenicity, the use of biological agents is limited to those patients exceeding certain severity thresholds in PASI and Quality of Life measures and who have failed to other standard therapies.

New efficacious and potent anti-inflammatory agents are needed to be given by either topical or oral route, and that may be safe and appropriate for chronic use, since none of the currently available alternatives provides an ideal treatment with appropriate cosmetic acceptability and risk/benefit profile for patients with psoriasis.

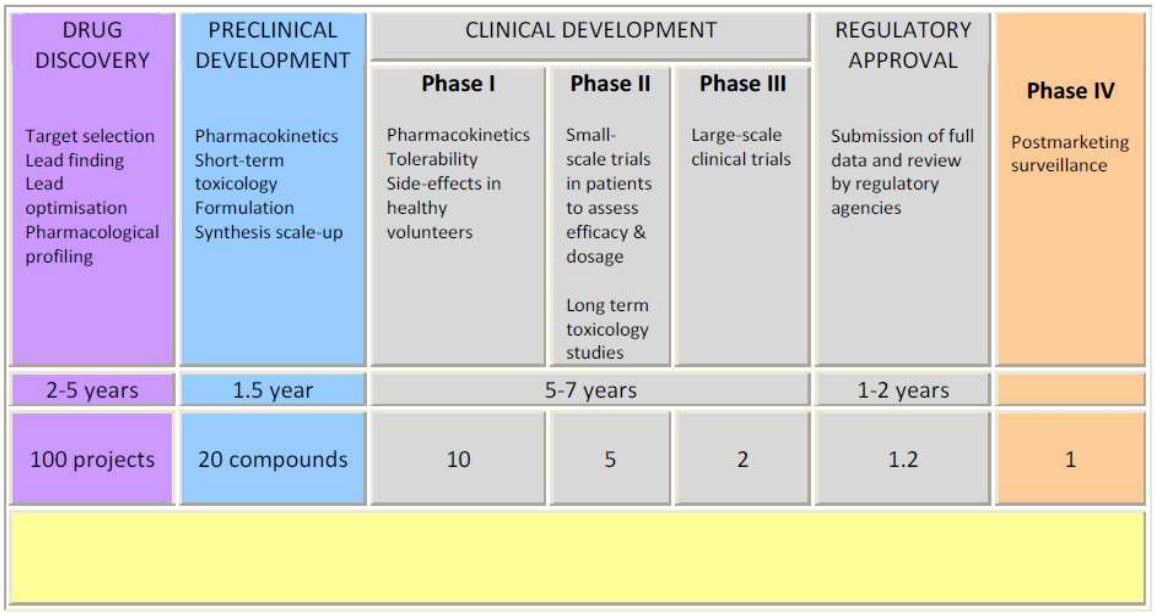
1.2. The drug development process

The process of developing a drug from the discovery to the market is a complex sequence of milestones that may take, in average, more than ten years. Moreover, not all molecules initially selected in the discovery phase will reach the clinical phase and even less will overcome all the clinical development phases and end up in market. In average, one in six drugs that enter clinical testing is eventually approved for marketing.[26] According to DiMasi et al,[26] although the global success rate has been stable since the decade of the 90's, during the recent years, failures tended to occur earlier during the development process. The duration, rate of failures and milestones vary greatly depending on the type of drug and the indication for which it is developed: the estimated clinical approval success rate for large molecules is 32%, much higher than for small molecules (13%) and the therapeutic classes with higher rates are the systemic anti-infective drugs, musculoskeletal and antineoplastic/immunologic drugs. On the other hand, CNS drugs have the lower success rates. The uncertainty about the regulatory standard that must be satisfied for different drug classes may account for these differences: efficacy endpoints for antibiotics are clearly defined and easily assessed in contrast to psychotropic compounds. More recently, Hay et al. reported that only one in ten of all indications development paths in phase I were eventually approved by the FDA.[27] This study also found that the success rate for lead indications was around 15% and that wide differences exist depending on the therapeutic area and type of drug, showing results in line with those reported by DiMasi. These data indicate that the productivity is poor. Hay suggests that progress in clinical science together with

regulatory risk-benefit assessment may improve the situation. Some of the steps proposed aimed at improving the success rates are the development of more predictive animal models, earlier toxicology evaluation and identification of biomarkers to be used during the early phases.

The whole process of drug discovery and development can be divided in three big phases: Drug discovery, preclinical development and clinical development. These phases often overlap and, as mentioned before, may vary depending on the type of drug. However, the main objectives and main activities performed in each of them for a molecule of chemical synthesis can be simplified in a diagram (Figure 3).[28]

Figure 3. The phases of drug discovery and development process



Modified from Rang and Dale 7th edition28

1.2.1. Discovery phase

In this phase, the candidate molecules are selected depending on their pharmacological characteristics.

The main activities in this phase are, in first place, the selection of a pharmacological target, followed by the search of molecules able to modulate the biological target. This process will end up with the selection of a lead compound that will be optimized in the later phases.

At this stage, compounds identified are tested in *in vitro* and *in vivo* tests so that a preliminary screening of safety, activity and physicochemical characteristics is performed to select compounds to be investigated further and discard those that are not promising or have any drawback.

1.2.2. Preclinical development

The preclinical development has the objective to meet all requirements for first in human studies. These requirements are mainly:

- Related to pharmacological tests to check that the drug does not produce any acute effect potentially dangerous or clearly serious such as broncoconstriction, cardiac arrhythmia, changes in blood pressure or ataxia. These are tested with specifically designed studies called safety pharmacology studies.
- Preliminary toxicology tests to discard genotoxicity and determine the maximum nontoxic doses of the drug, where changes in body weight and histopathological and biochemical changes are assessed.

- Pharmacokinetic studies to characterize the absorption, distribution, metabolism and elimination of the drug.
- Chemical and pharmaceutical development of the drug, to test purity, stability in different conditions and the preliminary development of a formulation for clinical use.

Most of the preclinical work mentioned above is performed under Good Laboratory Practices (GLP) conditions that include different aspects related to the procedures, register keeping, analysis of data, calibration of devices used in the experiments and training of personnel involved in the experiments. The objective of the GLP code is to ensure the accuracy of data obtained.

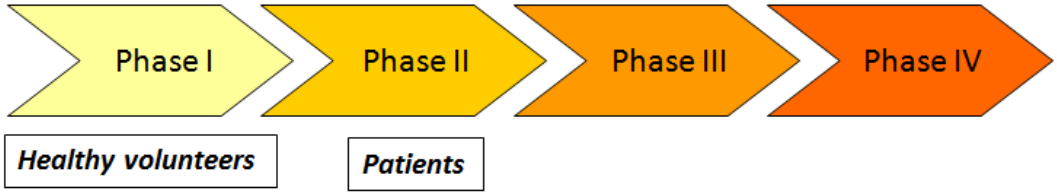
After a drug candidate goes through all the preclinical testing with satisfactory results, the regulatory bodies allow it to be tested in humans, but only after a thorough evaluation of all the information provided.

However, the preclinical or non-clinical work continues even after the clinical phase is ongoing, especially to generate toxicology data from long term use, which will be required either by the time late phase clinical studies will be initiated, or in all cases before the medicinal product can be placed into the market.

1.2.3. Clinical development

The clinical development phase is performed typically in 4 different phases:

Figure 4. Clinical development phases



Phase I:	Human Pharmacology: Safety – Tolerability – Pharmacokinetic/Dynamics – dose-response
Phase II:	Therapeutic exploratory: Dosing – Efficacy Safety
Phase III:	Therapeutic confirmatory: Efficacy compared to gold standard treatment Effectiveness
Phase IV:	Post-marketing surveillance (Therapeutic use) Effectiveness in the general population Safety

Phase I studies, which are performed in a small number of healthy (between 20 and 80 subjects) with the aim to discard the presence of potentially dangerous effects (cardiovascular, respiratory, hepatic or renal), assess tolerability and pharmacokinetic characteristics in humans. In this phase, pharmacodynamic effects can also be measured.

Phase II studies normally involve 100-300 patients and are intended to assess efficacy in patients and to test different doses in order to choose the dose/s to test in phase III clinical trials. The main reason to stop the development at this phase is the lack of the expected efficacy. Usually and especially in new chemical entities with new mechanisms of action, the drug may be tested in different diseases.

Phase III studies are mainly randomized double blind clinical trials, performed in more than one center and in different countries, including hundreds or thousands of patients. They usually include the standard of care as comparative arm.

Phase IV is the phase after the product has been marketed. Additional information and ongoing safety and tolerability assessment must be performed to proof that the drug keeps the favorable benefit-risk balance after commercialization, when larger number of patients are treated during long periods of time an under routine clinical practice conditions.

1.3. Exploratory development plans: proof of concept

For a new molecule, reaching the market is a long process demanding a big amount of resources. As mentioned before, the rate of attrition of molecules is very high and, although it depends on the area, in average, only around 15% of small molecules that enter the clinical development phase will eventually reach the market.[27]

The decision to discontinue the development of a molecule may arise at any time during the development process and will be in most cases due to safety concerns and/or lack of activity. Other reasons may be untoward pharmacokinetic profile, physicochemical issues or lack of commercial interest.

Thus, one of the main objectives during the process of developing new products is that of obtaining a proof of activity at an early phase of the development. Proof of activity has been traditionally performed after initial safety of the product has been ensured during the preclinical development and the phase I clinical trials.

In the context of the global product development plan, setting up an exploratory development plan aimed at obtaining an early proof of activity is a key point to organize which studies and the sequence in which to perform them is the ideal to obtain reliable evidence as soon as possible.

Phase II proof of concept studies typically include small populations, with restricted selection criteria and intensive monitoring of subjects, and should provide data to describe consistent therapeutic activity of the compound as early as possible, besides identifying the most common potential side effects. Although regulatory agencies do not regulate how these exploratory plans should be, requirements and standards for clinical trials with medicinal products are set out in ICH regions, and will apply to the exploratory phases of the development, by regulating the requirements of information of the product at each development phase.

Companies developing new medicinal products typically set milestones in the development, each of them being a go/no go decision point, clearly identifying experiments that would allow decision making. In general, although developers may attempt different strategies in their development plans, they use regulations, directives, guidelines and the experience of previous developments of similar products and of products in similar indications, to obtain a frame on which to support their plans.

During the development process it must be ensured that patients will not face undue risk of harm, and for this reason different amount of information is required at each stage of the development by regulatory bodies and ethics committees before the approval of the clinical trial protocols. The amount and type of data is determined by the presumed

exposure of the subject, the anticipated activity of the compound and the uncertainty on potential harmful effects.[29,30]

1.4. Regulations and guidelines

1.4.1. Ethical and regulatory review of clinical trial applications

Before administering an investigational product to humans in the context of a clinical trial, data regarding the safety of the product must be submitted both to the Regulatory Agencies (RA) and the Institutional Review Boards (IRB) or independent Ethics' Committee (EC).

Health authorities are responsible to watch over the health of the population, and thus, not only they regulate the entry of drugs on the market through their agencies but also the extent and kind of information that must be obtained before attempting every trial in humans.

Responsibilities of the IRB/EC according to the Good Clinical Practices (GCP) guideline include the safeguard of the rights, safety and wellbeing of all trial subjects.[31] They are responsible for the assessment of the equipoise of performing a clinical trial and for this reason they require information on the anticipated risks and benefits that the participation in the trial will imply.

Thus, the sponsor must provide enough information to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

A large body of legislation concerning different aspects of medicinal products has been developed during the last 50 years in Europe and the US with the intention to ensure a

high level of public health protection and to regulate the market while encouraging innovation.

Placing medicinal products on the market is subject to the granting of a marketing authorization by the competent authorities. However, during the 60s and 70s most countries implemented laws, regulations and guidelines for the reporting and evaluation of the data on safety, quality and efficacy of new medicinal products. As a consequence, the industry, that was becoming progressively more international and seeking new global markets, found that the divergence in technical requirements from country to country was such that it was needed to duplicate many time-consuming and expensive test procedures in order to place the products into the market in different countries.

In this context, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was created to bring together the regulatory authorities and pharmaceutical industry of Europe, Japan and the United States to discuss scientific and technical aspects of drug registration. It was created in 1990 and since then several tripartite harmonized guidelines have been implemented.

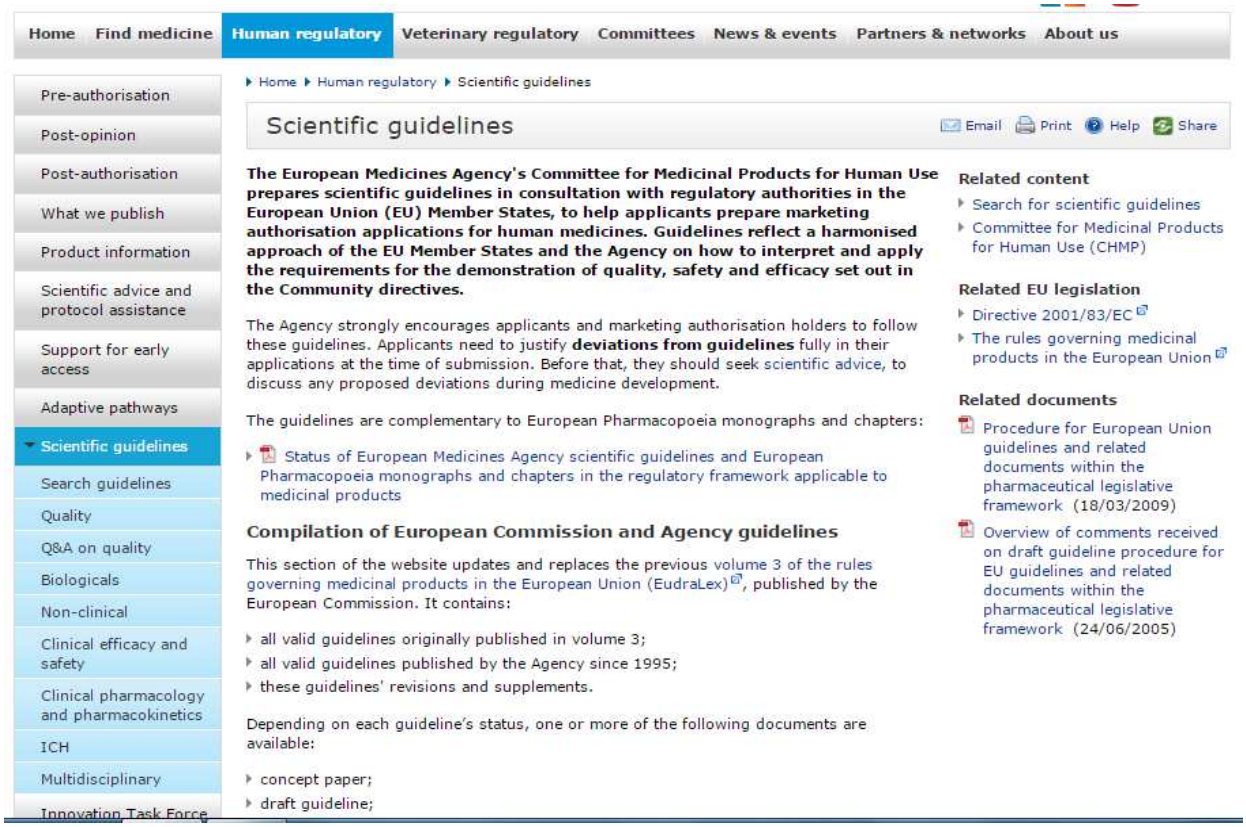
1.4.2. The legal framework governing medicinal products for human use in the EU

In Europe, since the mid-90s, community authorization procedures are in place and the system is supported by the European Medicines Agency (EMA) which is in charge of providing de European Union (EU) institutions with scientific advice on medicinal products.

The requirements and procedures for the marketing authorization for medicinal products for human use, as well as the rules for the constant supervision of products after they have been authorized, are primarily laid down in Directive 2001/83/EC and in the regulation (EC) Nº 726/2004. These texts also relate to other issues such as the manufacturing, wholesaling or advertising of medicinal products for human use.[32] Community legislation also provides for common rules for the conduct of clinical trials in the EU countries. The legislation is compiled at Eudralex website, and organized in 10 volumes that can be consulted separately.[33] All Community legislation in the area of medicinal products for human use is contained in the first volume of "The Rules Governing Medicinal Products in the European Union". The basic legislation is supported by a series of guidelines relevant for medicinal products for human use that are also published as volumes 2 (Notice to applicants and regulatory guidelines for medicinal products for human use), 3 (Scientific guidelines for medicinal products for human use), 4 (Guidelines for good manufacturing practices for medicinal products for human and veterinary use), 9 (Guidelines for pharmacovigilance for medicinal products for human and veterinary use) and 10 (Guidelines for clinical trials) of "The rules governing medicinal products in the European Union".

In addition, to facilitate the interpretation of the legislation and its uniform application across the EU, numerous guidelines of regulatory and scientific nature have additionally been adopted by regulatory bodies, including all ICH guidelines.

Figure 5. EMA scientific guidelines



Scientific guidelines are intended to provide a basis for practical harmonization of the manner in which the EU Member States and the EMA interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community Directives. They also help to ensure that applications for marketing authorization are prepared in a manner that will be recognized as valid by the EMA.

Thus, in principle, clear guidance on the drug development process is available from the regulatory agencies.

1.4.3. The regulation of medicinal products in the US

The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services whose responsibilities are protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices. The FDA is also responsible for the safety and security of most of our nation's food supply, all cosmetics, dietary supplements and products that give off radiation.

The FDA issues guidance documents representing FDA's current thinking on a topic, but alternative approaches can be used if the approach satisfies the requirements of the applicable statutes and regulations. These documents usually discuss more specific products or issues that relate to the design, production, labeling, promotion, manufacturing, and testing of regulated products. Guidance documents may also relate to the processing, content, and evaluation or approval of submissions as well as to inspection and enforcement policies.[34]

1.5. Topical treatments for inflammatory diseases of the skin

As indicated in previous sections, the mainstay of treatment of the atopic eczema is based on topical application of immunosuppressants and emollients. Systemic treatments are reserved for severe cases in which the benefits outweigh the risks. Similarly, for the treatment of mild to moderate plaque psoriasis, medicinal products applied topically are also of choice, leaving systemic immunosupressants for patients with generalized forms.

In recent years, a huge activity has been focused on the development of new systemic immunosuppressant treatments for severe inflammatory skin diseases, including monoclonal antibodies and small molecules, and aimed mainly for psoriasis,[35] but also for atopic eczema.[36] While new effective systemic treatments for psoriasis have become available, the research intended to find new targets and new molecules for the treatment of atopic dermatitis had few successes in the past, mainly due to the unknown underlying mechanisms of the disease.[37] Thus the recent advances in the field of disease mechanisms may open the door to new developments that will in brief be a reality.

However, despite most of the disease burden is attributable to mild to moderate disease, few new molecular entities (NME) aimed for topical treatment of inflammatory skin conditions have been approved, and research activity in this area seems focused on the development of generic products, new formulations, combinations of known active ingredients products and cosmetic dermatology.[38]

The development of new chemical entities for these diseases to be applied locally to the skin has its own particularities due to the topical route but also to the disease itself.

1.6. Particularities in the development of topical products applied to the skin

While the development path for equivalent or generic products is quite well defined, the development requirements for new topical entities are poorly defined.[39]

Both the topical safety profile and the systemic adverse effects of the product must be studied, which requires a specific non-clinical approach ensuring maximum validity of the experimental models used.[39] A number of animal models are available or both

pharmacokinetic testing and activity testing, used in both drug discovery and candidate development. Classical animal models for screening testing of anti-inflammatory products were based on inflammation induced by sensitizers or haptens, such as the oxazolone-induced ear edema in mice. However, these have been progressively replaced by the development of more specific models.[40, 41, 42]

For atopic eczema, animal models include passive sensitization with IgE, epicutaneous sensitization with allergen, such as ovoalbumin, house dust mite or , transgenic mice that either over-express or lack selective molecules, such as IL-4, IL31, IL18 and caspase 1, or thymic stromal lymphopoietin (TSLP), amongst others, and models of animals that spontaneously develop AE-like skin lesions, either engineered such as the flaky tail mice, NC/Tnd mice, cathepsin-E knockout mice or human apolipoprotein C1 transgenic mice, or spontaneously such as the Nc/Nga mice strain.[40,42,43]

Models for psoriasis include severe combined immunodeficient mice (SCID) with human psoriatic skin xenografts, and genetically engineered mice, both transgenic and knockout models, such as human leukocyte antigen B27 (HLAB27) transgenic rats, CD18 hypomorphic mice, K14/VEGF and Tie2 mice, K14/TGF-α, K5/TGF-β1, K14/KGF and K14/IL-20 transgenic mice, IKK2, JunB/c-Jun transgenic mice, K5.Stat3C mice, and K14/IL-6 and K14/IL-1αtransgenic mice. Nearly a hundred mutation mouse models leading to psoriasiform phenotypes have been documented, such as homozygous asebia (Scd1ab/Scd1ab) mutant mice, flaky skin mice (Ttcfsn/Ttcfsn), spontaneous chronic proliferative dermatitis mutation mice and so on, but they do not closely mimic the disease enough to be considered as good models of psoriasis.[40,42]

Topical administration of drugs on the skin aims to maximize local therapeutic action of the drug, by reaching the site they are intended to treat (usually below the *stratum corneum*) and minimize systemic absorption to avoid security problems. Thus, penetration is needed in sufficient amount to treat the condition, but not sufficient to reach the blood in concentrations that may produce systemic effects.[44] Besides, the assessment of systemic exposure becomes a critical aspect to be addressed along a development program for a topical dermatological product. The development of analysis methods able to detect very low plasma concentrations in all non-clinical species and in human biological matrices is required, and systemic and topical pharmacokinetic studies are along the decision path for the product. Drugs with high skin penetration rates and long plasma half-lives may be discarded early in the candidate selection phase.[45]

Special attention must be paid to the selection of the excipients (product vehicle) in a dermatologic drug product, since it may have therapeutic effect by itself (I ex: vehicles with emollient properties in atopic eczema), but also may enhance delivery and efficacy of the active compound, and should be compatible with the chemical properties of the active principle and ensure good stability. Also, the vehicle should not be irritant to the skin, nor enhance the potential local adverse effects of the active principle, and ideally should be comfortable, invisible and pleasant.[39]

Besides, the type of vehicle suiting one disease (I ex: ointment for psoriasis) may not suit another (I ex: occlusive properties of ointments are not appropriate for atopic eczema). When more than one formulation is developed, separate studies must be done to characterize their characteristics. Also, any change in the vehicle composition may alter

the product release from the formulation and modify the pharmacokinetic profile of the drug, its efficacy and / or safety. Thus, the pharmaceutical development of the future drug must be considered at an early stage, and any change along the product development may trigger the need for additional bridging studies or even clinical trials, creating additional costs and delays.[39]

However, although a number of no-go decisions can be taken at critical milestones of development, mainly due to safety or pharmacokinetic findings, animal models have a limited predictability of efficacy clinical success, and reliable proof of concept is not reached until clinical testing. Thus, development programs are very much focused on efficiently reaching a clinical proof of concept with the best use of time and resources. The choice of the trial design, in terms of risks due to likelihood and duration of an eventual systemic exposure, will determine the non-clinical requirements, and ideally should balance the development path and investment requirements with the need of reliable and predictive answers. Trials closely resembling clinical use will be more predictive than trials with a refined experimental setting, but the latter may be quite efficient for go-non-go decisions to be taken.[39]

Clinical trials of topically applied dermatological treatments have also a number of particularities and specific methodological and practical difficulties. Guaranteeing double blind conditions is often a challenge. For instance, for commercialized products intended to be used as a reference standard, the primary packaging is generally printed with the name/brand of the medicinal product. Although over labeling of the primary package may partially mask the product identity, yet the packaging may also have singular size and

shape, and be closed with special caps not commercially available. Changing the primary packaging for dummying may alter the microbiological and physical characteristics of the formulation, requires re-analysis of the final product, and thus development of the specific assay. Expiry dates after re-packaging are limited, and may complicate the drug supply logistics during the trial. Even if the external appearance is undistinguishable, the characteristics of the actual reference and test products may differ substantially in terms of color, appearance, viscosity and odor. Development of placebos for the reference product requires knowing the exact excipient composition of the formulation, which is usually held as industrial secret and not available to the public. Further, double dummy approaches are generally not suitable, since the application of a vehicle at the same location than the active may dilute the product and reduce the actual dose given.[46]

Also, the amount of product applied to the skin may greatly vary depending on the subject's disease extension and, when self-administered, the generosity of the subject at the time of dosing from the product container. Standardization of the dosing is particularly important in studies with pharmacokinetic objectives, since plasma levels will depend on the product concentration, the area treated, the amount applied per unit surface and the characteristics of the skin.[45] Volunteers with healthy skin may absorb smaller amounts of product than patients with impaired skin barrier, such as atopic eczema patients, but also increased *corneum stratum* and lichenification may impair absorption. Thus, distinctively from other therapeutic areas of research, pharmacokinetic studies in dermatology should be conducted in patients, and not in healthy skin volunteers. Further, children have substantially different skin composition and are

generally more prone to percutaneous absorption, so that extrapolation from adults should be very carefully evaluated.[45]

Moreover, controlling the patient's compliance requires complex approaches not always feasible. When using two different products in the same subject, there is risk of confusion or mixing of treatments, raising uncertainty in the quantity and quality of adherence. Such uncertainty may compromise the entire trial validity.[47] Administration by a third party may solve some of these problems,[46] but is highly demanding for the subject, especially if the posology requires twice daily application or more, and may require subject compensation for travel expenses. Using dedicated personnel to go to subject's home to treat them may be unfeasible if sample size is large and the geographical area is wide.

Activity and efficacy variables in dermatological clinical trials are based on visual inspection, and therefore are subjective, requiring methodological strategies to minimize inter-observer variability and possible biases. Composite variables integrating several assessments (I ex: intensity of skin severity plus extension of skin affected plus general perception by observer) are often used, in particular in clinical trials accomplishing criteria for good quality of reporting.[48] The relative accessibility of the skin to direct observation and sampling allows the use of a number of very specialized techniques that can objectivize and support the assessment of product activity. Skin biopsies may be useful to assess the pharmacodynamics of the product at the site of action, chromameters may objectivize erythema and blanching, and microdialysis can inform on product concentration at different levels of the skin. Newest techniques include confocal Raman

spectroscopy to objectivize skin water concentration or reflectance confocal microscopy to observe histological aspects in vivo, amongst others. Their use is increasingly being incorporated into clinical trial designs to support clinical assessments.[39,49,50]

Some other distinctive characteristics of clinical trials in inflammatory skin diseases relate to their intermittent clinical course. Flaring and self-remission of the lesions within the natural course of the disease complicate the interpretation of causality for any observed result. Also, there is a seasonal influence on the severity of skin inflammation, which may be related to the presence of allergens (I ex atopic eczema), to beneficial effect of sun exposure and to clothing covering or skin uncovering of affected areas (both in atopic eczema and psoriasis). Thus there is an effect on the disease severity of changing seasons that should be accounted for in the study design. Thus, it becomes critical to ensure that the trials are conducted under similar weather conditions, and because of that, recruitment periods may be very tight, to ensure that they are conducted only during one season.[46]

The fact that inflammatory skin diseases often affect symmetrical skin areas allow for the possibility of using contralateral controls within the same subject, who acts as its own comparator. Clinical trials with intra-subject designs have been reported as highly effective, provided that treatment compliance is carefully controlled.[47,46]

In summary, a priory, developing a topical product has particularities that may both facilitate or complicate the development. However, there seems to be little direct reference information to guide the design of a development plan for new molecular

entities applied topically. If we talk about how the first phases up to clinical proof of concept (PoC) should be approached explicit information is even more limited.[39]

For these reasons, it is considered appropriate to perform a systematic analysis of the information available and lacking to guide such developments, to identify the key aspects to design the development of a NME and to propose efficient designs of exploratory development plans objective driven that may facilitate the process of development up to PoC for topical application NME intended for the treatment of atopic eczema and psoriasis.

2. Hypothesis and Objectives

2.1. Hypothesis

During the development of NME aimed for the topical treatment of inflammatory dermatological diseases, setting up an exploratory clinical development plan objective driven using efficient PoC studies designs, maximizing variability control, leads to obtaining robust and conclusive in a short period of time, with minimal requirements of non-clinical and clinical data and minimizing the exposure of subjects to the investigational product thus ensuring safety of the subjects participating in clinical trials.

2.2. Objectives

2.2.1. General objective

- The general objective is to identify the most efficient approach to explore the clinical activity of a NME in terms of reliability of the results, non-clinical and clinical data requirements and in terms of exposed patients, time to obtain activity data and investment required.

2.2.2. Specific objectives

- Identify the objectives of an exploratory development of a NME aimed for the topical treatment of inflammatory dermatological diseases.
- Describe the need for clinical studies before starting the phase II studies as well as the designs of these studies to be able to meet the objectives of the development.

- Identify which non clinical data are needed before starting clinical studies up to phase II or proof of concept.
- Describe the different possible designs for clinical trials aimed at assessing the efficacy of a topical treatment intended for the treatment of inflammatory dermatological diseases.
- Propose an exploratory development plan driven by objectives, for each of the different exploratory clinical trial designs identified.
- Compare the efficiency of the different designs for PoC studies and their associated development plans to confirm or discard the activity of a product.

3. Methods

3.1. General Methods

The following general methods were proposed:

(A) Systematic review of

a. regulatory guidelines issued in the previous 20 years (1993 to 2013) by the International Conference of Harmonization, the European Medicines Agency and the US Food and Drug Administration,

b. public assessment reports of topical dermatological products issued in the previous 20 years (1993 to 2013) by both, the European Medicines Agency (European Public Assessment Reports) and the US Food and Drug Administration (Drug Approval Packages).

The review was focused in obtaining the following results:

- Describe objectives of an exploratory development.
- Describe which non-clinical studies are required to initiate Phase II or PoC studies.
- Describe which clinical studies are required to initiate phase II or PoC studies and their designs.

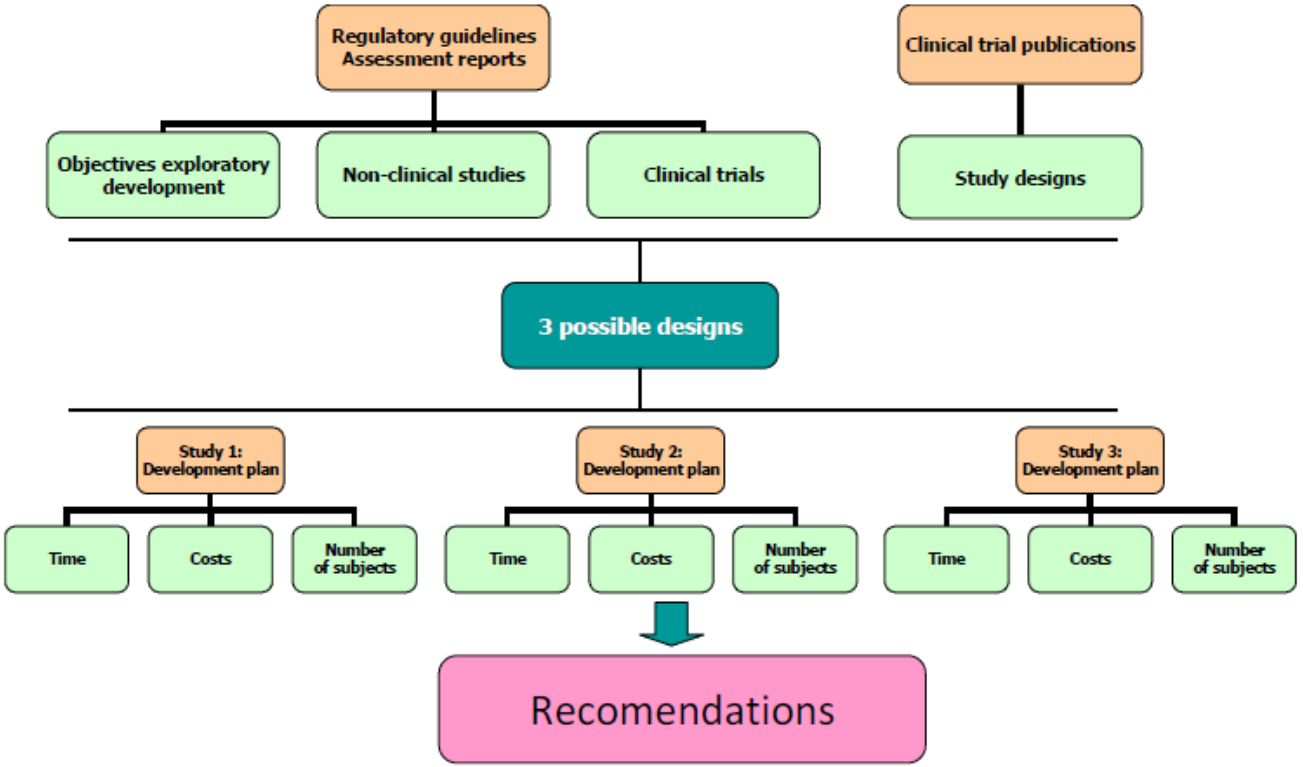
(B) Systematic review of clinical trials of topical dermatological products in AE and PSO published in the period from January 2003 to December 2013.

- Describe the type of designs used to obtain a PoC in terms of designs, number of patients, duration, type of variables and statistical tests.
- Identify the most relevant clinical trial designs for PoC in AE and/or psoriasis.

(C) For each type of design identified:

- Create a development plan with recommendations on which previous clinical and non-clinical studies are required and their design.
- Estimate costs and duration of each PoC study design, by comparing them in terms of:
    - Number of subjects required
    - Time required to finish the study
    - Costs of the study
    - Previous requirements of clinical data: time needed, subjects exposed and costs since the first administration in humans till the start of the PoC study
    - Previous requirements of non-clinical data: studies required and time needed since the start of the candidate development phase to the start of the first study in humans

Figure 6. General methods



3.2. Specific methods

3.2.1. Regulatory guidelines search and review

A search for guidelines that may give advice on how to develop a NME topically applied for inflammatory skin diseases has been performed. We performed a first search for specific guidelines in dermatology, dermatological pathologies or topical products applied to the skin, both clinical and non-clinical as a first step, followed by a search of general guidelines, from which guidance may be obtained for the development of topical dermatological products. The search was performed for documents issued by EMA, FDA or ICH. Both in force and superseded documents were reviewed.

Documents were selected by reading the title and introduction of the document, and were classified according to their scope:

1. Guidelines for clinical development of drugs for atopic dermatitis and psoriasis
2. Guidelines for clinical development of products in dermatology
3. Guidelines for clinical development of drugs intended for other dermatological conditions
4. General guidelines for clinical development of products
5. Guidelines for non-clinical development of drugs applied topically in the skin
6. General guidelines for non-clinical development of drugs

A thorough review of these documents was performed to systematize information on the following questions:

- Type and amount of pre-clinical data needed before going into a phase II trial
- Type and amount of clinical data is needed before going into a phase II trial
- How the design of the phase II clinical trial condition the type and amount of non-clinical and clinical data needed

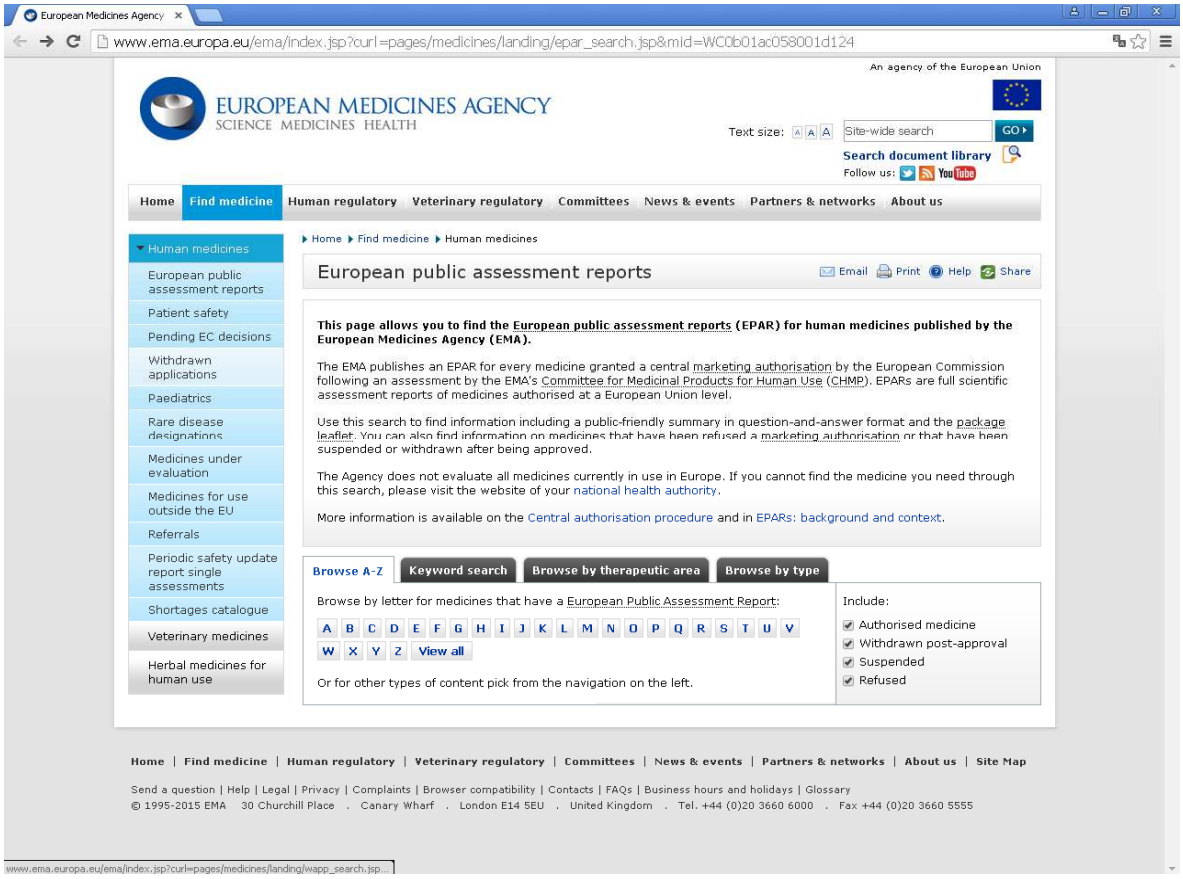
Data retrieved from the different guidelines was summarized in narrative format.

3.2.2. Assessment reports search and review

A search for the European Public Assessment Reports (EPAR) issued by the EMA and the FDA drug approval packages has been performed for topical dermatological products for the treatment of AE or PSO.

European Public Assessment Reports are available at the EMA website for all medicinal products which have been granted a central marketing authorization by the European Commission following an assessment by the EMA's Committee for Medicinal Products for Human Use (CHMP). The EPAR follows an assessment by the EMA of an application submitted by a pharmaceutical company. The search was performed by therapeutic area (skin and connective diseases/Skin diseases) to identify any product with dermatological disease indication applied topically to the skin, at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.

Figure 7. EMA website. European Public Assessment Reports



For every EPAR identified, a specific search was performed for an FDA assessment report for the same product. Drug approval packages (or reviews or summary basis of approval documents) are available on the FDA website since 1997 under the freedom of information act. The documents available are filtered summaries of clinical study reports and related documents written by FDA staff, mainly focused on pivotal trials. The documents have been searched by active substance at:

http://www.accessdata.fda.gov/Scripts/cder/drugsatfda/index.cfm.

Eventually, a search for topical products approved in Spain for the treatment of Atopic eczema and Psoriasis was done at the *Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) – Guía de Prescripción Terapéutica, Información de Medicamentos Autorizados en España*. For those active substances identified without an EPAR available, we tried to find the drug approval package at the FDA. The cutoff date was 1993.

Search for additional topical dermatological products at the FDA website was discarded, due to the scarcity of new approvals in recent years. New formulations and combinations were discarded as well.

Reviews were based primarily on EMA documents, when available, and the FDA drug approval packages were reviewed to further complement the information.

A database to extract the information of the reports was created, with the following fields:

Table 5. Information to obtain from the assessment reports

Product	in vitro percutaneous absorption studies (including human)
Indication	In vitro Skin metabolism studies
Date	Acute toxicity studies. Oral
NQE	Acute toxicity studies. Iv
Data available (EMA/FDA)	Acute toxicity studies.Dermal
Indication	Repeated dose toxicity studies. Oral
Treatment schedule/duration	Repeated dose toxicity studies. IV
Chronic Yes/no	Repeated dose toxicity studies. Dermal
Systemic safety studies	Reproduction studies oral/intravenous
Safety: CV	Reproduction studies dermal application
Safety: Resp	Genotox studies
Safety: CNS	Topical carcinogenesis studies
Additional safety	Systemic carcinogenesis studies

In vivo PK (IV, oral) studies nº species	In vitro Phototoxicity
in vivo PK nº species studied	In vivo Phototox
In vivo dermal PK studies n species	In vivo photosensitization
In vivo dermal PK nº species studied	In vivo photocarcinogenicity
In vitro human P450 enzymes inhibition studies	In vivo skin sensitization
In vitro distribution studies	Local tolerance/skin irritation
In vitro metabolism studies	in vitro percutaneous absorption studies (including human)

Information from the database was summarized to describe the amount of preclinical information that has been submitted with the application.

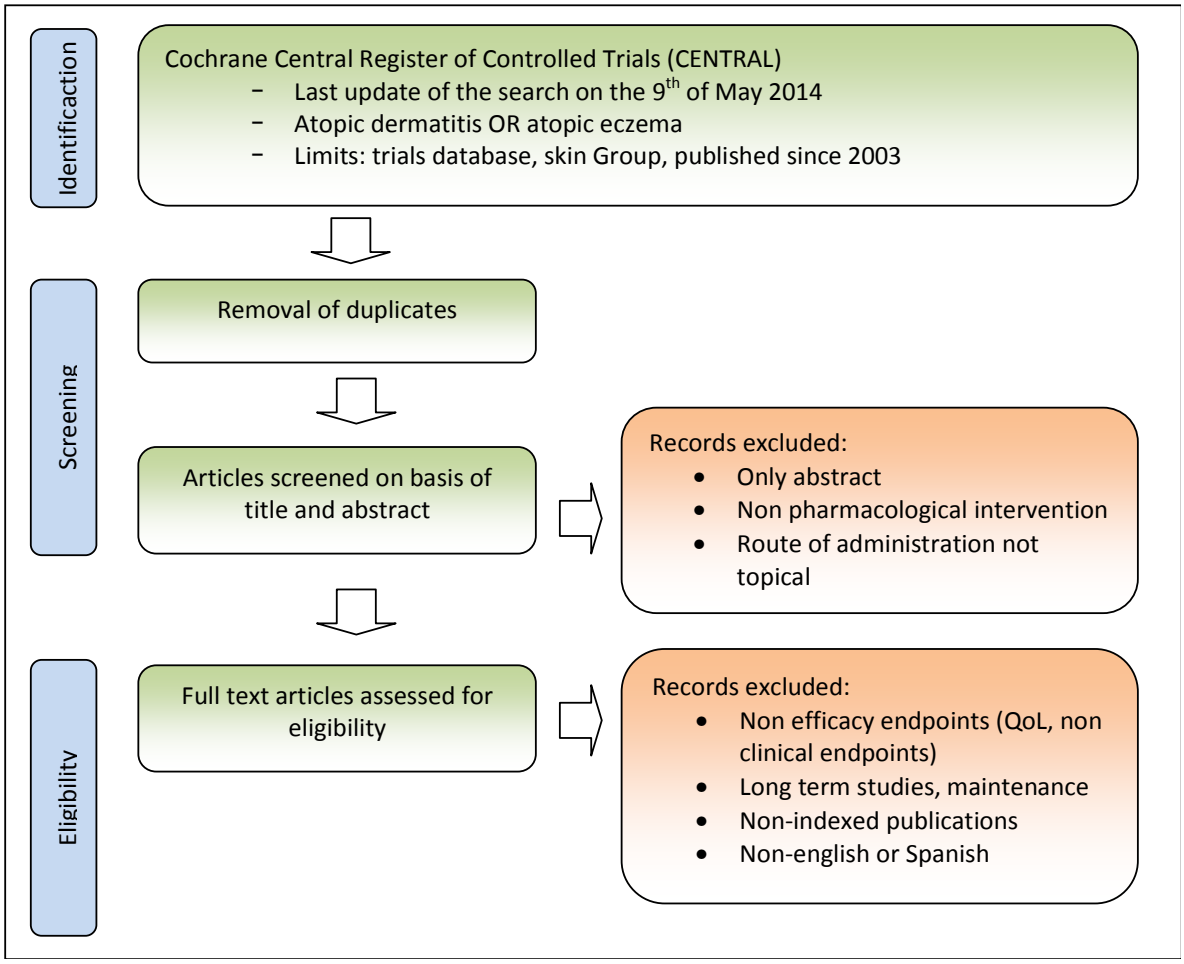
3.2.3. Publications of clinical trials: search and review

A search for original articles reporting clinical trials performed with topical dermatological products in atopic eczema and psoriasis was performed in the Cochrane Central Register of Controlled Trials (CENTRAL). It is a bibliographic database that provides a highly concentrated source of reports of randomized controlled trials. Records contain the list of authors, the title of the article, the source, volume, issue, page numbers, and, in many cases, a summary of the article (abstract). It contains all MEDLINE entries indexed as Publication Type 'controlled randomized trial' or 'controlled clinical trial' in humans. It also contains trial reports from EMBASE not indexed as trials in Medline. The database is complemented with entries from other databases and manual searches. In order to improve sensitivity, a free text search was performed.

3.2.3.1. Atopic Eczema

The search terms and the review process are indicated in the figure below:

Figure 8. Literature review process. Atopic Eczema



A first review of titles and abstracts was performed and entries were classified as full articles or abstracts presented at scientific meetings, type of intervention of the clinical trial, and route of administration of the intervention. The following table shows the

different categories assigned for the type of intervention. At this stage also, those studies detected as duplicated or as not being in AE were classified.

Table 6. Type of intervention assigned to publications

Pharmacological
Educational programs
Diets
Probiotics/prebiotics
Natural remedies, plants, oils
Physical treatments, including textile
Phototherapy
Homeopathy
Soaps
Intervention unknown
Other: studies which were clearly no CT to assess treatments

Only full publications reporting clinical trials with pharmacological treatments topically administered to the skin for the treatment of AE were selected in a first step. We considered pharmacological treatment a wide range of products including moisturizers, vitamins, oligosaccharides, antioxidant molecules, mite extracts, immunotherapy, psoralenes, but only those applied topically were considered.

In a second stage, abstracts and full articles when available were reviewed in depth to detect entries which were clinical trials in other conditions different from atopic eczema, with endpoints clearly not to assess efficacy, long term maintenance, QoL or non-clinical endpoints. Also, those articles in languages different from English or Spanish, or in non-indexed publications and thus, difficult to obtain, were excluded.

For records resulting from this selection, full articles were read with the purpose to extract relevant information from the designs and results of the studies.

A database to systematize information from these publications was created with the fields detailed in Table 7. Mainly, aspects regarding the design, number of patients, recruitment periods, treatments administered, variables measured and results were collected.

Table 7. Fields corresponding to the database

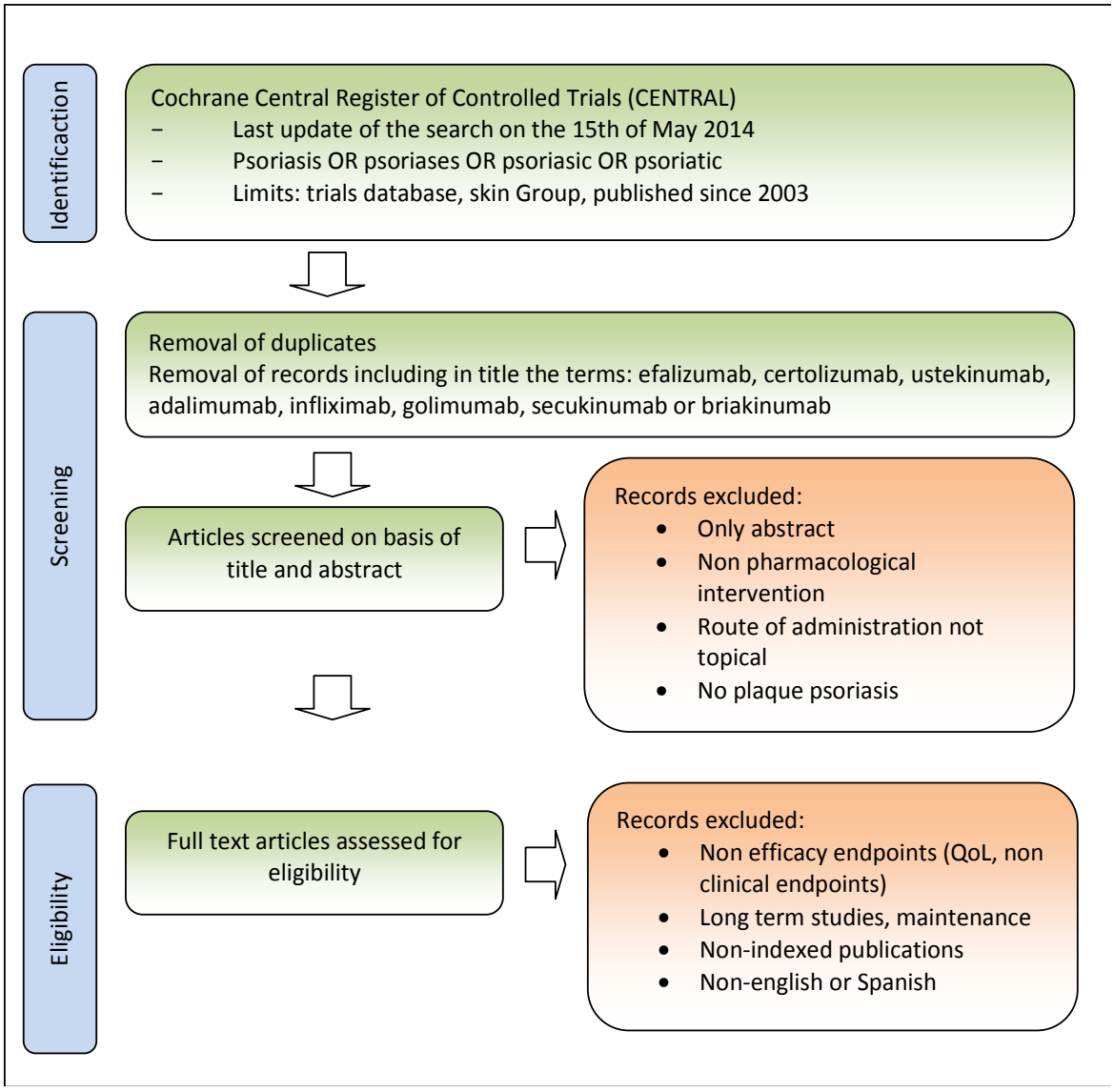
Field name	type of data	description
nº	Number	Number assigned in the search
any	Number	Publication year
dissenyloca	Text	study performed in one site or more
dissenyrandom	Yes/No	It is clearly state and minimally described that the study is randomized
assign	Text	Treatment assignment unit is the subject, a lesion or body side
dataini	Date	Month when the study recruitment is initiated
datafi	Date	Month when the study recruitment is finished
duraciottosem	Number	Weeks of treatment
duraciosegsem	Number	Weeks of follow up after treatment if any
CEIC	Yes/No	It is stated that protocol was approved by an IRB
CI	Yes/No	It is stated that patients gave consent or if approved by IRB+GCP compliance
Gavetat	Text	Severity of the disease expressed as mild-moderate-severe
gravetat obert	Memo	other details regarding inclusion criteria on the severity & extension of disease
nens	Yes/No	Children included
adults	Yes/No	Adults included (if only ages 16 up, considered adults)
intervencionquantas	Number	number of interventions
intervencionplacebo	Yes/No	is there a placebo or vehicle intervention?
intevencion1	Text	Name of the active principle concentration, pharmaceutical form
intervencionpauta1	Text	Treatment regimen in applications/day
intevencion2	Text	Name of the active principle concentration, pharmaceutical form
intervencionpauta2	Text	Treatment regimen in applications/day
intevencion3	Text	Name of the active principle concentration, pharmaceutical form
intervencionpauta3	Text	Treatment regimen in applications/day
intevencion4	Text	Name of the active principle concentration, pharmaceutical form
intervencionpauta4	Text	Treatment regimen in applications/day
ratio random	Text	Random ratio. For bilateral comparisons, if all patients receive 2 treatments is 1:1
enmascara	Text	Type of blinding
aplica	Text	Who applies the treatment
cumpliment	Yes/No	are methods for measuring treatment compliance reported?
cumplimentobert	Text	Methods for measuring treatment reported

Field name	type of data	description
N	Number	Total number of patients randomized
N por grupo	Text	number of patients per treatment group (when bilateral, lesions count as patients)
MAINvarmesura	Text	Main efficacy variable
MAINvaroutcome	Text	Main efficacy outcome
MAINvartime	Number	Timepoint for measuring main outcome
MAINvartimeweeks	Text	Timepoint for measuring main outcome units
SECONDvarmesura1	Text	Secondary efficacy variable
SECONDvaroutcome1	Text	Secondary efficacy outcome
SECONDvartime1	Number	Timepoint for measuring secondary outcome
SECONDvartimeweeks1	Text	Timepoint for measuring secondary outcome units
SECONDvarmesura2	Text	Secondary efficacy variable
SECONDvaroutcome2	Text	Secondary efficacy outcome
SECONDvartime2	Number	Timepoint for measuring secondary outcome
SECONDvartimeweeks2	Text	Timepoint for measuring secondary outcome units
SECONDvarmesura3	Text	Secondary efficacy variable
SECONDvaroutcome3	Text	Secondary efficacy outcome
SECONDvartime3	Number	Timepoint for measuring secondary outcome
SECONDvartimeweeks3	Text	Timepoint for measuring secondary outcome units
Evalua	Text	Who assesses the main variable
Validat	Text	Main variable is a validated measure
sta testsMAINVAR	Text	Statistical test for the main endpoint
stattestsSECONDvar	Text	Statistical test for the second endpoint
ResultMAIN	Text	results main endpoint (summary)
ResultMAINsign	Yes/No	Results main endpoint statistically significant
result SECOND	Memo	Results for secondary endpoints
comments	Memo	Open comments
calcul mostra	Memo	Sample size calculation (open)

3.2.3.2. Psoriasis

The search terms and the review process are indicated in the figure below:

Figure 9. Literature review process. Psoriasis



From this search, all records including any of the following as keywords were excluded: efalizumab, certolizumab, ustekinumab, adalimumab, infliximab, golimumab, secukinumab or briakinumab.

A first review of titles and abstracts was performed and entries were classified as full articles or abstracts presented at scientific meetings, type of intervention of the clinical trial, route of administration of the intervention and type of psoriasis (nail, scalp, palmoplantar). The following table shows the different categories assigned for the intervention and to the type of psoriasis different from plaque psoriasis.

Table 8. Type of intervention and type of psoriasis assigned to publications

Intervention	**Type of psoriasis**
Pharmacological	Nail Psoriasis
Educational programs	Plamoplantar psoriasis
Diets	Scalp psoriasis
Biologicals	Psoriasis guttata
Natural remedies, plants, oils	Scalp seborreic dermatitis
Physical treatments, including textile	No psoriasis: atopic dermatitis
Psoralenes + Phototherapy	
Soaps, baths	
Unknown	
Other (non CT, CT to measure non skin symptoms of psoriasis)	

Only full publications reporting clinical trials with pharmacological treatments or natural remedies, topically administered to the skin were selected in a first step. In addition, studies assessing psoralenes+phototherapy were selected at this stage. We considered pharmacological treatment a wide range of products including moisturizers, vitamins, oligosaccharides, antioxidant molecules, immunotherapy, psoralenes, but only those applied topically were considered. Studies in nail, scalp or palmoplantar psoriasis were also excluded.

After the initial selection, a second selection was performed excluding entries which were clinical trials in other conditions different from psoriasis, with endpoints clearly not to assess efficacy, to assess long term maintenance, QoL or non clinical endpoints. Also, those articles in languages different from English or Spanish, or in non indexed publications and thus, difficult to obtain, were excluded.

For records resulting from this selection, full articles were read with the purpose to extract relevant information from the designs and results of the studies. A database to systematize information from these publications was created with the same fields as detailed in Table 7 above. Although a separate database was created for AE and PSO, eventually, variables included were the same. Mainly, aspects regarding the design, number of patients, recruitment periods, treatments administered, variables measured and results were collected.

The review of clinical trials allowed the description of the type of clinical trials used to assess efficacy of topical products in both conditions (AE and PSO) in terms of designs, number of patients included, duration of the trial, type of variables used and statistical tests used.

3.2.4. Design of exploratory development plans

A separate exploratory early clinical development plan has been issued for AE and for PSO, each including more than one scenarios based on the selection of the most suitable and representative study designs for proof of concept from the previous review, and considering the different requirements to support the proof of concept execution. The design of the studies and their previous requirements has been guided by the results of

the review of clinical trials and EPARs, and the available recommendations from regulatory guidelines.

For each of the scenarios a complete development plan has been built up to the start of the non-clinical regulatory development phase. This has been done as a made up scenario where all the decisions are supported by the information reviewed.

Study outlines have been developed up to detail the number of subjects, number of visits and type of assessments at the visit level, as well as overall study duration, in order to allow further simulation. Gantt charts have been produced for each scenario.

3.2.5. Estimation of costs and times

The duration of the exploratory clinical development plan has been modeled for the different chosen scenarios, and compared. Also, overall clinic development costs have been approached through the quantification at the study level of the parameters that generally are parameterized to determine budgeting of outsourcing tasks to contract research organizations (CRO).

The parameters used were the number of subjects included and screened (number screened depending on the degree of selectivity of the inclusion criteria), the number of visits per subject and number of special procedures at the site (referred to specialized technique other than clinical assessment of lesions, such as ultrasonography or confocal microscopy), the number of routine laboratory measurements and bioanalytical measurements of the product, any volunteer compensation, the overall project duration (as an approach to project management costs), the number of pages of the CRF (as an

approach to monitoring, data management and analysis costs), number of sites involved (as an approach to fixed costs per site), and finally, activities independent from the actual study characteristics. The units were directly compared to allow estimation of task burden independent of the actual pricing policies of vendors, and also to avoid expiry of conclusions with time.

To ease interpretation and to account for proportional weight of each task within a project, the units of cost for each trial were then budgeted by applying dummy prices. The reference costs per task were extracted from 3 different European budget proposals already available from a previous dermatological development in 2007 (see table below).

Table 9. Items and dummy prices applied for clinical study units budgeting

Concept	**Real example budget in € (2007, EU)**	**N Units budgeted**	**PRICE PER UNIT**	**Proportional weight**
Nº screened subjects	90	90		
Nº subjects included	60	60		
Medical visits	120,301	445	270	31%
Nº specific procedures at site		0	60[a]	0%
Nº treatment visits (dispensations/applications)	3,600	1680	20	9%
Nº biochemical and hematological samples	21,900	265	83	6%
Bioanalysis PK (nº samples analyzed)		0	45 [a]	0%
Volunteers' compensation[b]	*140,580*	60	*2,343*	*36%*
Project duration in months (to extrapolate project management)	43,500	12	4,833	100%
Nº pages CRF (to extrapolate monitoring, data management and statistics)	58,710	5580	11	15%
Fixed costs per center (main documents, authorization, reporting, quality assurance, pharmacovigilance, drug supply)	30,360	1	30,360	39%
Fixed costs per study (includes protocol writing, general docs of the study and regulatory submission)	48,060	1	48,060	61%
Total study budget	**497,161**			**100%**
Cost per patient	**8,286**			
Budget depending on number of subjects - subtotal	387,091			78%	*6,452*	*Per patient*
Budget depending on number of site or fixed cost - subtotal	78,420			16%	*78,420*	*Per site*
Budget depending on months ongoing - subtotal	43,500			9%	*4,833*	*Per month*

a) Dummy price was applied from other contemporary budget proposals; b) customized in models as per study characteristics

4. Results

4.1. Regulatory guidelines search and review

All regulatory documents selected and reviewed are listed in Table 10. Documents containing guidance on preclinical and clinical data reviewed are summarized below.

4.1.1. Non clinical data

ICH general guidelines that set the type of non-clinical studies and the timing during the development process that have been reviewed are M3 (R2) (Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals)[30] and S7A (Safety Pharmacology Studies for Human Pharmaceuticals) [51]. Other documents detail how the studies referred to in these guidelines must be conducted (S3A toxicokinetics[52], S3B tissue distribution studies[53], S5 (R2) reproduction toxicity[54], S2(R1) genotoxicity[55], S7B QT[56], S10 photosafety[57]). These have not been reviewed with the exception of S10, and S2(R1) due to the relevance of phototoxicity and genotoxicity testing for products applied topically in the skin. The EMA guideline on non-clinical local tolerance testing of medicinal products is also summarized.

M3(R2) (Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals)[30]

This guideline establishes the type and duration of non-clinical studies and when should they be performed along the clinical development of the product with the aim of setting up the minimum data needed, but also to limit the number of studies performed to minimize the use of animals and speed the development process. The document explains

which are the goals of the non-clinical safety assessment, which include the characterization of the toxic effects in target organs, assess its dose-dependence and relation to the exposure, and its potential reversibility. With this information a safe dose to start experimentation in humans and the dose range to be explored can be defined as well as the need for specific monitoring of potential adverse events during clinical trials. According to this guideline, non-clinical studies required will depend on the stage of the development and the clinical study to be performed: the greater the population exposed and the longest the exposition time, the more data will be required. Thus, the development should follow a stepwise procedure that requires integration of the non-clinical and clinical information that becomes available.

In general, safety pharmacology studies with information on the main organs (cardiovascular, respiratory and central nervous system) is required before any exposure to humans. Non-clinical pharmacodynamic studies to investigate mechanisms of action and activity are useful for selecting the doses that can be expected to be active in humans, and before initiating human clinical trials, in vitro metabolic and plasma protein binding data for animals and humans should be available as well as systemic exposure data in the species used for toxicology. Further pharmacokinetic information is only needed when treating large numbers (phase III).

The guideline underlines that acute toxicity studies are not required as isolated studies, but information regarding acute toxicity should be obtained before phase III to characterize potential effects of an overdose, and that can it can be limited to the clinical route only.

The length of toxicity studies will depend on the length of the clinical studies they are intended to support: single dose toxicity studies should suffice to support single dose clinical trials, and repeated dose toxicity studies of duration equal or longer than the intended duration of the clinical trial treatment are required for repeated administration in humans. In general, studies should be in two mammalian species (rodent and non-rodent). It is also stressed the need to perform the studies with the route intended to be used in clinical trials.

From this guideline it can be concluded that toxicology studies in two species (rodent and non-rodent) with the final formulation to be used, with the same administration route and the same duration as the clinical trials will be required.

However, the guideline does not address the exceptional situation of products applied to the skin intending a local effect with null or negligible systemic absorption.

S7A (Safety Pharmacology Studies for Human Pharmaceuticals) [51]

This guideline sets out the minimum nonclinical safety studies necessary to initiate clinical studies. In the absence of any specific "concern" the safety pharmacology core battery should be done: CNS, Cardiovascular and Respiratory system. Further safety studies targeting other organs may be performed in a case by case basis.

The guideline states that for products applied topically for which pharmacology is well characterized and systemic availability is low, safety studies would not be necessary.

Table 10. Guidance documents reviewed

GUIDELINE TITTLE	Year	Agency	type		
Clinical investigation of corticosteroids intended for use in the skin	1987	EMA	guideline	clinical	dermatological
Questions and answers on guideline title: Clinical investigation of corticosteroids intended for use in the skin	2006	EMA	Q&A	clinical	dermatological
Pharmacokinetic studies in man	1987	EMA	guideline	clinical	general
Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents	1996	EMA	guideline	clinical	locally applied
Note for guidance on non-clinical local tolerance testing of medicinal products	2001	EMA	guideline	nonclinical	locally applied
Concept paper on the need for revision of the guideline of non-clinical local tolerance testing of medicinal products	2011	EMA	concept paper	nonclinical	locally applied
Guideline on non-clinical local tolerance testing of medicinal products. DRAFT	2014	EMA	guideline	nonclinical	locally applied
Note for guidance on photosafety testing	2002	EMA	guideline	nonclinical	general
Concept paper on the need for revision of the note for guidance on photosafety testing	2008	EMA	concept paper		

GUIDELINE TITTLE	Year	Agency	type		
Questions and answers on the "note for guidance on photosafety testing	2011	EMA	Q&A		
Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis	2004	EMA	guideline	clinical	specific disease guideline
Guidance. Topical dermatological corticosteroids: in vivo bioequivalence	1995	FDA	guideline	clinical	dermatological
Guidance for industry. Content and format of Investigational New drug applications (INDs) for phase I studies of drugs, including well characterized, therapeutic, Biotechnology-derived products	1995	FDA	guideline	nonclinical	general
Guidance for industry. Q & A. Content and format of INDs for phase I studies of drugs, including well characterized, therapeutic, biotechnology-derived products	2000	FDA	Q&A	nonclinical	general
Guidance for industry: Topical dermatological product NDA and ANDAs - In vivo bioavailability, Bioequivalence, in vitro release, and associated studies. DRAFT	1998	FDA	guideline	mixt	dermatological
Guidance for industry: photosafety testing	2003	FDA	guideline	nonclinical	general
Guidance for Industry. Acne vulgaris: developing drugs for treatment. DRAFT	2005	FDA	guideline	clinical	specific disease guideline
Guidance for industry, investigators and reviewers: Exploratory IND studies	2006	FDA	guideline	mixt	general

GUIDELINE TITTLE	Year	Agency	type		
Guidance for industry. Chronic cutaneous Ulcer and Burn Wounds - developing products for treatment	2006	FDA	guideline	clinical	specific disease guideline
Guidance for industry and review staff: nonclinical safety evaluation of reformulated drug products and products intended for administration by an alternate route. DRAFT	2008	FDA	guideline	nonclinical	general
Safety pharmacology studies for human pharmaceuticals S7A	2000	ICH	guideline	nonclinical	general
Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3 (R2)	2009	ICH	guideline	nonclinical	general
Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use	2011	ICH	guideline	nonclinical	General
M3(R2) Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions & Answers (R2)	2012	ICH	Q&A	nonclinical	general
Photosafety evaluation of pharmaceuticals S10	2013	ICH	guideline	nonclinical	General

S10 guideline (Photosafety testing of pharmaceuticals)[57]

This guideline sets out the recommendations for phototoxicity testing of pharmaceutical products and applies to new active pharmaceutical ingredients and new excipients clinical formulations for dermal application. The guideline proposes a decision algorithm to minimize the number of studies performed in animals while ensuring the information needed on the toxicity potential before human exposure.

The guideline distinguishes between photoirritation and photoallergy and proposes in vitro and in vivo non-clinical studies to assess the photoirritation potential, while discards nonclinical studies to assess photoallergy and recommends to test it in clinical studies in later stages of clinical development (during phase III).

In the case of products that absorb light in the wavelength between 290-700nm, the guideline proposes a high sensibility early screening for the phototoxic potential so that negative results can waive further studies. In vitro studies such as the 3T3neutral red uptake phototoxicity test with a cell line is an appropriate test to decide whether to continue testing or to stop it. Although in the United States, for products applied dermally, a clinical trial for photoirritation on the to-be-marketed formulation is warranted in support to product approval, for early clinical studies no further testing is needed.

Guideline on non-clinical local tolerance testing of medicinal products[58]

The guideline refers to non-clinical local tolerance testing of medicinal products, to assess tolerance at contact sites of the body following clinical use. It provides guidance on the

testing strategies to develop a product that will, or may potentially come into contact with different sites of the body. The guideline indicates that the non-clinical testing should take place before any administration in humans. For non-clinical testing of sites that might come into contact with the product accidentally (i.e. eyes) evaluation of tolerance may be delayed till later phases of the development, before large number of subjects are exposed. Local tolerance testing should be integrated in other toxicity studies with the aim of reducing animal use and "stand alone" studies are not considered. Moreover, evaluation in one species and one sex should be enough, with the intended final product at the concentration of active substance to be used in human administered at repeated doses. The species recommended for irritancy studies are rabbit or minipig.

Regarding sensitizing potential, unlike the 2001 document[59] the current guideline does not advice about timings and adequate studies.

4.1.2. Exploratory studies

The ICH (M3(R2),[29] and FDA[60] guidelines already stressed the need for early phase I approaches involving fewer resources, enabling sponsors to move ahead with the development in a more efficient way only with those drug candidates showing promising results and proposed how to do it in consistency with the regulatory requirements and maintaining the protection of exposed human subjects. The FDA guideline defines exploratory IND trials as those involving dosing of a limited number of subjects with a limited range of doses for a limited period of time aimed to assess feasibility for further development. As sponsors often provide more supporting information in their INDs than is required by the regulations, clarifying the flexibility allowed with regards to such

approaches is needed and that would allow more flexibility with regard to the preclinical testing required. Thus, for those studies in humans performed at early stages, usually first in human trials which are not aimed to elucidate the maximal tolerated doses and without therapeutic objective, may benefit from a reduced non-clinical package.

Finally an FDA guideline sets out the need for complete toxicology testing by the topical route in case of products previously approved by systemic route that are being developed for topical cutaneous use[61]

4.1.3. Clinical data

Guidance referring to in vivo bioequivalence studies has been issued to guide the development of generic medicines in dermatology. Though it is not the aim of this review to gather information on the data needed to demonstrate bioequivalence of two topical dermatological products, these guidelines give some insight on how to demonstrate bioequivalence and thus reference information on dermatopharmakokinetics and pharmacodynamic studies that can be performed with some types of products and the need to characterize the systemic exposure of certain products that may be useful for the planning of the clinical development of a new topical dermatological product.[62, 63, 64] Specific guidance for the development of generic products (mainly on bioequivalence requirements) of specific topically applied drugs is also available.[65,66]

A guideline issued in 1987 on the clinical development of corticosteroids intended for use on the skin[67] lists the specific characteristics of corticosteroids to be administered by this route that should be characterized during the clinical development. Pharmacodynamic

studies may place the new corticosteroid in the spectrum of corticosteroids by determining its potency. The induced vasoconstriction study in man may provide preliminary information of the anti-inflammatory activity of a TCE. Though it is clear from the guideline that the clinical efficacy should be tested in appropriate randomized double-blind studies, the value of the early pharmacodynamic for decision making is acknowledged. It is also stated that both psoriasis and AE are the most suitable conditions for testing clinically corticosteroids. A list of safety concerns common for all TCS that must be ruled out/characterized is provided although the timing during the development is not set up. The 2006 Q&A[68] document confirms that, the guideline, is still valid and give some insights on the use of pharmacodynamic clinical studies for bioequivalence purposes.

Human Pharmacokinetics: A European guideline issued in 1988[69] acknowledges the relevance of studying the relation between dose, plasma concentrations and therapeutic or toxic effects, but it also points out that in some cases, this may be impossible or of limited value. There's specific mention to the study of absorption of substances not intended to produce systemic effects. It is desirable to study the passage into the circulation, to rule out the possibility of systemic effects. However, there's no indication on when this information should be available during the development process.

Specific guidance on clinical development of products in atopic dermatitis and psoriasis is scarce. There's an EMA guideline issued in 2005 giving advice on the evaluation of new medicinal products for the treatment of psoriasis, with no differentiation of topical and systemically administered products.[70] As the document is intended to give guidance to applicants in planning the overall clinical development, little information is given in

reference to the early trials to proof efficacy and nonclinical data required at each stage of the development. Instead, it gives information on the duration of the pivotal trials, the need of long term safety and efficacy data and relevant endpoints. This guideline also indicates that studies with intra-individual comparisons would only be valid for exploratory trials due to the risk of cross-contamination and possibility of systemic effects and that the psoriasis plaque test can be a useful tool in exploratory phases.

Guidelines giving information on how products applied topically on the skin for other indications must be developed were also reviewed, in search of information that could be extrapolated.

A draft guidance issued by the CDER in 2005 is available, giving advice on the clinical development required for drugs intended for the topical treatment of acne. The guideline gives information on the safety requirements, pharmacokinetic studies and the sequence in which the studies should be performed during the development. Topical safety studies (phototoxicity, photoallergy…) are recommended with the final formulation and should be performed during phase II, despite some preliminary assessments of skin tolerability are advised at earlier stages of the development. In the case the products show irritation potential during phase II trials, formal irritation studies would not be necessary; otherwise, formal studies are needed. Information of systemic exposure must be obtained with the final formulation to be used, and studying the maximal area exposed, mimicking the real conditions in which it will be used.

Finally, though a guidance document for industry for the development of products for chronic cutaneous ulcers and burn wounds has been reviewed, the document reveals that

this is a very specific situation. Of note, the document points out some considerations that may be applicable to any other development regarding the measure of product absorption through the lesion and the relevance of the irritation potential as a drawback depending on the type of lesions intended to be treated.

4.2. Assessment reports search and review

4.2.1. Search results

The search for EMA EPARs retrieved only one topical medicinal product for the treatment of AE - tacrolimus - and 7 in other indications different from AE and PSO. (Table 12)

For all of them, FDA information was found and retrieved.

The results of the search for topical products approved in Spain for the treatment of Atopic eczema and Psoriasis that was done at the *Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) – Guía de Prescripción Terapéutica, Información de Medicamentos Autorizados en España* (guide last updated in 2010) is shown in table 10. Compounds for which no previous information had been found from EMA were searched at the FDA website. The search allowed finding information for 3 more products both for the treatment of AE or Psoriasis for which only FDA information is available (pimecrolimus, tazarotene and calcitriol). For the rest of the products (mainly corticosteroids) no information was available.

Table 11. Topical medicinal products approved in Spain for the treatment on AE and PSO (According to GFT)

Active principle	**Type**	**Indication**
Calcipotriol	Vit D analogue	Psoriasis
Calcipotriol + betamethasone dipropionate	Vit D analogue + TCS	Psoriasis
Calcitriol	Vit D analogue	Psoriasis
Tacalcitol	Vit D analogue	Psoriasis
Tazarotene	Retinoid	Psoriasis
Dithranol	Antracene	Psoriasis
Tacrolimus	Calcineurin inhibitor	Atopic Eczema
Pimecrolimus	Calcineurin inhibitor	Atopic Eczema
Prednicarbate	Corticosteroid	Psoriasis/AE
Methylprednisolone aceponate	Corticosteroid	Atopic eczema
Triamcinolone acetonide	Corticosteroid	Pruritus and inflammation
Mometasone furoate	Corticosteroid	Psoriasis/AE
Mometasone furoate + salicylic acid	Corticosteroid + salicylic acid	Psoriasis
Betamethasone dipropionate	Corticosteroid	Psoriasis/AE
Clobetasol propionate	Corticosteroid	Psoriasis/AE
Clobetasone butirate	Corticosteroid	AE
Diflucortolone valerate	Corticosteroid	Psoriasis/AE

Four of the products were not NME, meaning that the product had already been marketed and used by a different route and thus information was previously available. Tacrolimus, a calcineurin inhibitor for the treatment of AE, was first developed as an immunomodulator intended for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants, and thus, most of the information on the molecule regarding systemic toxicity and safety was already available at the time that the topical cutaneous indication was developed.

Calcitriol, a vitamin D analogue, which was marketed in Europe more than 2 decades ago for topical treatment of psoriasis, had been previously developed for the treatment of hyperparathyroidism, thus no documentation regarding this product has been considered.

Brimonidine and Eflornitine as topical treatments for the indication of Rosacea and hirsutism respectively were also not NME. Brimonidine, was previously approved as an ophthalmic solution for the treatment of intraocular pressure and glaucoma. It was first approved in the EU in UK in 1997 and by the FDA in 1996. No documents regarding this approval are available. Eflornitine was first approved by the FDA in 1990 as an intravenous form for the treatment of West African Trypanosomiasis and thus there's long experience of systemic use.

Seven products were developed primarily as topical treatments administered to the skin: one (pimecrolimus) for the treatment of AE and one for the treatment of psoriasis (tazarotene), and the remaining 5 were developed for topical administration to the skin in different dermatological conditions. (Table 12)

Finally, 5-aminolaevulinic acid, developed for the topical treatment of actinic keratosis in combination with photodynamic therapy was not considered because most data submitted for the approval of the product were bibliographic, as the product has been previously approved by the FDA with a different formulation. Moreover, data from the FDA was not complete regarding the preclinical testing.

Data was extracted from all products marked in bold in Table 12. Qualitative data extracted is presented in Table 13, Table 14, Table 15 and Table 16.

Table 12. Topical medicinal products approved by the EMA and FDA

Active substance	Name	Indication	Year approval	Developed primarily as topic	Documents available	Treatment schedule	Included in the review
Tacrolimus	Protopic	AE	2000/2002	No	EMA/FDA	Chronic	No
Pimecrolimus	**Elidel**	**AE**	**2001**	**Yes**	**FDA**	**Chronic**	**Yes**
Calcitriol		Psoriasis	2002/2009	No	FDA	Chronic	No
Tazarotene	**Zorac**	**Psoriasis**	**1996**	**Yes**	**FDA**	**Chronic**	**Yes**
Imiquimod	**Aldara**	**Topical treatment of external genital and perianal warts in adult patients**	**2001**	**Yes**	**EMA/FDA**	**3 times per week, maximum 16 weeks**	**Yes**
Retapamulin	**Altargo**	**Impetigo and secondary skin infections**	**2007**	**Yes**	**EMA/FDA**	**5 days**	**Yes**
5-aminolevulinic acid hydrochloride	Ameluz	Queratosis	2011/1999	Yes	EMA/FDA	Single applications	No
Eflornithine	Vaniqa	Facial hirsutism in women	2004	No	EMA/FDA	Chronic	No
Ingenol mebutate	**Picato**	**Cutaneous treatment of non-hyperqueratotic, non-hypertrophic actinic keratosis in adults**	**2012**	**yes**	**EMA/FDA**	**Once daily application for 2-3 consecutive days (depending on doses and lesion localization)**	**Yes**
Becaplermin	**Regranex**	**Chronic diabetic ulcers**	**1999**	**Yes**	**EMA/FDA**	**Up to 20 weeks**	**Yes**
Brimonidina	Mirvaso	Symptomatic treatment of facial erythema of rosacea in adult patients (currently approved as ophthalmic solution)	2013	No	EMA/FDA	Chronic	No

Table 13. Summary of preclinical data (I)

	Systemic safety studies	**In vivo PK (IV, oral) studies nº species**	**In vivo dermal PK studies n species**	**In vitro human P450 enzymes inhibition studies**	**In vitro distribution studies**	**In vitro metabolism studies**	**in vitro percutaneous absorption studies (including human)**	**In vitro Skin metabolism studies**
Elidel	Standard battery + endocrine	Mouse, rat, mini-pig	Rat, mini-pig	Yes	Yes	Yes	Yes (2 species)	Yes (human)
Zorac	Unknown	IV: Rat, rabbit, dog, cynomolgus monkey Oral: rat, cynomolgus monkey	Rat, rabbit, mouse, guinea pig	Yes	Yes	Yes	Yes human	Yes (human)
Aldara	yes, not specified	Rat, monkey, rabbit (reproduction)	Rat	Unknown	Unknown	Unknown	Unknown	Unknown
Altargo	Standard battery + renal and GI	Rat, cynomolgus monkey	Rat, rabbit, minipig	Yes	Yes	Yes	Unknown	Unknown
Picato	Standard safety battery, IV route	Rats, rabbits, dogs, minipigs	Mini-pig, rat	Yes	Rat, dog, minipig, human	Rat, dog, minipig, human	Rat, minipig, human	Rat, dog, minipig, human
Regranex	CV. considered to be acceptable for a topical product with little absorption	IV, SC. Rat, dog, cynomolgus monkey	Rat (full thickness wound application)	Unknown	Unknown	Unknown	Unknown	Unknown

GI: Gastrointestinal; CV: Cardiovascular; IV: intravenous; SC: subcutaneous; PK: Pharmacokinetic

Table 14. Summary of preclinical data (II)

	Acute toxicity studies. Oral	Acute toxicity studies. Iv	Acute toxicity studies.Dermal	Repeated dose toxicity studies. Oral	Repeated dose toxicity studies. IV	Repeated dose toxicity studies. Dermal
Elidel	Mouse, rat	Mouse, rat	rat	Mouse 2 w, 13 w Rat 13 w, 26 w Mini-pig 2w, 4w, 26 w Juvenile mini-pig 2w, 4w	No	Mouse 2 w, 4 w (FMF), 8 w (FMF), 13 w (non-fmf) Rats 13 w, 26 w Minipig 4w, 26 w Juvenile minipig 13w
Zorac	Rat, cynomolgus monkey	Rat, rabbit, dog, cynomolgus monkey	Rats, rabbits	Rat 90 days, 26 w Cynomolgus monkey 13 w, 6m, 12m	No	Rat abraded skin 4 w Mouse 4w, 13w Rat 4 w, 6m Minipig 13w, 12m
Aldara	Mouse, rat, monkey (route not mentioned)	Mouse, rat, monkey (route not mentioned)	Rabbits under occlusion	Rat up to 6 m Monkey up to 6 ms	No	Rat up to 4 m Mouse up to 4 m
Altargo	Rat, monkey	Rat	unknown	Rat 14 days, monkeys 14 days	rats 14 days	rabbit intact and abraded skin, minipigs abraded skin
Picato	No	Rat, rabbit	Minipig	No	(Bolus): Mice 7 days, rat 6 m, minipig 28 days Infusion studies (rats, dogs to support other indications), not relevant for dermal dosing	Rat 3days, rat 13 w, rat 6 m Minipig 3 days, 13 w (3 days cycles, 4 dosing cycles), 41 w (3 consecutive day cycle, total of 11 cycles)
Regranex	No	Mouse, rat, monkey (iv and SC)	No	No	Mouse, monkey (SC)	Rabbit 4 w (intact and abraded skin)

IV: intravenous; SC: subcutaneous; FMF: final formulation; m: Months; W: Weeks

Table 15. Summary of preclinical data (III)

	Reproduction studies systemic	Reproduction studies dermal application	Genotox studies	Topical carcinogenesis studies	Systemic carcinogenesis studies
Elidel	Rats and rabbits	Rats and rabbits	*In vitro, in vivo*	Mouse 52 w, rat 104 w	Oral rats 104 w, mouse
Zorac	no	Rat, rabbit	*In vitro, in vivo*	Mouse 104 w	Rat 13 w, 104w
Aldara	Rats and rabbits	Unknown	*In vitro, in vivo*	Mouse 18 m	Unknown
Altargo	rats	Unknown	*In vitro, in vivo*	no	no
Picato	Rat, rabbit	No	*In vitro, in vivo*	No	No
Regranex	No. Endogenous protein with short half life applied topically and poorly absorbed	No	*In vitro, in vivo*	No. Endogenous protein with short half life applied topically and poorly absorbed. No mutagenic	No

Table 16. Summary of preclinical data (IV)

	In vitro Phototoxicity	In vivo Phototox	In vivo photosensitization	In vivo photocarcinogenicity	In vivo skin sensitization	Local tolerance/skin irritation
Elidel	Unknown	yes	yes	no	yes	Eye irritation rabbits In vitro human epidermis model Skin sensitization in guinea pigs Local lymph node assay
Zorac	Unknown	Guinea pig	Guinea pig	Hairless mouse 12 m	Guinea pig	Ocular Rabbit
Aldara	No	No	No	YES (for melanoma indication)	No	Ocular and skin irritation in rabbits Vaginal irritancy in rats and rabbits
Altargo	Unknown	Unknown	Unknown	no	Guinea pig and mouse	Rabbits and mini-pig
Picato	No	No	NO	NO	No	No: the dermally dosed studies obviated the need for any specific local tolerance studies
Regranex	Unknown	Unknown	Unknown	No	Guinea Pig	Irritancy test in rabbits (skin, eye)

4.2.2. Summary of main findings

Systemic safety studies have been done for most of the molecules except for one in which it was justified for the negligible absorption expected. For the oldest report, it was not indicated.

In vivo systemic pharmacokinetic data are quite extensive for all molecules. However, topical (dermal) PK studies are more limited and in some species, according to the dermal toxicology guidelines, only in rodent species.

In vitro PK studies are not described or indicated in some reports, maybe due to the fact that they constitute early preliminary data which are superseded by in vivo studies at the time of the application for commercialization.

Acute toxicity has been performed by intravenous route with variable number of species studied.

Acute dermal toxicology by the dermal route is not available for all molecules. When present, it is done in less different species than toxicologies by the systemic route.

Repeated dose toxicity have been performed by systemic route (either oral or iv) always in rodent and non-rodent species and dermal route, usually in rodent and non- rodent with some exceptions in which it has been only performed in a rodent species.

Genotoxicity studies have been performed for all molecules in vivo and in vitro and carcinogenesis studies have not been performed for those products whose application is not intended to be on a chronic basis and in one case in which it has been justified due to the characteristics of the molecule.

Only the newest molecule included local tolerance testing in the dermal toxicology studies.

The timing of the implementation of studies and its duration is unknown from the reports and thus few conclusions can be drawn from the review of these reports.

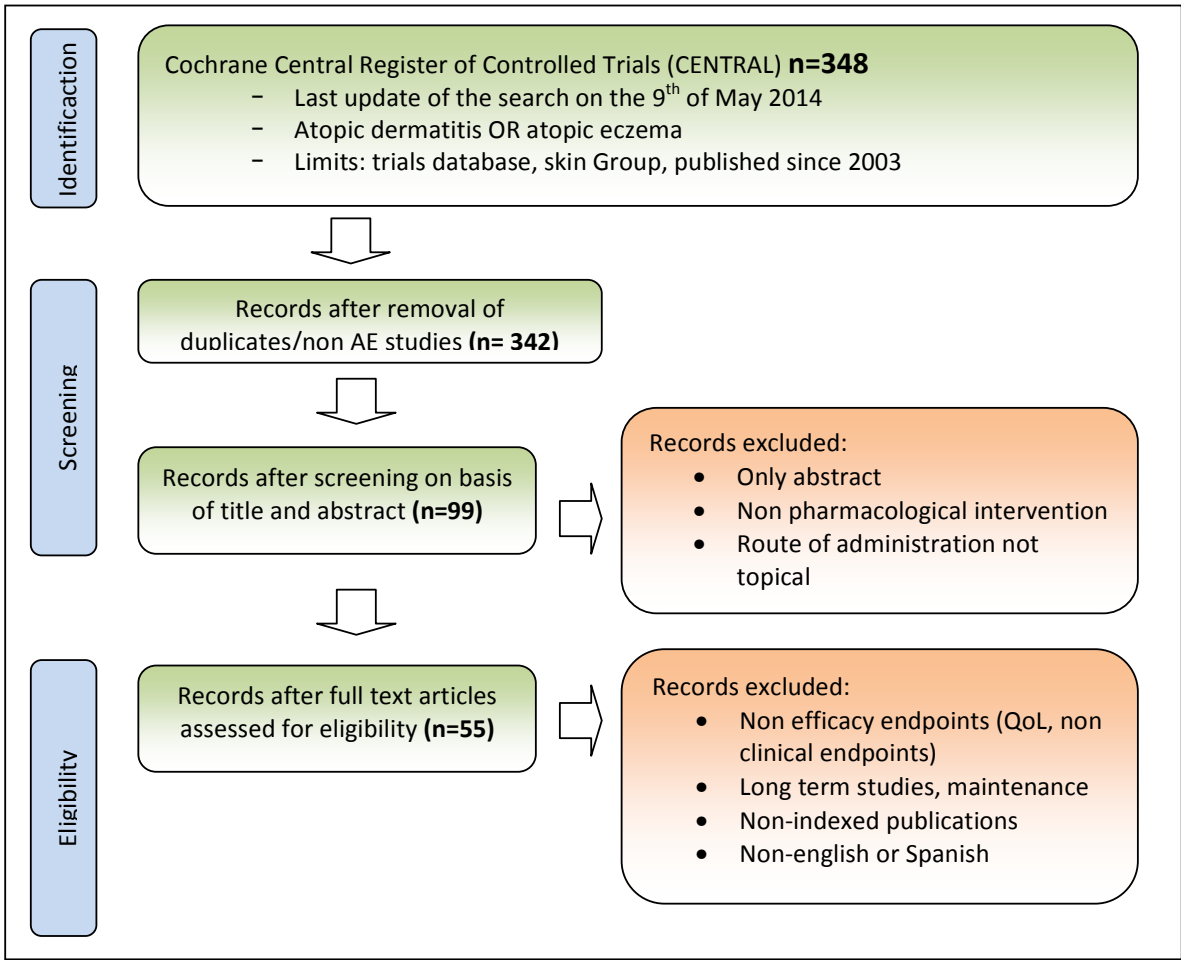
4.3. Publications of clinical trials: search and review

4.3.1. Atopic eczema

4.3.1.1. Selection of studies- AE

The overview of the selection of documents is as follows:

Figure 10. Publications reviewed for AE



With the search terms applied, 348 entries were retrieved. After the first review of titles and abstracts (if available) they were classified as full articles or abstracts presented at scientific meetings and type of intervention and route of administration of the clinical

trial. The following table shows the different categories assigned and which of them were discarded.

Table 17. Characteristics of the studies retrieved and discarded: atopic eczema

Studies in pathologies other than AE (Lupus, rectal bleeding, pitiriasis alba)	3
Studies duplicated	3
Type of intervention different from Pharmacological	129
Education programs	*19*
Diet	*4*
Physical therapies	*23*
Phototherapy	*10*
Probiotics/prebiotics	*31*
Herbs & natural remedies	*21*
Soaps/bath products	*20*
Homeopathy	*1*
Intervention unknown	4
Other (no CT to evaluate treatments)	5

From the 204 left, all which were not topical administrations were discarded

Table 18. Routes of administration: atopic eczema

Route of administration of the treatment other than topical	42
Intradermal	*4*
Intranasal	*1*
Intravenous	*1*
Subcutaneous	*3*
Sublingual	*1*
Oral	*27*
Unknown	*5*

From the 162 registries left, only 107 had a full article published. For 8 references, the full article was not obtained, due to non-indexed publications that made it difficult to localize the article, or due to language.

From the rest of the studies a second reading of the abstracts and in some cases of the full articles allowed to exclude the following registries:

Table 19. Other reasons for exclusion: atopic eczema

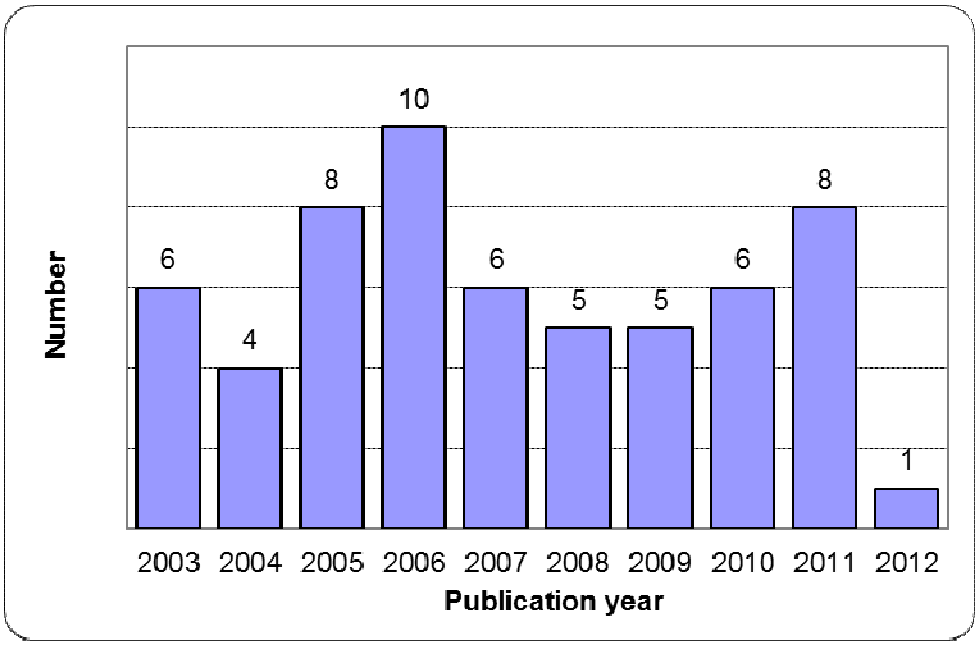
Non AE	2
Facial AE only	4
Oral treatment	1
Comparison of an oral versus topical treatment	1
Treatment with laser	1
Articles were a subanalysis of 3 studies previously reported	2
Study to validate measures	1
The type of endpoint identified was not efficacy (QoL, economic evaluation, utility measures, effect on growth…)	11
Studies were not included because the intervention was a long term maintenance approach to prevent flares.	15
Studies were excluded because they clearly had a non-inferiority objective.	4
Severe quality issues	1
Exclusively PK study	1

Thus, information was extracted from 55 publications. In 2 cases, the article reported 2 different studies and in 1 case 3 different studies which were treated as independent entries in the database. Finally, a database with 59 studies was obtained.

4.3.1.2. General description of the studies- AE

The years of publication are summarized in the figure below.

Figure 11. Year of publication of studies- AE



Regarding the general approach to the study design, 42 trials (71.2%) had a parallel comparison design, while 17 trials (28.8%) had an intra subject comparison design.

The main characteristics of the studies reviewed are summarized in Table 20, separately for studies with parallel and intra-patient comparison designs, and overall.

Table 20. Main study characteristics according to the study design – atopic eczema

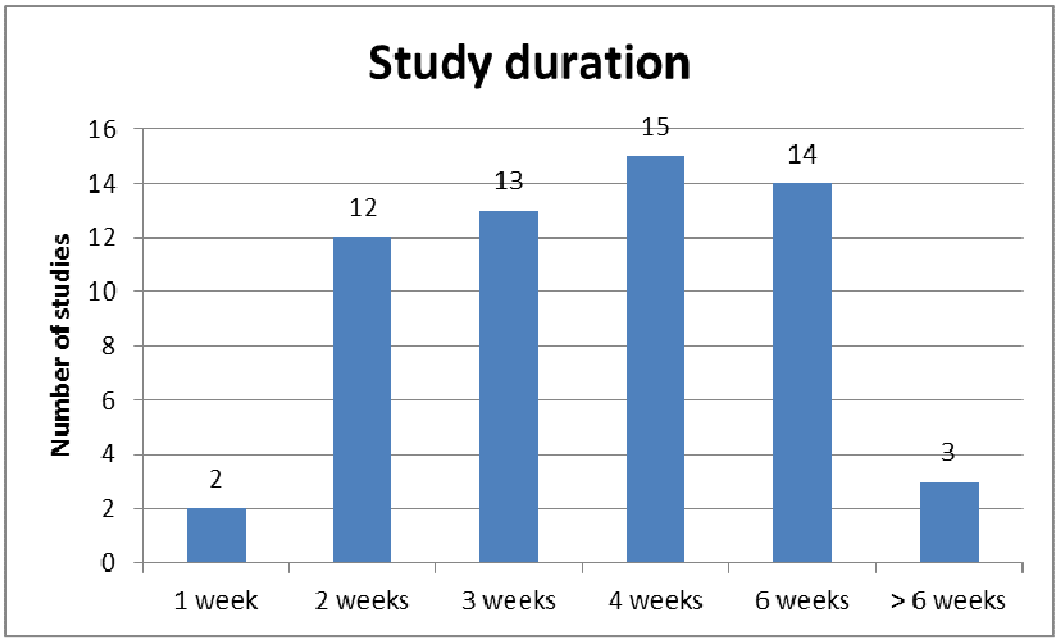
	Parallel		**Intra-patient**		**Total**	
	N	%	N	%	N	%
Design						
Parallel					42	71.2
Intra-patient comparison					17	28.8
Centers						
Unicentric	7	16.7	11	73.3	18	30.5
Multicentre	30	71.4	3	20	34	57.6
Unknown	5	11.9	1	6.7	7	11.9
Number of interventions						
2	36	85.7	14	93.3	52	88.1
3	6	14.3	1	6.7	7	11.9

	Parallel		Intra-patient		Total	
	N	%	N	%	N	%
Controlled with vehicle						
Yes	25	59.5	6	40.0	33	55.9
No	17	40.5	9	60.0	26	44.1
Duration of treatment						
1 week	1	2.4	0	0.0	2	3.4
2 weeks	7	16.7	4	26.7	12	20.4
3 weeks	9	21.4	4	26.7	13	22.0
4 weeks	11	26.2	4	26.7	15	25.4
6 weeks	12	28.6	2	13.3	14	23.7
> 6 weeks	2	4.8	1	6.7	3	5.1
Age of participants						
Only children	20	47.6	5	33.3	25	42.4
Children+adults	10	23.8	3	20.0	13	22.0
Only adults	10	23.8	6	40.8	18	30.5
unknown	2	4.8	1	6.7	3	5.1
Blinding						
Open	1	2.4	5	33.3	1	1.7
Double blind	31	73.8	3	20.0	41	69.5
Blind evaluator	7	16.7	6	40.8	14	23.7
Unknown	3	7.1	1	6.7	3	5.1
Administrations/Day						
1	3	7.1	2	13.3	5	8.5
2	37	88.1	11	73.3	48	81.3
3	2	4.8	2	13.3	4	6.8
As needed	0	0.0	0	0.0	2	3.4
Assignation ratio						
Balanced	33	78.6	15	100.0	50	84.7
Unbalanced	9	21.4	0	0.0	9	15.3
Overall study duration						
≤ 3 months	3	7.1	1	6.7	4	6.8
4-6 months	5	11.9	1	6.7	7	11.9
7- 12 months	5	11.9	4	26.7	9	15.3
> 1 year	4	9.5	1	6.7	5	8.5
Unknown	25	59.5	8	53.3	34	57.6
Number of patients						
≤ 30	3	7.1	11	73.3	14	23.7
> 30 ≤ 60	8	19.1	2	13.3	11	18.6
> 60 ≤ 100	6	14.3	2	13.3	9	15.3
> 100 ≤ 200	9	21.4	0	0.0	9	15.3
> 200 ≤ 300	9	21.4	0	0.0	9	15.3
> 300	7	16.7	0	0.0	7	11.9
	Mean (SD)	Min –Max	Mean (SD)	Min –Max	Mean (SD)	Min –Max
Number of patients	180.976 (149.45)	16-624	34.8 (24.26)	15-96	139.4 (142,4)	15- 624

Most studies included patients with mild to moderate intensity AE patients although a few studies included patients with severe AE. Most studies were multicentre and with a parallel design. Among studies with intra-patient comparison, different approaches were found (comparison of lesions, body side or extremities and cross-over designs). Most parallel designs were multicentre, while the majority of intra-patient design studies where unicentric. Roughly one fourth of trials had a single blind design.

The overall study duration was up to 4 weeks in most (71.2%) studies (Figure 12), likely to accommodate for 28 days toxicology coverage, and lower in studies with intra-subject comparison design.

Figure 12. Duration of clinical trials- AE

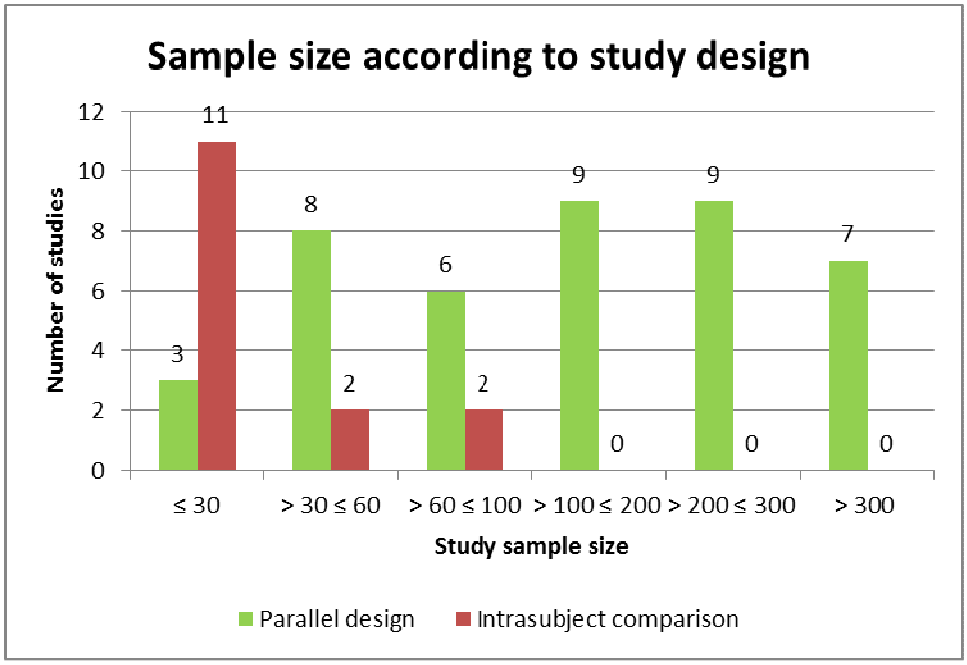


Other differences observed between the different approaches where the age of patients (parallel studies mostly performed in children and the other way round with intra-subject designs) and the blinding (intra-patient studies were less frequently double blinded).

Most studies compared an active test treatment with placebo vehicle (47.5%), and 32.2% compared two actives. Other types of comparisons were less frequent.

The mean number of patients included in the study was higher for parallel studies. While all intra-patient studies included less than 100 patients (and 82.4% less than 60 and 64.7% less than 30), in parallel studies 59.2 included more than 100 patients (Figure 13). Average number of subjects included in intra-subject comparisons was smaller (34.8 subjects) than in parallel comparison designs (181.0 subjects)

Figure 13. Sample size of clinical trials by design type- AE



In nearly all studies, the product application was performed at home by the patient (or parents). Only in one case it was stated that the investigator did the applications on visit days.

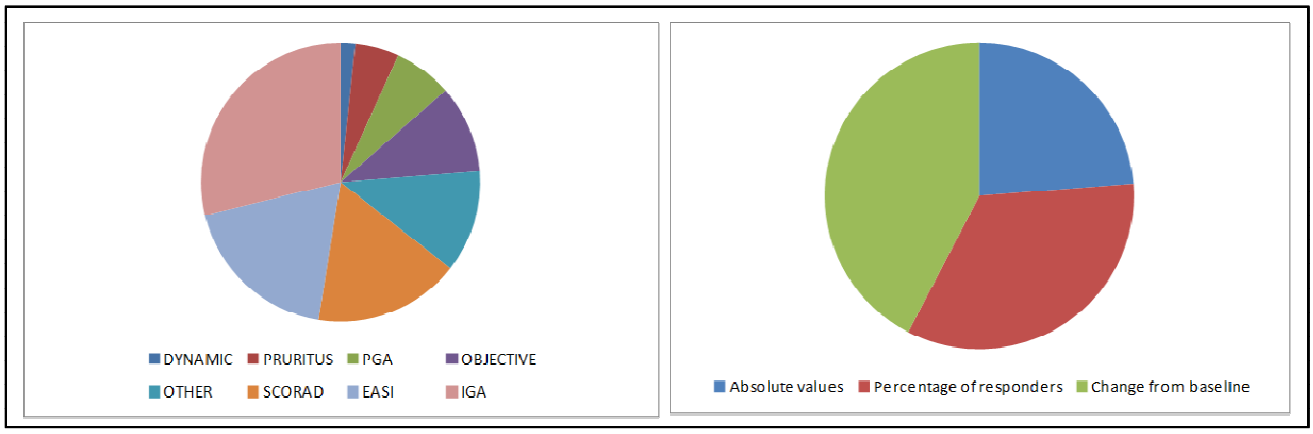
Regarding quality of reporting, in 7 studies the approval by an EC was not stated, in 11 studies, the need for informed consent was not mentioned, and formal sample size calculation was missing in 34 studies. Treatment compliance was only mentioned in 16 study publications, of those, the mentioned methods were the patient diaries, weighing of the returned tubes or counting returned containers.

4.3.1.3. Type of main variables- AE

Main variables included the Investigator Global Assessment (17 studies), the EASI and modified EASI (11 studies), the SCORAD and modified SCORAD (10 studies), and Patient Global Assessments (4 studies). In 3 studies the main variable was pruritus measured as a VAS or by means of a severity score.

Objective variables such as transepidermal water loss (TEWL), bacterial colonization or microcirculation measured by laser Doppler were also used in 6 studies, in which the main outcome was not clinical. Only in one study a dynamic investigator assessment of change was used.

Figure 14. Main clinical variables used in the studies – atopic eczema



Other clinical main variables were used in 7 studies, including the three items severity score, a modified SASSAD, a total symptoms score, and other grading systems (see Table 21 for more detail).

Table 21. Main variables used in the studies – atopic eczema

	Parallel		Intra-patient		Crossover		Total	
Scale	N	%	N	%	N	%	N	%
IGA	14	33.3	3	20.0	0	0.0	17	28.8
EASI	9	21.4	2	13.3	0	0.0	11	18.6
SCORAD	8	19.0	2	13.3	0	0.0	10	16.9
PGA	3	7.1	1	6.7	0	0.0	4	6.8
Pruritus	1	2.4	0	0.0	2	100.0	3	5.1
Dynamic Scale	0	0.0	1	6.7	0	0.0	1	1.7
Other scales ***G**rading score 0-4 AD signs* ***M**odified Costa's simple scoring method* ***M**odified SASSAD score* ***T**IS (Three Item Severity) score* ***T**otal AD score* ***T**otal symptom Score (TSS)*	4	9.5	3	20.0	0	0.0	7	11.9
Objective biologic measures ***E**pidermal Water content* ***B**acterial colonization* ***E**LAM-1* ***M**icrocirculation (laser Doppler)* ***D**rug plasma levels* ***T**EWL*	3	7.1	3	20	0	0.0	6	10.2
Total	42	100.0	15	100.0	2	100.0	59	100.0

The main outcomes were most frequently analyzed as change from baseline (25 studies) or percentage of patients with response, mainly defined as IGA 0-1 (in 20 studies).

Table 22. Analyses applied to main outcomes – atopic eczema

	Parallel		Intra-patient		Crossover		Total	
	N	%	N	%	N	%	N	%
Absolute value	12	28.6	2	13.3	1	50.0	14	23.7
Change from baseline	13	31.0	10	66.7	1	50.0	24	40.7
% of responders	17	46.5	3	20.0	0	0.0	20	33.9
Total	42	100.0	15	100.0	2	100.0	59	100.0

4.3.1.4. Statistical significance for main variable- AE

While a 62% of the studies with a parallel design reached statistical significance for the main study variable, only 47% of intra-subject studies obtained statistically significant results for the main variable.

In general, studies with larger number of patients reached statistical significance more frequently. For parallel design studies, the mean number of patients for studies reaching statistical significance was 214 while for those not reaching it was 126.

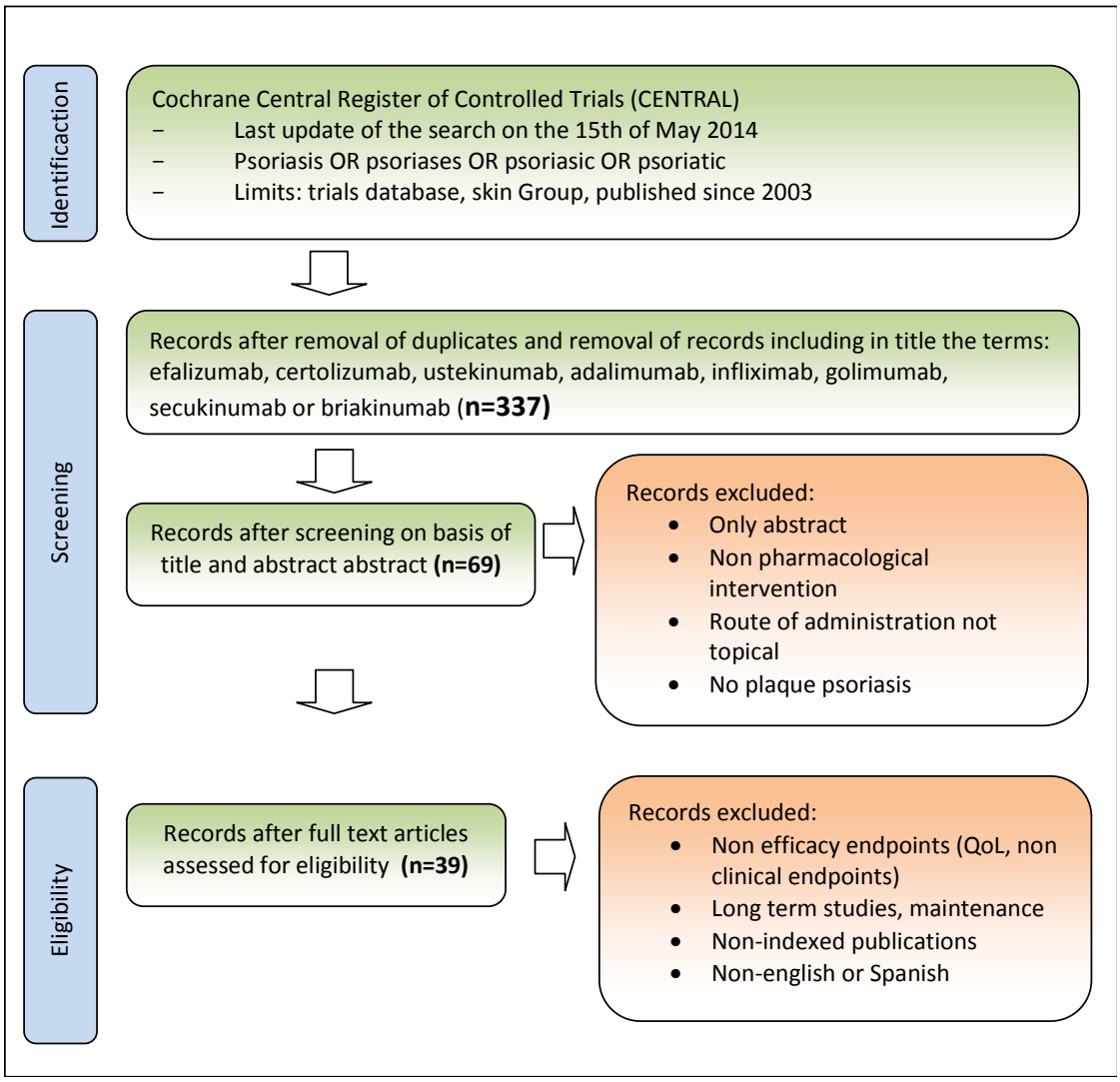
For intra-subject design studies, the mean number of patients for studies with a statistically significant result for the main variable was 45 versus 25 for non significant studies.

4.3.2. Psoriasis

4.3.2.1. Selection of studies- Psoriasis

The overview of the selection of documents is as follows:

Figure 15. Publications reviewed - Psoriasis



With the terms applied, 337 entries were retrieved

After the first review of titles and abstracts (when available) entries were classified as full articles or abstracts presented at scientific meetings and type of intervention and route of

administration of the clinical trial and the type of psoriasis. The following table shows the different categories assigned and which of them were discarded.

Table 23. Type of intervention: Psoriasis

Type of intervention different from Pharmacological	98
Education programs	*8*
Diet	*2*
Physical therapies	*1*
Phototherapy	*71*
Biological products	*12*
Soaps/bath products	*2*
Intervention unknown	2
Other (no CT to evaluate treatments or treatment of symptoms different to cutaneous)	11

This first screening left 228 entries, from which all clearly non topical administrations were discarded.

Table 24. Route of administration: Psoriasis

Route of administration of the treatment other than topical	85
Intradermal	*1*
Intramuscular	*7*
Intravenous	*20*
Subcutaneous	*4*
Parenteral	*1*
Oral	*46*
Unknown	*6*

From the 143 registries left, all which were clearly studies in psoriasis different than plaque psoriasis where also excluded

Table 25. Type of psoriasis

No plaque psoriasis	23
Palmoplantar only	*2*
Nail psoriasis	*3*
Scalp psoriasis	*17*
*Atopic dermatitis**	*1*

* Already identified in the AD search

From the 120 left, 51 were not published as full articles.

For 5 references, the full article was not obtained due to non indexed publications that made it difficult to localize the article or due to language.

From the rest of the studies a second lecture of the abstracts and in some cases of the full articles allowed to exclude the following registries:

Table 26. Other reasons for exclusion: psoriasis

Non psoriasis (AE* and alopecia areata)	2
Intervention tested: soap	1
Type of psoriasis different than plaque psoriasis	8
Combination with oral treatment	2
The type of endpoint identified was not efficacy (QoL, adherence, long term prophylaxis…)	10
Oral administration	1
Only title, with no mention to randomization and design	1

* Already identified in the AE search

Thus, information was extracted from 39 publications. In one case the article reported 2 different studies which were treated as independent entries in the database. Finally, a database with 40 cases was obtained.

Finally, a separate search and assessment has been done for plaque assay studies. Our initial search found only 2 psoriasis plaque tests and one of them was initially discarded because the treatment tested was intended for scalp psoriasis.[71] As we figured out that this could be due to the fact that this type of studies might not be classified as clinical trials, we performed a specific search for “Psoriasis plaque test” or “Scholtz-Dumas bioassay” or “microplaque assay” without further limits. The new search allowed us to recover the initially discarded article and to review 11 additional publications reporting results of this type of studies. The characteristics of these 13 studies have been summarized in Table 27.

Results are described in section 4.3.2.2. on the basis of 39 publications (40 studies) initially identified.

Table 27. Summary of Psoriasis plaque test studies

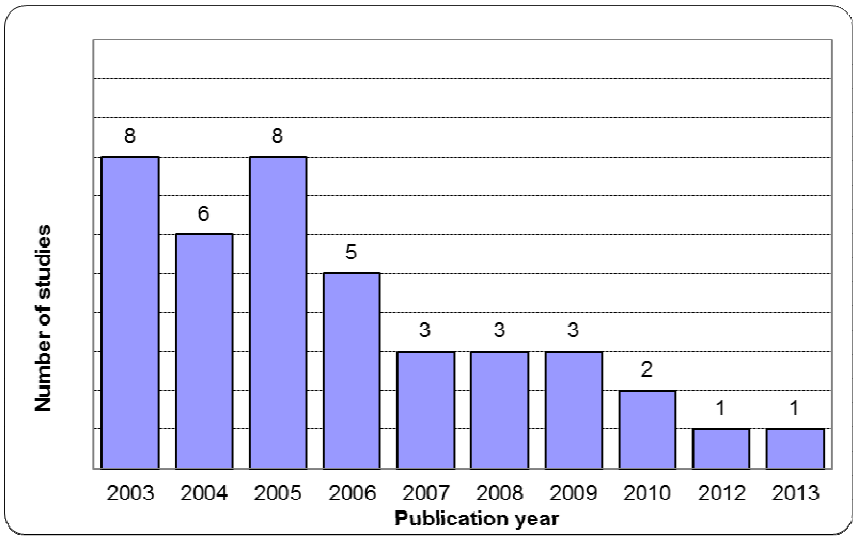
Author	Year	N	Test fields	Application	Treatment duration	Occlusion	Assessments
Snape SD et al[72]	2016	15	6	Daily	3w	Yes	US(weekly)
Queille-Roussel C et al[73]	2015	24	4	Daily (d1-6)	4w	Non occlusive	Clinical (twice weekly) TCS
Queille-Roussel C et al[74]	2013	22	5	Daily (d1-6)	3w	Non occlusive	Clinical (twice weekly) TCS
Queille-Roussel C et al[74]	2013	24	8	Daily (d1-6)	3w	Non occlusive	Clinical (twice weekly) TCS
Queille-Roussel C et al[75]	2012	24	6	Daily (d1-5)	3w	Non occlusive	Clinical (twice weekly) TCS
Korting HC et al[76]	2012	22	3	Daily (d1-6 and 8-11)	12 days	Yes	US and clinical D4, 8 & 12
Buder K et al[77]	2010	14	7	Daily	11 days	Yes	Clinical sum score
Lee CS et al[78]	2009	5	4	Day 1, 3, 5, 7, 10 and 12	12 days	Yes	Clinical
Geilen CC et al[79]	2000	7	2	Daily	3w	Yes	Clinical sum score
Remitz A et al[80]	1999	16	6 + 6	Day 0, 2, 5, 7, 9 and 12	2w	Yes	Clinical (weekly)
Mrowietz U et al[81]	1998	10	4	Daily	2w	Yes	Daily scoring
Rappersberger K et al[82]	1996	15	4	Daily	10days	Yes	Clinical Scoring every other day
Bangha E et al[83]	1996	10	3				Chromametry, visiometry, US

US: Ultrasonography; TCS total clinical score

4.3.2.2. General description of the studies - Psoriasis

Most of the studies were published at the beginning of the studied period, with few clinical trials reported by or after 2010. Figure 16 shows the date of publication of the studies described

Figure 16. Date of publication of studies - psoriasis



Regarding the general approach to the study design, 19 trials (47.5%) had a parallel comparison design, while 21 trials (52.5%) had an intra-subject comparison design.

The main characteristics of the studies reviewed are summarized in Table 28 separately for studies with parallel and intra-patient comparison designs, and overall.

Table 28. Main study characteristics according to the study design - psoriasis

	Parallel		Intra-patient		Total	
	N	%	N	%	N	%
Design						
Parallel					19	47.5
Intra-patient comparison					21	52.5
Centers						
Unicentric	3	15.8	16	76.2	19	47.5
Multicentre	16	84.2	3	14.3	19	47.5
Unknown	0	0.0	2	9.5	2	5.0
Number of interventions						
2	10	52.6	17	81.0	27	67.5
3	7	36.8	1	4.8	8	20.0
4	2	10.5	2	9.5	4	10.0
7	0	0.0	1	4.8	1	2.5
Controlled with vehicle						
Yes	9	47.4	14	67.7	23	57.5
No	10	52.6	7	33.3	17	42.5
Duration of treatment						
1 week	1	5.3	0	0	1	2.5
2 weeks	2	10.5	2	9.5	4	10.0
3 weeks	0	0.0	1	4.8	1	2.5
4 weeks	5	26.3	3	14.3	8	20.0
6 weeks	0	0.0	1	4.8	1	2.5
8 weeks	4	21.1	7	33.3	11	27.5
12 weeks	7	36.8	7	33.3	14	35.0
Age of participants						
Only children	0	0.0	0	0.0	0	0.0
Children+adults	2	10.5	1	4.8	3	7.5
Only adults	17	89.5	18	85.7	35	87.5
unknown	0	0.0	2	9.5	2	5.0
Blinding						
Open	1	5.3	1	4.8	2	5.0
Double blind	9	47.4	9	42.9	18	45.0
Single blind	2	10.5	2	9.5	4	10.0
Blind evaluator	6	31.6	6	28.6	12	30.0
Unknown	1	5.3	3	14.3	4	10.0
Administrations/Day						
1	3	15.8	2	9.5	5	12.5
2	13	68.4	13	61.9	26	65.0
3	2	10.5	1	4.8	3	7.5
Other	0	0.0	2	9.5	2	5.0
unknown	1	5.3	3	14.3	4	10.0
Assignation ratio						
Balanced	13	68.4	21	100.0	34	85.0
Unbalanced	5	26.3	0	0.0	5	12.5
Unknown	1	5.3	0	0.0	1	2.5

	Parallel		Intra-patient		Total	
	N	%	N	%	N	%
Overall study duration						
≤ 3 months	1	5.3	1	4.8	2	5.0
4-6 months	3	15.8	2	9.5	5	12.5
7- 12 months	1	5.3	0	0.0	1	2.5
> 1 year	2	10.5	1	4.8	3	7.5
Unknown	12	63.2	17	81.0	29	72.5
Number of patients						
≤ 30	2	10.5	12	57.1	14	35.0
> 30 ≤ 60	2	10.5	8	38.1	10	25.0
> 60 ≤ 100	2	10.5	0	0.0	2	5.0
> 100 ≤ 200	5	26.3	1	4.8	6	15.0
> 200 ≤ 300	1	5.3	0	0.0	1	2.5
> 300	7	36.8	0	0.0	7	17.5
	Mean (SD)	Min –Max	Mean (SD)	Min –Max	Mean (SD)	Min –Max
Number of patients	292.8 (307.8)	18-1028	33.9(32.6)	5-168	156.85 (247.8)	5 - 1028

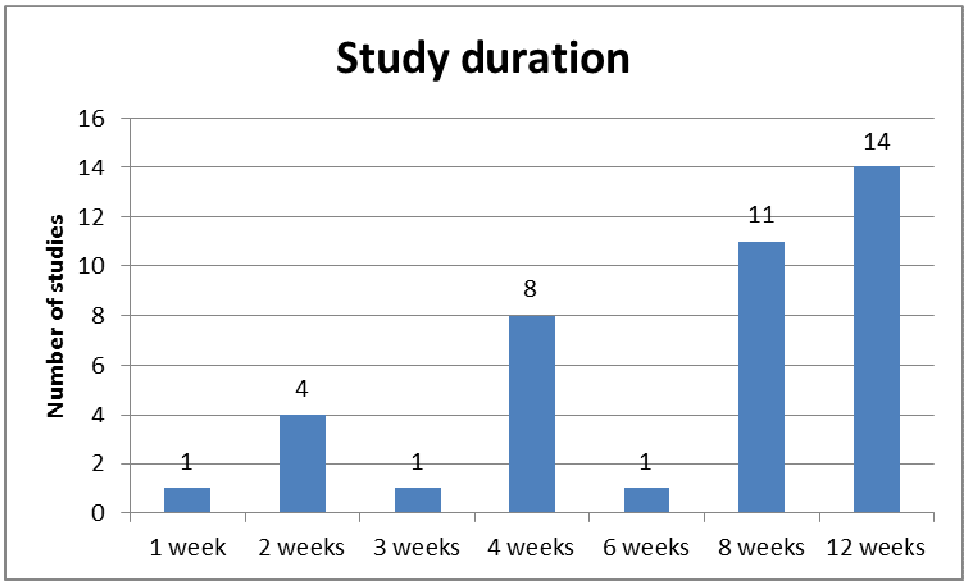
The severity of psoriasis varied from mild to severe, although in 8 studies there was no mention of the intensity of the disease either as mild-moderate or severe or defining a minimum or maximum Body Surface Area (BSA) or scores for symptoms (for the whole body or target plaques). In studies with intra-patient comparison designs, the severity of the disease was more frequently missing.

Half of the studies were multicenter and half unicentric, and the parallel design was found in less than half of the publications. 84.2% of the parallel designs were multicenter, while the majority (76.2%) of intra-patient design studies where unicentric. Among studies with intra-patient comparison, different approaches were found (comparison of lesions, body side or extremities or different areas in the same psoriasis plaque).

Roughly one third of studies were conducted under single blind conditions.

The study duration was in average longer for psoriasis trials than for atopic eczema trials, so that 40% of trials had durations in excess of 4 weeks (Figure 17).

Figure 17. Duration of clinical trials- psoriasis



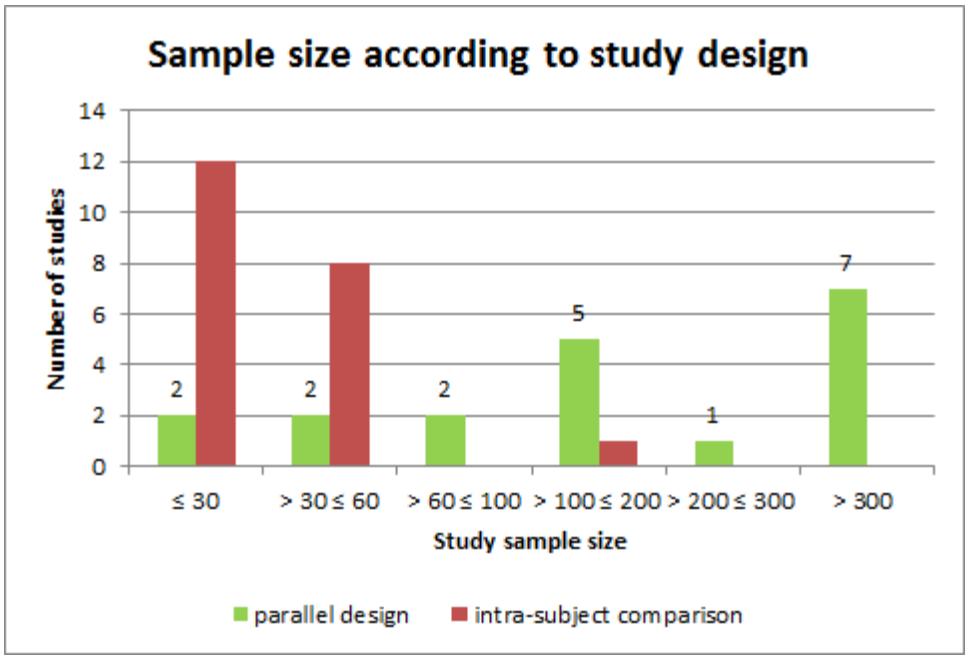
Other differences observed between the different design approaches were the number of interventions, and the ratio of assignment.

Regarding the treatment arms of the study, most studies had two or 3 treatment arms, this was pronounced in intra-patient studies, where 81% of studies had only 2 treatments tested. When analyzing which type of treatments were compared, 32.5% of studies tested one active versus vehicle and 20% compared two actives. 17.5% of studies tested different formulations either comparing them with vehicle or with other active treatments. 12.5% of studies tested different strengths of the same compound. Only two studies tested different actives versus vehicle. Finally, few studies compared different combinations.

The mean number of patients included in the study was higher for parallel studies. Nearly all intra-patient studies included less than 100 patients and more than half included less than 30 patients (Figure 18).

The average sample size was larger for parallel trials (292,8 subjects) than for intra-subject comparisons (33,9 subjects). One parallel comparison psoriasis trial had up to 1028 subjects.

Figure 18. Sample size of clinical trials by design type



In most studies, the product application was performed ambulatory by the patient (87.5%). Only in three cases the application was done at the center or by a nurse (intra-patient designs) and in one case it was a mix of both patient and nurse on visit days.

Regarding quality of reporting, in 7 studies the approval by an EC was not stated, in 9 cases, the need for informed consent was not mentioned and formal sample size calculation was missing in 24 studies. Treatment compliance was only mentioned in 11 study publications, of those, the mentioned methods were the weighing of the returned tubes and patient interview or patient diary.

4.3.2.3. Type of main variables- Psoriasis

Main variables included the Psoriasis Area and Severity Index which was the most frequently used main variable in parallel studies, the sum of signs scores (sum of severity scoring of erythema, scaling and induration with different scores ranges) and the sum of the scores of these signs plus the pruritus score, measured for each lesion. The IGA was also used in some studies also with different scorings, and only two studies (intra-subject both) used dynamic approaches. Also in one study the approach of "best lesion" was used.

Figure 19. Variables used in the studies – psoriasis

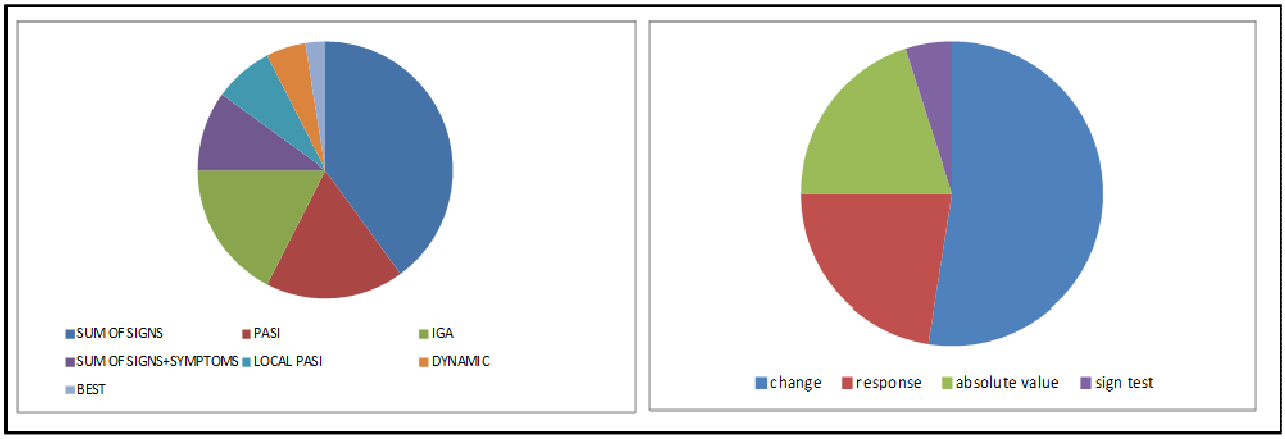


Table 29. Main variables used in the studies – psoriasis

	Parallel		Intra-patient		Total	
Scale	N	%	N	%	N	%
Sum of signs scores	4	21.1	12	57.1	16	40.0
PASI	7	36.8	0	0.0	7	17.5
IGA	5	26.3	2	9.5	7	17.5
Sum of signs + symptoms score	2	10.5	2	9.5	4	10.0
Local PASI	1	5.2	2	9.5	3	7.5
Dynamic Scale	0	0.0	2	9.5	2	5.0
Best lesion	0	0.0	1	4.8	1	2.5
Total	19	100.0	21	100.0	40	100.0

The most frequently used main outcomes were change from baseline (21 studies) and percentage of patients with defined response and absolute values were less frequent.

Table 30. Analyses applied to main outcomes - psoriasis

	Parallel		**Intra-patient**		**Total**	
	N	%	N	%	N	%
Absolute value	3	15.8	5	23.8	8	20.0
Change from baseline	10	52.6	11	52.4	21	52.5
% of responders	6	31.6	3	14.3	9	22.5
Sign test	0	0.0	2	9.5	2	5.0
Total	19	100.0	21	100.0	40	100.0

4.3.2.4. Statistical significance for main variable - Psoriasis

Statistical significance was obtained for the main study variable in 73.3% of the studies with a parallel design, while only 52.4% of intra-subject studies were obtained statistically significant results. In general, patients with larger number of patients reached statistical significance more frequently.

This was especially evident for parallel designs, where studies reaching statistical significance had a mean number of included patients of 374 subjects, while the mean sample size of studies not reaching statistical significance for the main variable was 65 subjects. For intra-subject studies, there was not such a clear difference as even studies with very small sample size reached statistical significance for the main variable (N=41 and 27 for non significant and significant respectively).

4.3.3. Identification of study designs

Four main types of studies were identified to assess the activity of a product applied topically on the skin.

4.3.3.1. Randomized, inter-subject parallel study:

In this design patients are randomized to be treated with one of two or more treatments. Patients treat all lesions and the severity of the disease is assessed for the whole body even if a target lesion for each patient may be identified and assessed individually. The duration of treatment is usually at least 4 weeks. Most frequently only two interventions are compared, but occasionally more than 2 treatments are compared. The severity of the disease is pre-specified in the inclusion criteria.

Parallel studies in AE included a mean of 181 patients, with 43% of studies including more than 100 patients and 17% more than 300 patients. For PSO studies, the mean sample size in parallel studies was 293 patients with around 70% of studies with more than 100 patients and 36% of studies with more than 300 patients.

The most frequently used variables were changes from baseline in whole body measures, such as PASI or SCORAD and global impression scales; other variables such as quality of life or analytical measures (biomarkers) were applied for secondary analysis. Pharmacokinetics, either in all subjects or in a selected subgroup, is often included as a secondary objective. A multicenter approach is generally used.

4.3.3.2. Randomized, intra-subject parallel study

In this design, the same patient receives two (or more) treatments. Treatments may be applied in two similar and symmetric lesions, in two extremities, or on each half of the

body. The maximum difference in the severity of the lesions to compare, as well as the size, is established in the inclusion criteria. There are no whole body assessments, only the effects of the treatment on the lesion are evaluated. If the unit of assignment is the lesion the amount of product applied is small.

For AE studies the duration of treatment is short and only 20% of studies have treatment duration longer than 4 weeks. However, the studies in PSO with this design generally test longer treatments. Thus, the duration of treatment may depend more on the characteristics of the treatment applied and the disease treated than on the study design.

In general, less than 100 patients are included in these studies, with most of them including less than 30 patients

Typically, outcome variables include either investigators global assessment of the severity of the selected lesion, or the sum of scores grading of the signs of the lesion. Assessments are frequently dynamic and analyzed as improvement or change from baseline, but an analysis of responders is sometimes applied using thresholds for changes from baseline or percentages of skin clearance. Because two lesions are treated in the same subject, a direct comparison assigning a “winner” lesion is also possible.

These studies are generally performed at one study site only, which is usually a dedicated unit at a CRO or academic center. To avoid unblinding due to organoleptic characteristics, mixing of products or application mistakes, sometimes a third party application is used so that the subject is visited daily for product application by study personnel. When this is done, often subjects receive travel allowances or even volunteer compensation. The latter recognizes the lack of therapeutic benefit of treating limited areas of skin.

4.3.3.3. Randomized, cross over study

In this design, the same patient receives two (or more) treatments but in subsequent periods of time, separated by a washout period. Patients are randomized to the sequence in which the treatment is administered. Only two studies were identified that used this design, both in AE, and both used pruritus as the main outcome measures. No other applications of the crossover design were identified.

4.3.3.4. Pharmacodynamic studies

Although objective variables such as transepidermal water loss (TEWL), bacterial colonization or microcirculation measured by laser Doppler have been used in atopic eczema, they are not regarded in general as predictive of efficacy in a clinical setting; they are mostly considered as useful for assessment of individual components of the product effects, rather than useful proof of concept studies.

Contrarily, consistent approach to proof of concept in psoriasis through the plaque assay has been identified as a frequent pharmacodynamic approach to clinical proof of concept. In these studies the same patient receives different treatments on the same lesions at the same time. Several treatments can be tested in the same affected area/plaque, with minimal product application and short duration. This type of study generally tests several formulations/compounds at the same time in the same patient, and includes a limited number of patients with big, stable and homogeneous psoriasis plaques allowing for multiple similar testing sites within the same lesion. Whether psoriasis is stable is usually checked during a 2 week screening period. Once the patient is selected, the test sites are delimited. There are several variations in the size, shape, number and location of the test

sites among different studies but they are standardized in detail in each study. A pre specified amount of test product is applied, which may vary depending on the size of the test site, but in all cases is less than the intended for clinical use. In the original assay described by Scholtz-Dumas Back in 1967 the application sites were covered (occlusive application). Variations of this test consist on different degrees of occlusion or even non occlusion. Due to the complexity of the applications, they are performed at the test centers by a nurse. Some of the study treatment schedules include once daily or every other day applications, or may skip weekends to manage recruitment and compliance problems.

Clinical assessments are performed before reapplications or less frequently, and treatment duration typically does not exceed 4 weeks. Even if it's not the main variable, most studies include ultrasound measures of skin thickness and inflammation, skin biopsies or any other type of non-invasive objective measures.

Pharmacokinetics are not routinely done in these studies since the applied amount of drug is extremely small.

4.4. Design of an exploratory development plan

Taking the previous designs identified into consideration, the following scenarios for exploratory development plans have been created.

4.4.1. Development plans for atopic eczema

Since pharmacodynamics models are not applicable to atopic eczema, the following two scenarios have been considered:

- Scenario 1: Proof of concept based on a conventional parallel clinical trial
- Scenario 2: Proof of concept based on an intra-subject comparison clinical trial

A brief description of the clinical trials and a list of preclinical data is presented in Table 31 for each scenario, and the calendar planning is shown in Figure 20 and Figure 21. The detailed plans can be found in annex I.

4.4.2. Development plans for psoriasis

Three scenarios have been considered for psoriasis:

- Scenario 1: Proof of concept based on a conventional parallel clinical trial or
- Scenario 2: Proof of concept based on an intra-subject comparison clinical trial
- Scenario 3: Proof of concept based on a psoriasis plaque test

A brief description of the clinical trials and a list of preclinical data is presented in Table 32 for each scenario. Figure 22, Figure 23 and Figure 24 provide an overview of the calendar planning of each scenario. The detailed plans can be found in annex II.

Table 31. Summary of development plans for 2 different scenarios in atopic dermatitis

	Scenario 1	**Scenario 2**
PoC study	Double-blind randomized parallel groups proof of concept study comparing the product at low strength, medium strength and high strength, placebo and reference active product when applied for 28 days.	Double-blind randomized within subject proof of concept study comparing the product at low strength, medium strength and high strength, placebo and reference active product when applied for 28 days to lesions of patient-volunteers with mild to moderate plaque psoriasis affecting symmetrical flexural areas.
Non-clinical studies	• In vitro target/receptor profiling • Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection • Core battery of safety pharmacology • Genotoxicity: o Ames assay (Bacterial mutation assay) o Mammalian cell assays (in vitro/in vivo) • Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to different animal species. • Toxicities up to 28 days by the oral route in two species (one non-rodent). • Cutaneous route toxicology up to 28 days, including tolerability assessment in two species (one non-rodent) • Toxicokinetic supportive studies.	• In vitro target/receptor profiling • Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection • Core battery of safety pharmacology • Genotoxicity: o Ames assay (Bacterial mutation assay) o Mammalian cell assays (in vitro/in vivo) • Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to different animal species. • Toxicities up to 28 days by the oral route in two species (one non-rodent). • Cutaneous route toxicology up to 28 days, including tolerability assessment in two species (one non-rodent) • Toxicokinetic supportive studies.
Phase I CT	• Study of the irritation potential of the product at low strength, medium strength and high strength. • Phase I maximal use pharmacokinetic study to determine the bioavailability of the product in healthy volunteers.	• Study of the irritation potential of the product at low strength, medium strength and high strength.

Figure 20. Exploratory development plan for atopic eczema: scenario 1

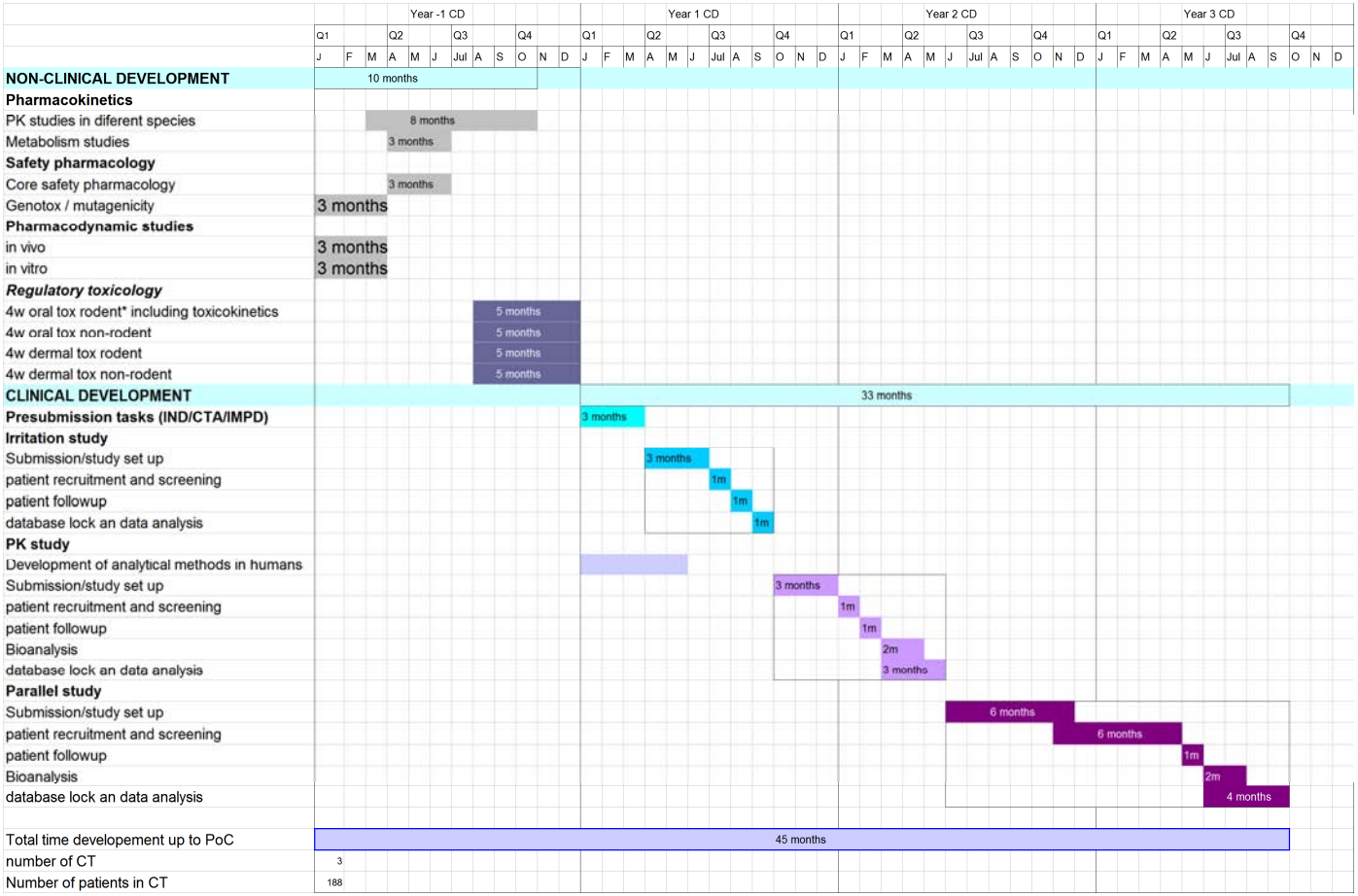


Figure 21. Exploratory development plan for atopic eczema: scenario 2

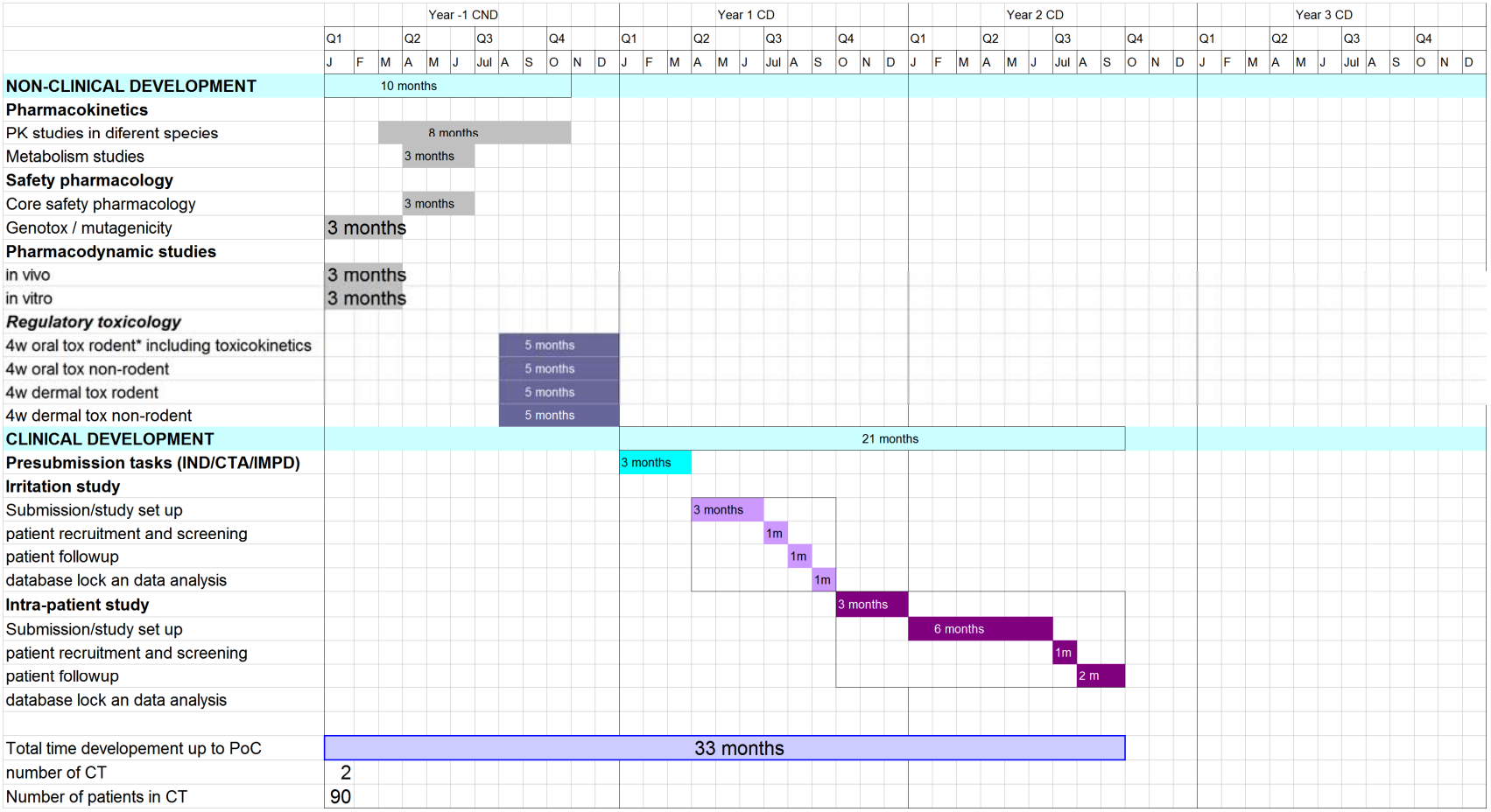


Table 32. Summary of development plans for 3 different scenarios in psoriasis

	Scenario 1	Scenario 2	Scenario 3
PoC study	Double-blind randomized parallel groups proof of concept study comparing the product at low strength, medium strength and high strength, placebo and reference active product when applied for 28 days.	Double-blind randomized within subject proof of concept study comparing the product at low strength, medium strength and high strength, placebo and reference active product when applied for 28 days to lesions of patient-volunteers with mild to moderate plaque psoriasis affecting symmetrical flexural areas.	Phase I, randomized trial to assess the antipsoriatic effect of three strengths of the product, vehicle and an active control using a psoriasis plaque test
Non-clinical studies	• In vitro target/receptor profiling • Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection • Core battery of safety pharmacology • Genotoxicity: Ames assay (Bacterial mutation assay) Mammalian cell assays (in vitro/in vivo) • Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to different species. • Toxicities up to 28 days by the oral route in two species (one non-rodent). • Cutaneous route toxicology up to 28 days, including tolerability assessment in two species (one non-rodent) • Toxicokinetic supportive studies.	• In vitro target/receptor profiling • Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection • Core battery of safety pharmacology • Genotoxicity: Ames assay (Bacterial mutation assay) Mammalian cell assays (in vitro/in vivo) • Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to different species. • Toxicities up to 28 days by the oral route in two species (one non-rodent). • Cutaneous route toxicology up to 28 days, including tolerability assessment in two species (one non-rodent) • Toxicokinetic supportive studies.	• In vitro target/receptor profiling • Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection • Core battery of safety pharmacology may be waived, at this stage • Genotoxicity: Ames assay (Bacterial mutation assay) Mammalian cell assays (in vitro) • Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to different species. • 2-week repeated dose toxicology by topical route in rodent • Confirmatory toxicology study by non-topical route in non-rodent (at the anticipated NOAEL exposure in rodent), 2 weeks
Phase I CT	• Study of the irritation potential of the product at	• Study of the irritation potential of the product at low	• None

	Scenario 1	Scenario 2	Scenario 3
	low strength, medium strength and high strength. • Phase I maximal use pharmacokinetic study to determine the bioavailability of the product in healthy volunteers.	strength, medium strength and high strength.	

Figure 22. Exploratory development plan for psoriasis: scenario 1

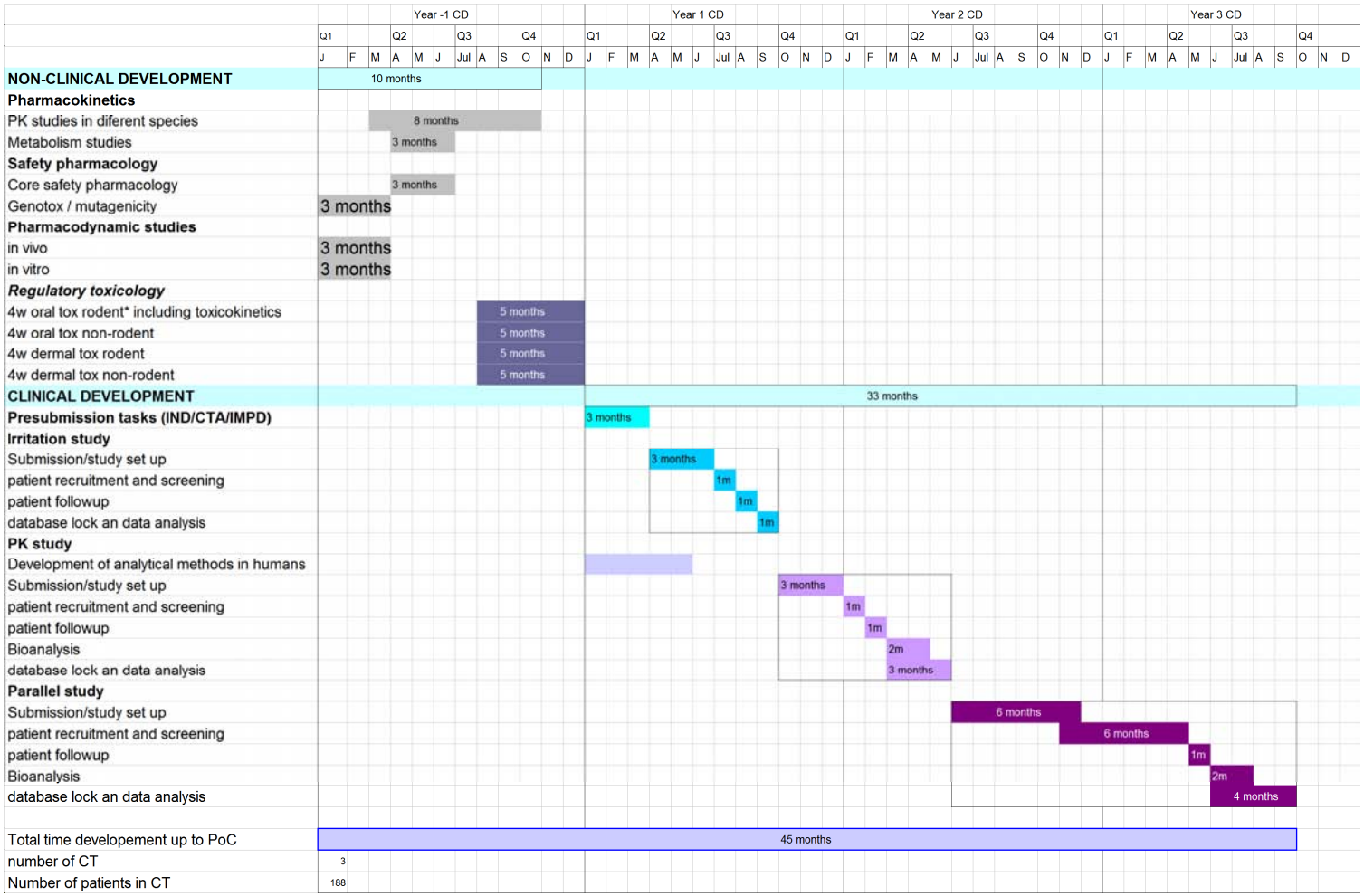


Figure 23. Exploratory development plan for psoriasis: scenario 2

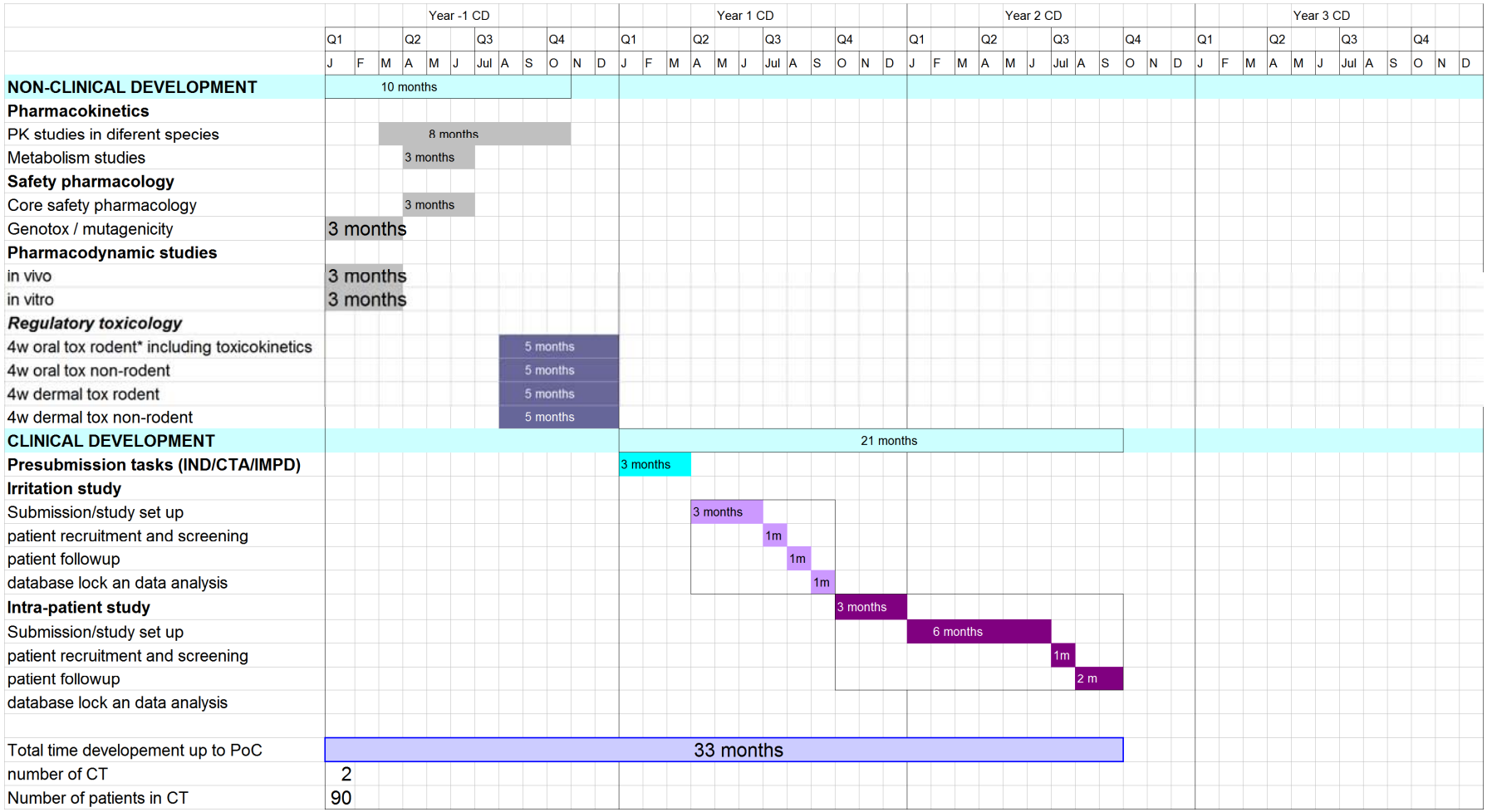
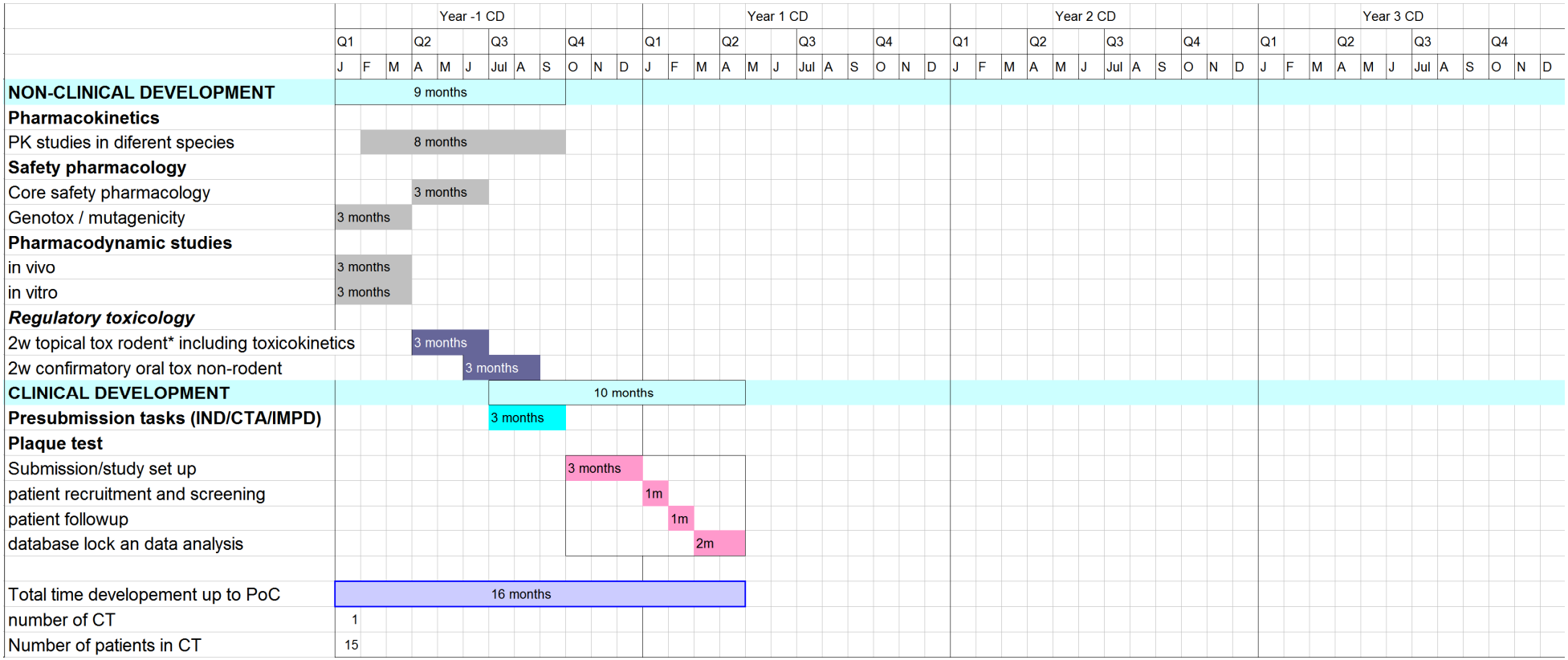


Figure 24. Exploratory development plan for psoriasis: scenario 3

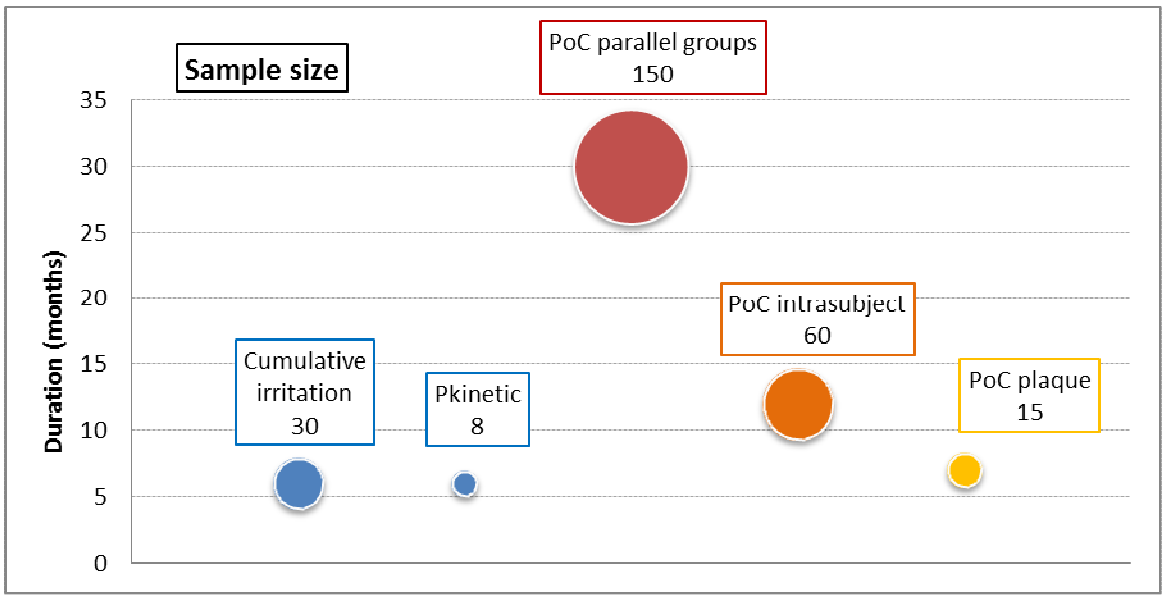


4.5. Estimation of costs and duration

4.5.1. Modeling of study costs and duration

Using the study outlines, the duration of the studies and the number of patients to be included were summarized. Since atopic eczema and psoriasis studies shared similar designs and determinants of cost, the simulations were done only once to be applied to both indications. These are summarized in the figure below.

Figure 25. Sample size and duration of each clinical study



The number of units for each of the concepts to be budgeted were extracted, and summarized; the number of visits was deduced from the objectives and the usual frequency of medical assessments in each design, and the number of pages of CRF was calculated accordingly.

The simplest study was the pharmacokinetic study, and the most complex, large and long study was the parallel groups proof of concept. (see table below).

Table 33. Parameterization of proposed studies for cost and duration modeling

	Cumulative irritation	**Pharmaco-kinetic**	**POC parallel**	**POC intra-subject**	**POC plaque**
Nº screened subjects	33	9	200	85	25
Nº subjects included	30	8	150	60	15
Nº medical visits	150	72	1050	445	115
Nº specific procedures at site	0	0	0	0	180
Nº treatment visits (dispensations/applications)	630	7	600	1680	210
Nº blood draws	93	112	800	265	40
Nº biochemical and hematological samples	93	16	500	265	40
Bioanalysis PK (nº samples analyzed)	0	112	150	0	0
Volunteers' compensation(customized per study)*	18000	9600	0	30000	12000
Project duration in months (to extrapolate project management)	6	6	30	12	7
Nº pages CRF (for costs of monitoring, data management and statistics)	1170	464	9600	5580	1005
Nº Centers (for costs of TMF, authorization, reporting, quality, pharmacovigilance, drug supply)	1	1	15	1	1
Fixed costs per study (for costs of protocol &CRF, general docs of the study and regulatory submission)	1	1	1	1	1

Similarly, since the determinants of costs were similar in both indications, the modeling was done only once to be applied to each condition. Thus, the application of the dummy costs per unit was applied to the different studies, with customized costs for volunteer compensation according to the study requirements and characteristics. The most expensive trial was the parallel groups trial, which had dummy costs 2.7 fold higher than the intra-subject comparison trial and 59 fold higher than the plaque test proof of concept trial. Phase I trials had all costs within a similar range, from 7.4 fold and 5.5 fold

lower than the parallel trial. A summary of the calculated dummy costs per study is summarized below.

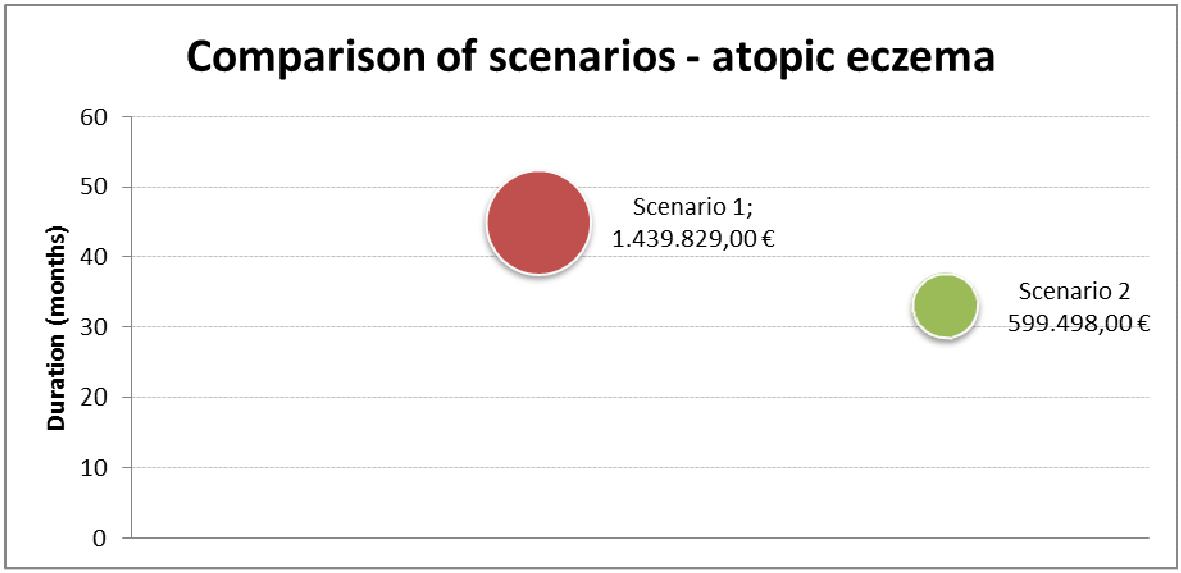
Table 34. Summary of dummy costs per study

	Cumulative irritation	**Pharmaco-kinetic**	**POC parallel**	**POC intra-subject**	**POC plaque**
Medical visits	40,551	19,464	283,856	120,301	31,089
Specific procedures at site	-	-	-	-	10,800
Treatment visits (dispensations/applications)	12,600	140	12,000	33,600	4,200
Routine laboratory	7,686	1,322	41,321	21,900	3,306
Bioanalysis PK	-	5,040	6,750	-	-
Volunteers' compensation	18,000	9,600	-	30,000	12,000
Project management	29,000	29,000	145,000	58,000	33,833
Monitoring, data management and statistics	12,310	4,882	101,006	58,710	10,574
TMF, authorization, reporting, quality assurance, pharmacovigilance, drug supply	30,360	30,360	455,400	30,360	30,360
Protocol and general docs, regulatory submission	48,060	48,060	48,060	48,060	48,060
Total	**198,567**	**147,869**	**1,093,393**	**400,931**	**184,222**

4.5.2. Modeling of development plans for atopic eczema

The application of the clinical trial costs to the development plans in atopic eczema showed the following results:

Figure 26. Comparison of clinical development scenarios for atopic eczema

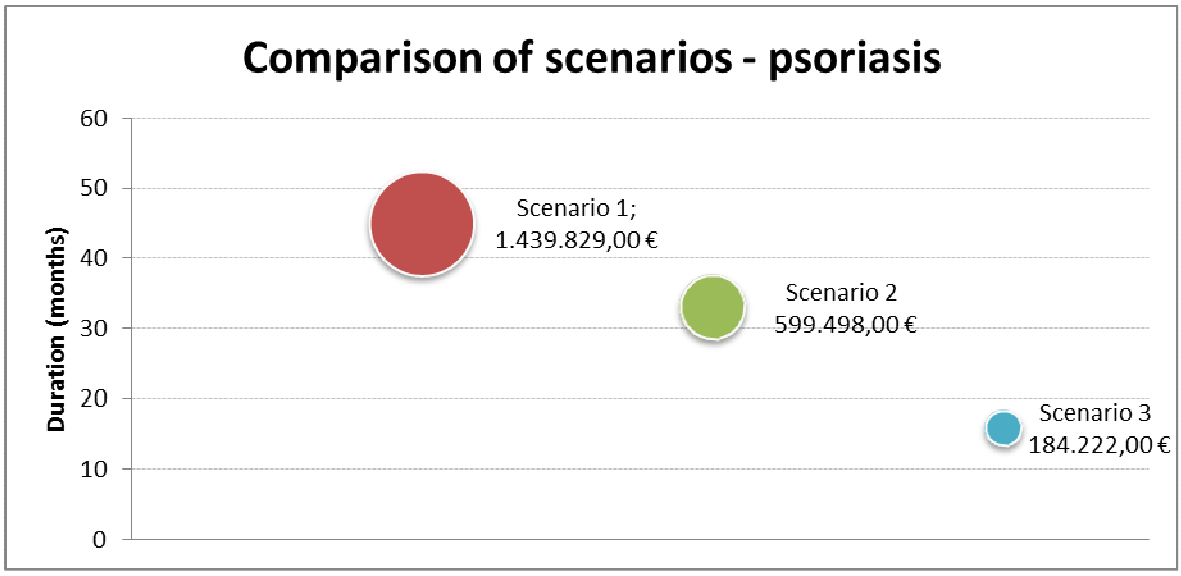


	Duration	Dummy costs
Scenario 1	45 months	1,439,829 €
Scenario 2	33 months	599,498 €

4.5.3. Modeling of development plans for psoriasis

The application of the clinical trial costs to the development plans in psoriasis showed the following results:

Figure 27. Comparison of clinical development scenarios for psoriasis



	Duration	Dummy costs
Scenario 1	45 months	1,439,829 €
Scenario 2	33 months	599,498 €
Scenario 3	16 months	184,222 €

5. Discussion

A systematic analysis of the information available and lacking to guide dermatological developments has been done, to identify the key aspects to design the development of a NME and to propose efficient designs of exploratory development plans driven by objectives, with the aim to facilitate the process of development up to PoC for topical application NME intended for the treatment of atopic eczema and psoriasis.

5.1. Regulatory guidelines search and review

Our work confirmed that there is little information on how to plan the de development of a new molecular entity for the treatment of atopic eczema or psoriasis by the topical route. Differences of these products with respect to systemically administered products in terms of systemic exposure, safety issues and others are evident and thus, this should impact on the development plans, easing the need for certain types of information but making some additional information needed.

While for a marketing authorization topical products may require more testing than systemically administered drugs, in early phases a faster track to obtain activity data may be possible. The aim would be obtaining a proof of efficacy as fast as possible with minimal waste of resources, so that products with promising results can advance further in the development and that products with no or minimal activity are discontinued from further testing.[39]

Reducing animal testing has been the objective of the 3R principles (Replacement, Reduction and Refinement).[84] According to these principles, any researcher planning to

use animals in their research must first show why there is no alternative and what will be done to minimize numbers and suffering. This is reflected in the newest guidelines which no longer consider essential some of the studies, encouraging to replace the use of animals with alternative techniques, or delay the testing to late phases (i.e. eye irritancy in rabbits), reduce the number of animals used to a minimum and to obtain information from fewer animals or more information from the same number of animals (i.e. including dermal irritancy and even genotoxicity in dermal toxicology studies).[29,57,58] However, up to know, the lack of straight forward guidance has often resulted in excess of testing. We believe that concise instructions would improve this.

Topically acting products are products which are applied locally and are assumed to exert their effect at the site of application; systemic action, if any, would be considered as an undesired effect. The M3(R2)[29] does not address the issue of topical dermatological products, but it states that it is necessary to perform non-clinical toxicology studies with the route intended for clinical use and the final formulation to be used in clinical trials. The aim of such studies is thus the characterization of the effects of the product on target organs; in case of products with minimal absorption and negligible systemic exposure when administered by the topical route, topical toxicology studies will not be able to meet this objective and thus, administration by a systemic route is required to achieve relevant systemic exposure. These studies would then be useful to establish the safety margins of a topical exposure. However, it can be argued that if no systemic exposure from the topical route is expected in humans, such characterization is not relevant, as no

systemic exposure will ever be achieved through the topical dermatological route when administered to humans.

Studies of systemic absorption with the intended clinical route can be performed in animals and *in vitro* studies using human skin obtained from biopsies or surgery, and the expected systemic disposition can be estimated before any human exposure. However, the systemic exposure cannot be discarded with all certainty before the product has been tested in humans. Thus, systemic toxicology studies are advised as a cautionary measure, in order to establish a reasonable safety margin in the worst scenario of unpredicted exposure. Obviously, toxicology studies by the topical route are always needed before any administration in humans.

In view of the uncertainty on non-clinical requirements, most sponsors and/or regulators may be more comfortable when 2 systemic toxicology studies (rodent and non-rodent) of duration covering the exposure in clinical trials and topical toxicology studies in 2 species (rodent and non-rodent) are available. It may be reasonable to have this information available at the time of marketing the product or before exposure of large number of patients during long periods of time, but a straightforward approach during the early phase of the development could be applied, not only in duration of the studies but in number of species or routes tested.

Both EMA and FDA have issued guidance on exploratory clinical trials, defining them as studies done with very low doses (microdosing), which are expected to produce a pharmacologic, but not a toxic effect.[29,60] Such studies may be performed without the need of an extensive non-clinical toxicology package, because the potential risk to human

subjects is deemed to be less than for a traditional phase I study seeking to establish the maximum tolerated dose (MTD). Thus, depending on the type of clinical study to be performed, the characterization of toxicological effects on target organs could be delayed to later phases of the development, or even be reduced. This would delay long and expensive non-clinical studies until the product has reached an advanced phase of development and reduce the number of animals used in human experimentation.

Existing guidance allow a great deal of flexibility in the amount of data to be submitted, depending on the goals of an investigation, the specific human testing being proposed, and the expected risks. Despite this allowance, sponsors have not taken full advantage of such flexibility, and often provide a more extensive preclinical database than actually needed to support their studies.[29,60]

In conventional developments, safety and pharmacokinetic information in a limited number of humans is needed before proceeding to studies in patients, which is obtained in phase I trials. For products applied topically in the skin this will not always be needed at this stage. Local tolerance testing is requested before marketing of the product or exposure to large populations. For limited exposures, one may think that no local tolerance testing in humans would be necessary; however, preliminary data on irritation potential in humans is easy and quick to obtain, and provides substantial safety information that, when adverse, may determine an early no-go decision for the formulation, or even the product. In this sense is cost-effective to do this kind of studies before investing in more expensive and lasting trials. Sensitization and phototoxicity

testing in humans would not be needed if limited exposure under controlled conditions is performed.

The right moment to perform a pharmacokinetic study to characterize the systemic absorption of the product when administered in normal conditions is not clear. The guidelines do not indicate neither how a clinical pharmacology PK study should be performed to discard or characterize systemic disposition of the active principle for products applied topically to the skin. Methods to study the dermatokinetics are described in some of the guidelines, but are basically intended to proof bioequivalence of formulations by proving the same absorption and disposition of the product at the different skin layers. Available methods include in vitro studies of drug release through an artificial membrane and/or human skin membrane, to determine the rate and extent of drug release or permeation, and also in vivo tape stripping and microdialysis techniques.[85]

The specific guidance for psoriasis emphasizes that a validated human pharmacodynamic model, the psoriasis plaque test, is available, which allows testing of different products or formulations in one patient by applying minimal amounts of product to a psoriatic lesion. Similarly, the vasoconstriction test can be used to test corticosteroids potency and bioequivalence between two TCS formulations. Both type of studies can provide a fair screening tool to discard poor performing products, but their value as proof of concept predicting clinical efficacy is questioned. However, as a clear benefit, these studies could with all probability benefit from a reduced non-clinical and clinical package.

Other options for non-traditional proof of concept trials would be left-right intra-subject comparison studies. This approach may imply a reduced and supervised application of the

product during limited periods of time, and for this reason in theory they could be carried out without extensive clinical data support.

Thus, when planning early clinical trials, a request for advice to the concerned regulatory authorities is recommended on the extent and suitability of the supporting information to conduct human studies. However, different opinions may arise both from regulatory bodies and ethical review boards, mainly due to the lack of guidance and reference on this issue.

Our review of guidelines has not been useful to provide much information on how an early clinical development of a new chemical entity intended to be applied topically on the skin should be planned. It is made evident that information on the minimum requirements of data previous to exposure of humans in clinical trials is lacking, and that current guidelines leave room to different interpretations.

We believe that a clear guidance covering the most frequent situations could be helpful to design development plans able to provide robust and conclusive results in a short period time and with an optimal use of resources. Minimizing requirements of non-clinical and clinical data will ensure animal protection while ensuring the wellbeing of participating subjects in clinical trials.

Even considering that early development of a topical product may have many different situations and scenarios, a standardization of minimal requirements could be easy to develop. However, most guidelines are focused on regulatory requirements for marketing authorization application. It is understood that marketing authorization of medicinal

products is a matter of public health and a key responsibility of the authorities, while the strategy to select and develop candidate products to a confirmatory clinical phase is on the remit of the manufacturers/sponsors. Thus, input of regulators on methodological aspects of this phase of the development is only referred to the quality of the product to be used in clinical trials and some ethical aspects regarding the safety of participating subjects, the latter being shared responsibility with independent review boards and ethics committees.

Since issues such as how to assess the risks of exposing patients/healthy subjects to research drugs during early development, animal welfare and possibility of Replacing and Reducing the use of animals are of great importance to all actors involved in the decisions at this stage, it should be stressed that their decisions may have a considerable impact, not only on the development of the product but also on the safety of patients. In that sense, more involvement would be desirable to improve standards of assessment.

5.2. Assessment reports search and review

The search for regulatory assessment reports of dermatological products has shown few results, which is consistent with the paucity of new chemical entities developed in this particular therapeutic area in last years.[37]

Besides, only medicinal products approved by the centralized procedure have available reports at the EMA. For products which followed decentralized procedures, no thorough information is generally available, and because of that we tried to cover this gap through the search at the national Spanish level, recovering few additional products for whose information on the marketing application contents were searched for at FDA.

Further, for products assessed and authorized many years ago, data from FDA or EMA reports were mostly incomplete and extremely brief, very much focused on the pivotal efficacy and safety evidences; information on exploratory development is poorly detailed. Thus, only very few reports could be included in our review, and the amount of information that we were able to retrieve was small; in particular chronology and sequence of the studies (both non-clinical and clinical) were hardly deducible from the reports. Because of data being scarce in number and detail, lacking quantitative aspects of product development, we decided to do a qualitative review of data only.

To note, four of the products licensed for treatment of AE or PSO were not NME, meaning that these products had already been marketed for a while and used by a different route, so that (clinical) safety information for systemic uses was previously available. Such an approach (i.e.: re-profiling a systemic product for topical use) modifies the need for specific studies since the safety aspects of the product do not require to demonstrate lack of systemic exposure after dermal application and/or exhaustive clinical safety. Straightforward developments may be then applied to such products, an approach which can be very efficient.[86]

However, although the dermatological development of already known molecules could theoretically be much simplified, this is not always the case. As an example, the calcineurin inhibitor tacrolimus, an immunomodulator widely used to prevent transplant rejection, had a substantial amount of information on systemic exposure and safety available at the time that the topical cutaneous indication was developed, allowing to waive many trials which might had been requested otherwise. Yet, since bioavailability by

the dermal route was unknown, and the product is a potent immunosuppressant, there was a requirement for exhaustive pharmacokinetic studies including metabolism in skin, and also to qualify safety in the target population, especially regarding risks for cutaneous or systemic malignancies in children.[87,88,89, 90,91,92,93]

Although the type and scope of available documents did not allow to directly derive a draft of product developments pathway with indication–specific settings and characteristics, yet the extracted information has been valuable to identify a number of standard tasks and studies which are generally required. Also, it has allowed us to identify the most relevant development objectives shared by all products, and to learn many critical reflections on the study designs and potential results, with their corresponding implications for the risk/benefit assessment. All of these learnings have proven useful to understand the research questions and priorities leading clinical development planning in the dermatological setting, and to be able to make reasoned choices to propose the 5 clinical development scenarios for AE and PSO.

5.3. Publications of clinical trials: search and review

A total of 59 studies in AE and 40 in psoriasis have been identified, and data on general design features has been extracted. The identification of the phase of the study has been difficult, because either the trials did not detail the development phase in the text, or whether the study was exploratory or confirmative was not detailed in the study objectives. Yet, 7 out of 59 studies in AE (12%) and 13 out of 40 studies in PSO (32.5%) had 3 or more different treatments compared within the study, suggesting that they had

some exploratory or dose finding objective. Figure for psoriasis was 17/43 (39.5%) if psoriasis plaque test was accounted for.

Differences in the proportion of exploratory trials between AE and PSO may be due to a number of reasons. First, the fact that AE is mostly a pediatric condition makes it less feasible to explore safety and activity in patients, since on one side, adult AE is less frequent and has differential features, and on the other side clinical trials in children are only justified if the research is responsive to their health needs or priorities and the research cannot be carried out in a non-vulnerable group.[94] Besides, the clinical course of the lesions in AE is less constant than in PSO, and clinical measurement are generally measuring several aspects of the disease through composed variables that include many components, which make sense to assess efficacy of the compounds in clinical setting. However, this fact makes it challenging to preliminary assess product activity and potency in limited lesions, and whether the effect may be due to anti-inflammatory effects, vasoconstriction, anti-itching properties or emollient properties of the compound may be difficult to ascertain.[95] In addition, although the condition is generally bilateral and symmetric, allowing intra-subject comparisons, clinically AE is less easy to standardize, since the limits of affected areas may depend on inflammation, which in turn may be variable depending on itching, scratching, contact with clothing and ambient temperature. It is not always easy to determine the limits of the lesions, and there is a higher degree of variability in clinical expression of the disease in AE than in PSO, making it difficult to get a reliable and predictive sign of treatment activity in AE.

Instrumental measurements which might be used to objectivize treatment effects are not ideal either. As an example, transepidermal water loss (TEWL) measurement is a non-invasive quantitative measurement that can be easily obtained, and provide a surrogate of the skin barrier integrity that correlates to some clinical scores of activity.[96,97] However, abnormal results in AE can be obtained at both lesional and non-lesional skin sites,[98,99] and its use as a surrogate marker of response to treatment is generally done in parallel with clinical assessments. Similarly, the measurement of microcirculation by Doppler ultrasound has been reported to be a marker for inflammation,[97] but again should be used in parallel with clinical assessments. Itching is a constant and reproducible symptom of AE that can be used as a model for proof of activity of specific symptomatic treatments, even in cross-over designs;[100,101] PSO models have also been used for the assessment of antipruritus agents[102] and it is one of the symptoms included in the assessments of PSO clinical trials.

Clinical characteristics of psoriasis are more suitable for exploratory clinical research. Firstly, it is a prevalent disease affecting 2% of adult population, and mild disease is neither substantially impairing the subject wellbeing, nor requiring urgent treatment, so that the identification of a potential patient volunteer population for studies without direct therapeutic benefit is possible, thus allowing for studies with closely controlled experimental settings and pharmacodynamic-like measurements and investigations. Typical plaque lesions are clinically easy to delimitate, have relatively wide homogeneous areas, and can be used to obtain reliable activity results within a short period of time. As in AE, bilateral lesions are the rule and allow for intra-subject product comparison.

Regarding variables, in addition of clinical measurements, the measurement of skin thickness by ultrasound imaging is a reliable variable able to distinguish healthy and diseased skin and quantitatively useful, that has proven to be reasonably predictive of clinical response to treatment.[103] Also, biopsies of skin lesions can be used in very preliminary stages to guide early development decisions, but non-invasive alternatives such as *In vivo* reflectance confocal microscopy (RCM) may provide similar information in a non-invasive way, and have proven to correlate reasonably with clinical measures such as PASI.[104,105]

An explanation for the reduced number of trials we identified may be the combination of a relatively low research activity in the field and publication bias. It is well known that studies with negative results are underrepresented in the medical literature, mainly due to perceived lack of clinical interest,[106] and this can be particularly troublesome in a field with relatively low research in new chemical entities and not so developed attention to methodological aspects as compared to other fields of research.[107] Also, we cannot discard that, in the case of innovative compounds, a role may be played by reluctance to share competitive intelligence by companies.

New chemical entities not previously tested were the exception, rather than the norm, with most of the identified studies related to new formulations of already known substances. This fact likely reflects the business opportunity of what can be considered "low-risk" approaches to product development, since in general safety risks are greatly diminished from those faced in a new chemical entity scenario.[108]

In terms of quality of the study reports, a formal approach was not done, but some key features of study design quality were described. Many CONSORT standards[109] had low rates of compliance; I ex: double-blind randomized trials represented 69.5% of AE and 45% of PSO trials, formal sample size calculation was missing in 57.6% of AE and 60% of PSO trials, treatment compliance was not reported in 72.8% of AE and 72.5% of PSO studies, no reference to ethical review was done in 12% of AE and 17,5% of PSO studies, and 18.6% of the studies in AE and 22.5% in PSO did not comment on informed consent procedures. The description of patient disposition was generally not met, and when present, it was mostly done in narrative form across the text, or informed in the denominators of graphs and tables, and thus difficult to retrieve. The quality of reporting was also low in terms of identification of the principal variable, with many reports referring only general objectives ("to compare efficacy and safety") and providing all results with no prioritization of variables or hierarchical approach. In relation to this fact, often multiplicity issues were not addressed nor discussed, with all hypothesis testing presented at the same level and with the same threshold of significance (namely 5%). Dermatological clinical trials have been previously noticed to have some methodological reporting deficiencies.[107]

Yet, despite these limitations, the review of the studies has been useful to identify and select 4 types of designs and their main characteristics, whose advantages and disadvantages are discussed below and summarized in Table 35.

Randomized, inter-subject parallel study:

This is the classical clinical trial design where all patients are treated simultaneously and receiving only one of the studied options in a way similar to that of routine clinical practices. The design is less prone to medication errors, since only one medication option is delivered to patients, and frequent administration posologies can be studied (BID), since the medication can be delivered to the subjects for self-treatment. Also, the amount of product used in each subject is larger and thus also the likeliness of systemic exposure. Because of that, this design requires some previous safety data that other designs might not, such as prior pharmacokinetic studies in humans. Also, secondary objectives often include pharmacokinetic assessments. Besides, parallel studies require larger sample sizes than other designs.

The duration of treatment may vary depending on the studied product, but is often of 4 or more weeks, especially for psoriasis trials. Thus, supportive toxicologies of equal or longer duration than the study are required to support clinical trial application.

Since all lesions are treated, the assessment of disease severity can account for percentage of skin involvement respect to the whole body, regardless of whether a target lesion for each patient may be identified and assessed individually. Since the effect on both intensity of signs and extension of disease are relevant to clinical interpretation of product efficacy, the relevance to predict future efficacy in confirmatory trials can be regarded as better than that of other designs. Thus, the main advantage of this design is the unquestionable translatability of results obtained, especially if all lesions of the patients are treated and assessed, and the fact that they generate results which are

clinically meaningful. Actually, this is the design that the regulatory authorities will require for their benefit-risk assessment.

The use of clinical endpoints does not preclude that supportive measurements may include objective measurements of thickness, biopsies, confocal microscopy or other parameters useful to characterize the mechanism of action.

Since inflammatory skin diseases have a fluctuating course, it is important to have a negative control to account for spontaneous improvement due to disease course, so that frequently the studies have a vehicle treated arm. Similarly, it is recommended to conduct trials during cold or “long-sleeve” season to avoid interference. Considering that the sample size is large, this may be logistically challenging to accomplish.

The confluence of larger sample sizes and short periods of time to recruit is generally managed by using multicentre studies; when the period to recruit is assessed as too short and constrained by seasonality, the combination of sites located in the North and South hemispheres may provide a solution to continue recruitment all year long.

Our review showed that inter-patient parallel studies reach statistical significance for the main variable more often that in intra-subject studies. This finding may be related to different factors: the statistical significance depends not only on the actual efficacy of the product tested, but also on the design and execution of the trial. It is not unusual that the intra-subject design is used as a proof of concept and becomes the first trial in patients to assess the activity of the product, based only on limited activity data coming from animal studies. Contrarily, inter-subject comparisons are done later in development and the risk

of lack of confirmation of the working hypothesis in a well-designed clinical trial is reduced.

Another factor related to reaching statistical significance was the number of patients included in the study: statistically significant studies included larger number of patients, and many non-significant studies seemed to be underpowered. Should this be the case, some of the negative trials might have reached statistical significance if a formal sample size calculation had been done. This is noteworthy in the case of inter-subject parallel studies both of AE and PSO and for AE intra-subject studies, but not for those in psoriasis.

Several limitations can be identified for inter-subject design when it is used for proof of concept. The large number of patients needed will often require multicenter approach, and this will increase heterogeneity in the assessments, type and severity of patients included and study procedures. Solving these issues may require a considerable amount of resources directed to ensure the quality and the validity of data obtained from the study.

The assessment of treatment compliance is also challenging, since each patient needs a different amount of treatment depending on the affected area, and weighing returned containers won't give an objective control of the compliance. Treatment adherence of topical dermatological treatments has been reported as suboptimal with adherence to treatment as low as 55% in psoriasis trials.[110] A pilot study evaluating different formulations of a product for psoriasis found that patients reported better adherence than the one evidenced by electronic monitors.[111] This means that patient reported adherence is not a good tool to measure compliance. Many reasons may account for this

and they are mostly related with patient perceptions of the tolerability and efficacy of the product; the latter may even lead to overdosing when a beneficial effect is perceived by the patient.

The time from the inception of the study and the availability of results is long in inter-subject studies, due to several factors: The setup of the different centers of the study is longer than the start of the study in one single center, and especially if the center is a dedicated unit either in a CRO or in an academic research center. Even if the participating sites have a database of patients eligible to participate in the study, the recruitment rate is often not met, especially because of the large number of patients needed. Finally, as already discussed, the non-clinical and clinical requirements to support home-based treatment of large areas of skin for 4 weeks or more is wider than for other study designs.

Randomized, intra-subject parallel study:

In this design, the same patient receives two (or more) treatments. Treatments may be applied in two similar and symmetric lesions, in two extremities or bilaterally on each half of the body and there are no whole body assessments, only for the lesion. If the unit of assignment is the lesion, the amount of product assigned is small and the duration of treatment may depend more on the characteristics of the treatment applied and the disease treated.

One drawback of this design is the limited clinically meaningful data that it may provide since no global assessments of the disease are performed. Other limitations include practical aspects: since randomization is done based on body side, when trials are double-blind the application of treatments is challenging, especially when ambulatory treatment

is decided and applied by the patient in an unsupervised fashion. Because treatments have been masked to be undistinguishable, errors on the side of application may occur, hampering the study validity.[47] Third party application may be used to reduce risk of errors in application, but may be logistically demanding and bothersome to participants, not feasible for application frequencies higher than twice daily or durations longer than 1 month.[46] Also, patients must be willing to withhold treatment different from emollients in the rest of the body lesions, and if the rest of the lesions exacerbate the patient must receive an alternative treatment and be withdrawn from the study.

Patient needs to have two similar lesions in certain areas of the body and this may limit the eligibility of candidate patients, making it difficult to achieve initial recruitment estimates,[46] in some cases hampering the statistical significance of the results. In the case of AE, we have found in our review that contralateral studies in AE the number of patients included was related with the statistical significance for the main variable.

Pharmacokinetic assessments make no sense if the same patient is receiving two strengths of the drug or different drugs in small skin areas.

One of the main advantages of this design would be a smaller number of patients needed, allowing to perform the study in one site (or two). Dedicated units at a CRO or academic centers where patients are pre-registered and can be easily recruited are especially efficient.

Randomized, cross-over study:

In this design, the same patient receives two (or more) treatments but in different periods of time. The flaring course of the disease makes the period effect important, and

may be difficult to ensure that all patients undergo all periods without changing seasons. Also, if the product is disease modifying, the sequence of treatments will interfere with assessments.

Thus, this type of studies would be adequate only for measures such as pruritus in patients with stable disease. Thus this design would not be suitable to be used in most situations for proof of concept.

Pharmacodynamic studies:

This type of study allows for the testing of several formulations/compounds at the same time in the same patient, thus needing only a limited number of patients and minimizing variability. One of these assays and the one that would fit for all type of treatments for psoriasis is the psoriasis plaque test. The original assay was described by Scholtz-Dumas back in 1967, and since then several variations in the size, shape, number and location of the test sites have been proposed among different studies.[112] For instance, the original assay described that the application sites were covered (occlusive application) with the objective of maximizing the effect, and variations of this test consist on different degrees of occlusion or even non occlusion.

Due to the complexity of the applications, these studies are performed at specialized test centers where a nurse or technician apply the treatments daily or every other day. Clinical assessments are performed before reapplications or less frequently, and treatment duration does not exceed 4 weeks. Even if it's not the main variable, most studies include ultrasound measures or any other type of non-invasive objective measures.

This test is regarded as a valuable tool in the assessment of the activity of antipsoriatic treatments. In most studies, a dose response relationship is detected. For this reason it has been frequently used to screen new compounds, select doses and screen and select vehicles. However, in some occasions, treatments which have shown good activity and even a dose response in plaque testing, have later failed to show its clinical utility in further confirmatory clinical trials. This is the case of calcineurin inhibitors.[77,81,82] The authors draw attention to the occlusive application as well as the previous desquamation with salicylic acid performed in some studies that may be responsible for a larger absorption of the active principles that would reach the target site of action; this may not be achieved in the normal clinical situation and this may be the reason why the results have not been reproduced in clinical trials. In fact in a review of non-published Scholtz-Dumas assays performed by Katz et al.[113] the authors found that very low strengths of corticosteroids show activity in the model, and they conclude that occlusion may magnify the activity of the compounds, not only by increasing its bioavailability, but also because occlusion itself has been shown to improve psoriasis.

The little number of patients needed and the rapidity in obtaining results may make it a suitable design in some situations.

Table 35. Characteristics, advantages and disadvantages of the study designs

Design	Main Characteristics	Advantages	Limitations
Randomized, inter-subject parallel study	Classical study, two or more parallel groups	External validity and extrapolability, if all lesions of the patients are treated and assessed. Allows pharmacokinetic objectives.	Higher number of patients needed, heterogeneity.
Randomized, intra-subject parallel study	Bilateral lesions or bilateral affectation needed. Two or more treatments. Side randomization.	Less patients needed, reduced variability due to intra-subject control.	No assessment of extent of disease. Difficult recruitment since equivalent bilateral lesions needed. Risk of dosing errors. Not suitable if systemic absorption
Randomized, cross-over	Classical cross-over study, two or more sequences	Less patients needed, not necessary to have bilateral lesions, reduced variability due to intra-subject control.	Statistical loss if subjects are lost to follow up, carryover, period and sequence effect.
Pharmacodynamic studies: psoriasis plaque test, corticosteroid vasoconstriction test	Studies where several treatments are tested in the same area/plaque, with minimal product application.	Few patients needed, short duration, few supportive data required (could be considered as exploratory (microdoses)	Not for drugs with systemic absorption Limited extrapolability

5.4. Design of an exploratory development plan

We proposed different scenarios for AE and PSO according to the clinical proof of concept to be used, based on all the information obtained from our reviews.

For AE, only two possible scenarios were taken into account: the classical parallel randomized clinical trial and the intra-subject study design, since no reliable pharmacodynamics proof of concept was identified. For PSO, both the previous scenarios were considered and the option of a psoriasis plaque test was also included.

The characteristics of every single development depend on the characteristics and target product profile of each product, and in that sense are unique. Thus, depending on the product, our exercise might have led to different decisions. Our intention was to establish a framework that could be useful as a starting point to build up the development plan of any product in the same indication. For each scenario the best possible study was designed, including every characteristic which was considered an advantage and all strategies to overcome the disadvantages of the design itself.

Scenario 1

Regardless of the cost and time issues, scenario 1 appears as the ideal one. In the event of positivity of the inter-subject comparison proof of concept study, it would provide the best situation to proceed with the confirmatory development without delay. We proposed a study testing 3 different product strengths, and comparing with vehicle but also with an active control. A dose range estimated to be active and safe in humans is calculated based on data from the non-clinical pharmacology studies. In a standard

development, a phase IIa PoC study may usually test the maximum dose in this range as the main objective is to find out if the product has any effect. While for dermatology this may also apply (the highest strength is potentially the most active), high strengths of topical treatments may also be associated to higher irritation potential[46] and thus, the effect of a high dose may be masked by the negative effects of the irritation that cannot be differentiated from the disease itself. It is then necessary to incorporate the concept of "dose finding" at this early stage, and a minimum number of 3 strengths seems to be advisable. Besides, demonstration of dose-dependence of effects is a clear sign of efficacy by itself.[114] If proof of concept results are conclusive, it will allow to proceed with the development to phase III pivotal studies once all the requirements of data before phase III are fulfilled, and skip a formal dose finding phase.

The comparison with vehicle is essential in trials where the course of the disease is in some cases self-limited, allowing to distinguish the effect of the treatment and that of the natural evolution of the disease. Moreover, vehicles have an effect on the disease by themselves and thus if no vehicle control is included, the effect on the lesions may be attributed to the test product when in fact it is the effect of the moisturizing properties of the vehicle that improved the disease.

As an example, (data not published, J Uriach & Cía S.A. , *A double blind pilot study, randomized, active-treatment controlled to assess the clinical efficacy, skin tolerability and pharmacological activity of a new topical compound (UR-1505 0.5% and 2%) in patients with mild to moderate plaque-type psoriasis*) an intra-subject study performed in psoriasis compared two strengths of an investigational product (0.5 and 2% versus an

active treatment, betamethasone) and showed a percentage of healing of the lesions at day 28 of 63.2% for the 0.5% strength , 65% with the 2% strength, and of 77% for the active control group. This led to the sponsor to consider that the range of efficacy for the new product was similar to the control and enough to continue with the development of the product. A later study performed with the same intra-subject design but comparing 3 strengths of the product, the vehicle and an active control, was not able to find differences between the vehicle and the test product but found differences between vehicle and the active control (data not published, Palau Pharma S.A. – *Double blind study, randomized, active and placebo controlled to assess the clinical efficacy, skin tolerability and pharmacological activity of UR-1505 ointment at three different strengths in patients with mild to moderate plaque-type psoriasis*, EudraCT number 2007-005672-13). The conclusion was that, as the second study did not show a difference between the test and the vehicle, but showed a clear difference between the active control and the vehicle, the activity observed in the first study was attributable to the effect of the vehicle.

This example highlights that the inclusion of a placebo vehicle in the comparison is essential at this stage of the development, especially when the activity of the test product is still not proven. To include an active control that has proven activity on the disease studied provides an internal validity testing that becomes critical in case of a negative study, allowing discarding the activity of the product.[46]

Before patients are exposed to large amounts of the product in such a PoC study, the product's safety must have been characterized by non-clinical studies to ensure that patients are not exposed to excessive risks.[30]

In the same way, a dedicated clinical local tolerability study will be required. Though irritation data from animal studies is available before administering the product to humans, it is sensible to test the irritation in human studies before moving to phase II where a considerable amount of patients will be exposed. A study in healthy volunteers, testing different strengths intended to be used in future clinical trials, with a positive and a negative control, is the ideal setting to elucidate the irritation potential of a product and to avoid including an irritating dose in phase II.

Irritation studies have standard designs and have been mainly used for the testing of cosmetics and chemicals.[115, 116] However poor correlation has been found between the results obtained in animal models and humans. In addition, the need to reduce animal testing has led to new approaches for irritation testing. As advocated in guidelines related to human drug development, stand alone in vivo animal testing for irritation is not considered adequate anymore, and irritation should be tested integrated in dermal toxicology studies.[29,59]

Also, the systemic bioavailability of a product to be tested in humans must have previously shown minimal absorption in studies performed in different animal species. A confirmation of this negligible or minimal absorption in humans is necessary before administering the product in large areas, during a prolonged period of time and to a considerable number of patients. For this purpose we included a systemic bioavailability

trial in healthy volunteers in scenario 1. The proposed study is aimed to confirm that the results regarding systemic disposition of the product when applied to the skin, as observed in non-clinical studies, are confirmed in human skin, and also to establish a safety margin.

It has been described that the degree of systemic disposal of a product applied to the skin depends among other factors of the integrity of the skin.[117] Healthy skin is not equivalent to the skin where the product will be applied, and thus the results obtained with the study in healthy skin may not reflect what it will be found in real life. The objective of the BA study is to measure the systemic absorption of the product when it is applied to healthy skin at maximal doses, and is aimed to discard any significant exposure when the product will be applied to patients. Under this premises, it has been advocated that this type of studies should be performed in patients instead of healthy volunteers, so that data obtained is extrapolable to the population treated in the clinical trials, and eventually to the population that will be treated once the product is in the market.[45] While this is a reasonable argument we advocate for the former (I e: healthy volunteers) due to the following reasons:

- The study in healthy volunteers allows administering high strengths to a large area mimicking the worst case scenario, with no changes in the skin surface along time.
- Both AE and PSO are different from normal skin in terms of systemic drug absorption. The efficiency of skin barrier is lost. However, if the treatment applied to diseased skin modifies the skin characteristics, the degree of bioavailability will change over time, thus making interpretation of results of the study difficult.

In the second and third scenarios, this study would not be deemed necessary if sufficient non-clinical data show that the systemic absorption is minimal, as the exposure to the product is limited regarding the area treated and the number of patients exposed.

Scenario 2

The second scenario proposed is simpler in terms of the PoC trial, requiring a substantially lower sample size. However, a full package of safety and toxicology studies is also required.

For scenario 1 and 2 a comprehensive toxicology testing is proposed. While no specific guideline exists for products applied topically to the skin, the review of guidelines as well as the review of the assessment reports, lead us to propose toxicology testing in two species (rodent, non-rodent) by the iv and topical route to characterize the toxicology of the product. ICH M3(R2) guideline stresses the need for characterization of toxic effects of products intended to be used in humans characterizing the toxic effects in target organs, their relationship with the exposure to the product and its potential reversibility.[29] This will allow to calculate a safe initial dose and dose range to be tested in human studies. Also, Toxicology studies should be performed using the route to be used in human clinical trials in two species (rodent-non-rodent). Under this premise, toxicology studies for topical dermatological products should be performed by the topical route. While these studies will characterize the toxic effects exerted by the drug in the skin of the animal and the extent of systemic bioavailability of the product when applied in high doses to the skin, if systemic absorption is minimal or negligible as desired for this type of products, the objectives of the toxicology trial - characterization of the toxic effect in

target organs- in all probability will not be met. The reason is that it may be impossible to achieve relevant blood exposure to reach a MTD when applying the product to the skin, due to the low systemic absorption. While this could be considered a reason not to perform iv or systemic route studies because the same behavior is anticipated when applied to humans - and thus, no systemic exposure is expected -, we consider that characterization of toxicity in target organs is mandatory before a considerable exposure in humans and the only way is to administer the drug also by a systemic route. This leads to double testing for toxicity unless there is reliable proof of the negligible systemic absorption in humans, making these developments more demanding in terms of time and resources. Whether some of this testing may be waived at an early stage of the development is a decision that is now taken on a case by case basis on consultation to the regulatory authorities.

It is also considered sensible to perform a dedicated clinical local tolerability study with different strengths within the dose-range intended to be tested in future clinical trials.

Intra-subject designs allow for smaller sample size, can reduce the risk of confounding factors and reduce intra-subject variability. Advantages and disadvantages of this design have already been discussed in the previous section. In terms of clinical data required, no PK studies would not be required as far as the non-clinical data preclude a non-significant systemic absorption.

In summary, this scenario provides somewhat a simpler path till generation of clinical data on the activity of the product, with fewer patients exposed. However, in case the hypothesis of activity is met, further clinical data will be needed before proceeding to

phase III. Although the burden of time and patients exposed until decision on feasibility is lower, in case of success the overall effort will be bigger when considering the whole development as a whole.

Scenario 3

The third scenario proposed for psoriasis is the use of a psoriasis plaque test assay as a PoC. Characteristics and advantages and disadvantages of this design have already been discussed.

As a main consideration, the use of microdosing in this model may allow lower pharmaceutical development and non-clinical requirements, since requirements on toxicology may be lower and thus the kilo scale might not be necessarily in place. Also, the final formulation might not be still completely defined; alternatively, a raw solution of active principle or preliminary raw formulations may be used for the proof of concept, which can provide support to the choice between final candidate formulations.

The toxicological requirements will depend on the non-clinical results regarding bioavailability of the compound, the total amount of product intended for application per subject in the proof of concept study, and the product potency and safety profile in non-clinical models.

Our proposed scenario assumes the most favorable microdosing scenario and thus the less stringent regulatory requirements in pre-clinical and clinical qualification. Following the consideration that the product has previously shown minimal absorption in studies performed in different animal species, and the limited amounts of product applied to

subjects in this type of study, it seems reasonable to assume that a minimal preclinical testing will be necessary.

Both ICH and FDA guidelines[29,60] recognize that in some cases generation of human clinical data at an early stage, can provide improved insight into human physiology/pharmacology of the candidate drug, knowledge of drug candidate characteristics and therapeutic target relevance to disease. Thus, clinical studies intended to be conducted early in Phase I, involving limited human exposure, with no therapeutic intent, and not intended to examine clinical tolerability may have a different consideration in terms of requirements. The most extreme situation is that of minimal exposure in human studies. According to the ICH M3(R2) guideline, *"The amount and type of nonclinical supporting data that is appropriate in these situations will be dependent on the extent of proposed human exposure, both with respect to the maximum clinical dose used and the duration of dosing*". Scenario 3 proposed for PSO fits the approach 5 proposed in the guideline: "*Studies with dosing up to 14 days and not to exceed the duration of dosing in non-rodent; into therapeutic range but not intended to evaluate MTD*".

We considered that scenario 3, where treatment will be administered during 14 days and the study is not intended to evaluate clinical MTD, fits this approach and thus we based the plan on this recommendations. It is recommended to perform a standard 2-week repeated dose toxicity study in rodents and a confirmatory study in non-rodent at the anticipated NOAEL exposure observed in the rodent study with duration at least the intended clinical study duration. This approach allows for a reduced animal testing in non-

rodents limiting the number of animals needed. As alternative approaches not described in the guidance are encouraged, we have done an ad hoc interpretation of this approach to adapt it to our scenario 3, where a topical product with negligible systemic absorption is being tested. In this scenario, human testing will use very limited amounts of product that will be applied in limited areas in an occlusive way to maximize the penetration of the product into the skin. In this scenario, we consider that with a product with minimum or negligible systemic availability, it is anticipated that the systemic exposure in humans will be negligible and thus it is not necessary to characterize toxicity on target organs at this stage.

On the other hand, a dermal toxicology study will contribute with the following information:

- Toxicokinetics will obtain complementary data of the systemic bioavailability of the product when applied in large amounts on the skin of animals
- Toxicity evaluation will give insights on the toxicity on the skin
- Irritation testing on animal skin can be incorporated in such studies and this data should be available as no dedicated human study testing irritation will be performed before the psoriasis plaque test

It has been considered that data provided by the toxicology package proposed will provide sufficient information to assess the risks of performing a microplaque assay in humans. This approach may avoid unnecessary testing and in consequence the use of resources and time spent in the testing.

There are however, some drawbacks for this scenario. The first one is that data generated by the PoC study is not directly clinically meaningful. That means that in the event of a positive result, a full phase II phase will have to be done, as well as additional phase I trials, and there are some chances that the results are not consistent with those of the plaque assay. Although a negative result in a well-designed microplaque test will in all probability preclude the development of the product, many products showing positive results in such trials have failed in further clinical trials as it has been discussed in the previous section.

Regarding non-clinical data, the reduced package that was generated will have to be extended, and in most situations it will mean ending up in larger non-clinical testing.

5.5. Estimation of costs and times

Even if there are particularities for both conditions (AE and PSO), the estimation of time and costs for scenarios 1 and 2 has been done indistinctly of the condition studied. Some of these particularities would be affecting recruitment of patients, and have been already discussed in section 5.3.

Scenario 1 is the longest and more expensive one. A lot of resources must be invested before having any clinical sign of the activity of the product, but on the other hand, results obtained from a well-designed and well conducted dose-finding study provide a solid base for decision making, and positions the product halfway to the marketing authorization application in case that the results are positive. In this case, scenario 1 is the most efficient approach.

However, from the point of view of reaching a first clinical sign on the potential of the product to be effective in patients, scenario 2 for AE and scenario 3 for PSO represent more favorable situations, reducing the time to decision by 27% (12 months) in the case of scenario 2 and by 65% (29 months) in the case of scenario 3 with the psoriasis plaque test. Clinical development dummy costs simulated for scenario 2 are 40% of those of scenario 1, and those of scenario 3 represent 12.3% of scenario 1 and 30.1% of scenario 2.

It must be taken into account that several factors may influence the timelines anticipated for a clinical development. Delays in the regulatory and IRB assessments, administrative issues with the study sites and delays in recruitment due to different factors are frequent and vary between countries.[118] Although they are mainly out of the control of the sponsor, strategies to minimize them and to help milestones to be reached on time can be implemented. However, we anticipate that multicenter trials will accumulate more delays related to administrative issues with the sites. Regarding the assessments of the regulatory agencies and the IRB, we anticipate that any approach with reduced data may be questioned by the evaluators that, in order to ensure patient safety, will be unlikely to approve any unconventional approach, and may ask for clarifications or additional justifications for the chosen strategy, thus delaying the implementation of the study.

Delays in recruitment of patients will be mostly related to strict inclusion criteria and unavailability of the type of patients to be included in the study. For this reason, limiting exclusion criteria to those strictly necessary and a thorough review of eligibility criteria at the time of estimation of recruitment are strategies that may help avoid such situations. Also, the stricter the requirements for the participant are (i.e. number of visits, avoiding

treatment of lesions different to the target lesions, invasive tests) the more difficult is that the patient would give consent to participate in the study.

Finally, it should be reminded that relatively small delays in the timelines may represent a quantic impact on the calendar, since losing the season period may imply many unfit months for patient recruitment and follow-up.

The calculations of time and costs have been performed limited up to proof of concept study and do not account for the different time and costs that will be attributable to the confirmatory development in case that the development progresses further. Costs have been modeled only for clinical activities.

One of the conclusions after analyzing time and costs from the scenarios proposed is that the decision of choosing one or another scenario will greatly impact time and costs of further development in case that the decision to continue is taken. In view of that, it seems interesting to perform a sort of Markov modeling in which probabilities of success and costs for each scenario are assigned to calculate a final "cost-benefit" for each path.[119] However, although costs can easily be attributed based on standard assumptions as we have done in our work, the probabilities to be assigned in the decision nodes are not so straightforward, and should be based on extensive databases fed with real data, so that conclusions drawn from the analysis could be reliable.

Fairly good information on rates of success in drug development is available from private sources. Such data are used by the pharmaceutical industry to calculate a sort of risk premium, useful for budget planning, company value and investors. However, they are

generally considered sensible competitive intelligence, and are not accessible for research purposes.

5.6. Overall discussion

The objective of this work was to give some insights on the development of new molecular entities for the topical treatment of chronic inflammatory skin conditions. We chose two different pathologies, psoriasis and atopic dermatitis, that have different characteristics but share common features that make possible recommendations common for both of them. The aim was to generate some recommendations based on guidelines and on previous developments.

As a first step, all current information regarding the issue was searched and reviewed. We focused on all development, from the candidate selection to the phase II proof of concept studies, with the hypothesis that, having in mind the study aimed to proof the activity of the compound, a complete development can be drafted and followed straight and that this would save time and resources.

The present work confirms that very few NME have been developed in the period studied, and that information on this type of developments, especially that related to early phase, is scarce.

Regulatory guidelines, apart from some references in general guidelines to the topical application of products and some dedicated to the local tolerance non-clinical testing and photosafety testing, contribute with little information, transferring the decisions of what is the most adequate strategy at an early stage to the sponsor. Also, responsibility relies

on regulatory authorities and IRB, which may in turn lead to subjective decisions on the acceptability of the approaches.

This may put into risk the integrity of the subjects participating in early clinical research – either by allowing the testing in humans of not sufficiently characterized products, or by requiring larger exposures of patients for the sake of gathering sufficient amount of data. Also, may hamper the development of such products by requiring the sponsor to generate unnecessarily extensive data that will delay and raise the costs of the development up to a proof of concept; this may discourage the continuation of research programs, especially for small companies with scarce resources.

The existence of a clinical model as the psoriasis plaque test, allows obtaining a fast proof of concept for treatments intended for psoriasis. We would recommend this strategy for NME with new mechanisms of action, and small *a priori* evidence or rationale on their mechanisms of action and activity. These products have a higher risk of failure, and thus investing in previous work to generate supportive data for phase II trials may be deemed too risky in business terms.

For products with a robust a priori evidence of their viability, plaque assay studies may be used to screen formulations or strengths to be used in phase II trials, but our recommendation is to consider a proof of concept with an intra-subject left-right comparison that will save time and costs. Moreover, preclinical and clinical data generated previous to the PoC study will allow the development to continue with a phase IIb study, with minimal additional data.

Unfortunately, there is no equivalent for the plaque assay proof of concept in atopic eczema. The most efficient approach for products with small amount of evidence would then be a parallel intra-subject clinical trial.

The scenario in which the PoC study is a parallel inter-subject study is the most unfavorable in terms of time and costs, and we would only recommend it in a “low risk” scenario where the *a priori* probabilities that the product is successful are considerable. An example could be the topical development of a product already available by the systemic route.

The recommendations that we propose are based on the assumption of a minimal or negligible percutaneous absorption shown in animal species. We have proposed the designs that will maximize the probabilities of obtaining robust data for decision taking and proposed strategies to ensure validity of the studies. Factors such as the nature of the NME, the intended indication and *a priori* available data are key to decide which approach is the most adequate. Development plans different form the ones proposed in this work may be necessary, depending on the individual circumstances of each product and development.

A general guidance specific for topical dermatological products would improve the developments, standardizing the sequence of tasks during the development and as a consequence making the development process more efficient and predictable. We advocate for the regulatory agencies to issue a minimum set of recommendations for early stage development requirements to adjust the amount of non-clinical testing to an extent that guaranties the safety of subjects exposed during the development phases at

the same time that avoids excessive use of resources. We believe that this would encourage companies to develop more products in this area, filling many unmet medical needs.

6. Conclusions

1. There is no clear regulatory nor any scientific guidance on the best approach to exploratory development of dermatological products aimed to treat chronic inflammatory dermatological diseases.

2. The minimum set of objectives for an exploratory development of a NME aimed for the topical treatment of chronic inflammatory dermatological diseases include to obtain a preliminary formulation, the required guarantees of safety to perform exploratory clinical trials, namely genotoxicity, toxicology and pharmacokinetics, and to obtain an early proof of clinical activity.

3. The need for clinical studies before starting the phase II studies depends on the clinical trial designs, and in particular on the extent and duration of exposure. Clinical testing of dermal tolerability and systemic BA are needed depending on the degree of exposure planned in PoC studies

4. Minimum non-clinical data needed before starting clinical studies up to phase II or proof of concept includes chemical and pharmaceutical development studies, genotoxicity studies *in vitro*, toxicology by topical route in two species covering the duration of exposure in clinical trials and preliminary pharmacokinetic data. Depending on the clinical trial design, genotoxicity studies *in vivo*, core safety pharmacology, toxicology by systemic route in two species covering the duration of exposure in clinical trials and pharmacokinetic data in different animal species may also be required.

5. Possible designs for clinical trials aimed at assessing the efficacy of a topical treatment intended for the treatment of inflammatory dermatological diseases include inter-subject parallel comparisons and intra-subject parallel comparisons for atopic eczema, and also plaque assay test for psoriasis only.

6. Exploratory development plans driven by objectives have been proposed for atopic eczema including two different scenarios, based on inter-subject parallel and intra-subject parallel clinical trials, and for psoriasis including three scenarios, based on inter-subject parallel, intra-subject parallel and plaque assay studies.

7. The most efficient design in terms of time and dummy costs for atopic eczema is the scenario based on intra-subject parallel clinical trial, and for psoriasis, is the scenario based on plaque assay study. However, the efficiency of the different designs should also consider the impact of the exploratory plan in the overall development plan, since the ability to allow for a seamless continuation of the product development varies substantially.

8. A general regulatory guidance for early stage development requirements specific for topical dermatological products would be useful to adjust the amount of non-clinical testing to an extent that guaranties the safety of subjects exposed during clinical trials at the same time that avoids excessive use of resources, easing the development process and making it more efficient and predictable. We believe that this would encourage companies to develop more products in this area, filling many unmet medical needs.

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Annex I. Clinical Development Plan

Product- exploratory development in:

Atopic Eczema

1 Table of contents

2 Introduction

2.1 Background

2.1.1 Disease and currently available alternatives

To be tailored to the product

2.2 Rationale for the development

To be tailored to the product

2.3 Scope of development

The product is currently intended for the treatment of AE.

The scope of development is from candidate selection to clinical proof of concept, and consistent with the Target Product Profile

2.3.1 Target product profile

Indication	Short- and intermittent long-term treatment of mild to moderate and moderate to severe atopic dermatitis (eczema)
Route of administration	Topical dermal
Pharmaceutical form	Cream
Posology	Aimed to once daily – two daily could be acceptable
Main target population	Adults and children 2 years of age and older
Claims to be supported through the clinical development.	1) Efficacy: About 30% of the patients should show at least 90% improvement after 12 weeks of treatment based on EASI scale. 2) Clinically relevant improvement, as assessed by both clinical evaluation and patient (parents) perception of significant efficacy in less than 2 weeks of treatment, and signs and symptoms such as erythema, infiltration and papulation reduced within 8 days of initiating therapy 3) Less than 50% relapse within 2 weeks following the end of treatment of those patients treated successfully (90% improvement) 4) No skin atrophy, no discoloration. 5) No teratogenicity warnings 6) No lymphoma warnings 7) Systemic absorption from skin not clinically relevant 8) Neither photo allergy nor photo toxicity properties
Regions where the product should be marketed:	Global (or EU + USA)
Regulatory agencies that will be involved	EMA, Local national agencies within EU FDA

3 General investigational plan

3.1 Objective (s) of the development

The objective of the development is to explore the activity of the product by investigation of dose-response or superiority to placebo in mild to moderate AE.

Once there will be evidences to support the product activity in the indication, further development will be focused in refining dose selection and obtaining confirmation of such activity for regulatory purposes, as well as to generate any needed supporting information on the product to apply for a new drug authorization in EU and USA. This second phase of development is out of the scope of the present document.

3.2 Milestones of the development:

The main milestones, as relevant for the exploratory clinical development plan, are summarized below for each of the three main development areas.

3.2.1 Chemical- Pharmaceutical

1. First milestone: gram scale and pre-formulation. Obtain product and preliminary formulations for early testing, a formulation that has acceptable release properties with at least 3 months stability and a range of concentrations to be tested in clinical setting.
2. Second milestone: scale to kg and clinical samples. Obtain an improved final formulation with emollient properties appropriate for the treatment of psoriasis, which has acceptable release properties, at least 6 months stability and supports the relevant range of concentrations required for the clinical development of the product.

3.2.2 Non-clinical

1. First milestone: Activity data. Provide the minimum evidence necessary for supporting the product activity.

2. Second milestone: 28 days data. Provide the necessary safety, pharmacokinetic and toxicological information to allow proof of concept up to 28 days with preliminary formulations.

3.2.3 Clinical

1. First milestone: Tolerability. Demonstrate that the product can be applied locally to the skin, with no substantial local irritation potential and with no systemic effects.
2. Second milestone: Proof of activity. Demonstrate that the product has an effect in mild to moderate AE in adults, without substantial local adverse effects and with no systemic effects.

4 List of studies required to support the clinical proof of concept

Only listings are included; full study information including results of completed studies can be cross-referred to the product investigator's brochure.

CMC development and listing of studies is not included in the present document. Unless otherwise specified, it is assumed that production has been escalated to Kg scale, that a preliminary pharmaceutical development has selected a clinical formulation with a minimum stability of 6 months and appropriate release properties that is available for toxicology and clinical trials, and that analytical methods have been developed and validated for application to biological matrices.

4.1 Scenario 1

4.1.1 Non clinical development

- Pharmacodynamic studies supporting activity and proposed mechanism of action of the compound. In vitro target/receptor profiling and appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model that allows to support human dose selection.
- Core battery of safety pharmacology (CV, CNS and respiratory system)
- Genotoxicity: Ames assay (Bacterial mutation assay) and mammalian cell assays (in vitro/in vivo)
- Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to animals.
- Acute toxicity and toxicities up to 28 days by the oral route in two species (one non-rodent).
- Cutaneous route toxicology up to 28 days, including tolerability assessment.
- Toxicokinetic supportive studies.

4.1.2 Clinical development

4.1.2.1 Safety and tolerability

- Study of the irritation potential of the product at low strength, medium strength and high strength.
- Phase I maximal use pharmacokinetic study to determine the bioavailabilty of the product in healthy volunteers.

4.1.2.2 Proof of activity

- Double-blind randomized parallel groups proof of concept study comparing the product at low strength, medium strength and high strength, placebo (vehicle) and reference active product when applied for 28 days to patients with mild to atopic eczema.

4.2 Scenario 2

4.2.1 Non clinical development

- Pharmacodynamic studies supporting activity and proposed mechanism of action of the compound. In vitro target/receptor profiling and appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model that allows to support human dose selection.
- Core battery of safety pharmacology (CV, CNS and respiratory system)
- Genotoxicity: Ames assay (Bacterial mutation assay) and mammalian cell assays (in vitro/in vivo)
- Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to animals.
- Acute toxicity and toxicities up to 28 days by the oral route in two species (one non-rodent).
- Cutaneous route toxicology up to 28 days, including tolerability assessment.
- Toxicokinetic supportive studies.Clinical development

4.2.2 Clinical development

4.2.2.1 Safety and tolerability

- Study of the irritation potential of the product at low strength, medium strength and high strength.

4.2.2.2 Proof of activity

- Double-blind randomized within subject proof of concept study comparing the product at low strength, medium strength and high strength, placebo (vehicle) and reference active product when applied for 28 days to lesions of patient-volunteers with mild to moderate plaque atopic eczema affecting symmetrical areas.

5 Study outlines

5.1 Patch test cumulative irritation phase 1 study

Description: A phase I randomized, vehicle-controlled, within subject study, double-blind for the study preparations and observer-blind for the controls, to assess cumulative irritation potential of the product when applied to healthy skin.

Objective: To assess nonspecific, local irritating reactions of the study preparations on intact skin in subjects with healthy skin.

Design: Single-center, randomized, controlled, double-blind, intra-individual comparison of treatments. The determination of the sample size is based on experience with similar studies

Methods:

- Subjects:

33 male or female volunteers, giving written informed consent, aged 18 years or older, with healthy skin in the area of the test fields are randomized to get at least 30 evaluable cases.

- Treatment:

Occlusive application of the study preparations and controls to test fields with intact skin on the back will be performed once daily, from Mondays to Saturdays during a 21-day treatment period (18 treatments). Altogether 6 test fields on the back will be examined: 3 different strengths of the product, vehicle without active ingredients, negative control (Aqua demin.) and a positive control (0,1% sodium dodecyl sulfate (SDS). Approximately 200 µl of each study preparation or control will be applied to the respective test fields (approximately 2.5 cm^2) using Finn Chambers® of 18 mm inside in diameter. The individual test chambers will be filled daily in accordance with the permutation in the randomization list. The test chambers will be fixed with adhesive patches. The outline of the test field will be drawn on the skin using a stencil. The chambers and adhesive patches will be removed daily before the next application.

- Endpoints

Main endpoints: Erytema assessment for the test fields will be performed on study days 2 - 6, 8 - 13, 15, 20 and on study day 22 and graded according to an ordinal scale (0 to 4). A cumulative irritation score (CIS) will be calculated by day, adding up all previous assessment scores including day X. Also, a cumulative irritation index (CiII) Will be calculated dividing the CIS by 4 (maximum value for the scoring system) multiplied by the number of evaluable patients and the number of evaluations, expressed as a percentage.

Safety variables: Medical history physical examination incl. vital signs and laboratory parameters at screening and final clinical examination, recording of adverse events.

Planning

First patient in: Day 0

Last patient out: + 2 months from day 0

Final report: + 3 months from day 0

5.2 Phase I maximal use pharmacokinetic study to determine the absorption and excretion of the product in healthy volunteers.

Description: This is a dedicated pharmacokinetic study aimed to qualify if any systemic exposure occurs. It is required prior to a parallel comparison for 28 days in PSO patients.

Objectives: The main objective is to obtain pharmacokinetic data of the product administered topically after single and repeated applications.

Design: Phase I open label study.

Methods:

- Patients/volunteers: eight healthy male or female volunteers aged over 18 and less than 65, with phototype I to IV are planned.
- Treatment: The product will be applied at the highest intended dose to a broad skin area (double of the intended surface in clinical studies) during 7 days. The treatment applications will be performed daily at the study site.
- Outcome measures: Levels of the product in plasma and urine. Plasma levels will be measured at day one, day 4 and day 7. Cmax, Tmax, T1/2, AUC0-t at day one and at day 4 and 7.

Planning:

First patient in: Day 0

Last patient out: + 1 month from day 0

Final report: + 5 months from day 0

5.3 Proof of concept parallel controlled 4 weeks study (scenario 1)

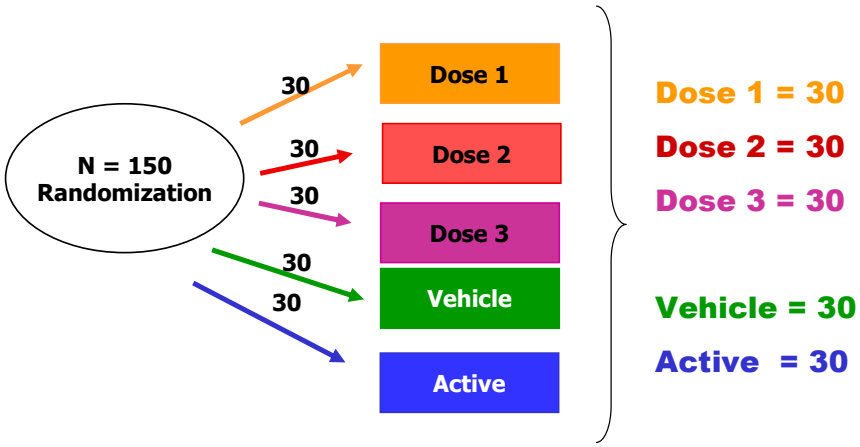
Phase IIa, active and placebo parallel controlled study, to assess the clinical efficacy and skin tolerability of the product at three different strengths in adult patients with mild to moderate atopic dermatitis.

Description: Double-blind randomized parallel groups proof of concept study comparing the product at low strength, medium strength and high strength, placebo and reference active product when applied for 28 days.

Objectives

- Primary: To compare the clinical efficacy of the product at low strength, medium strength and high strength, applied once daily for 4 weeks, with that of product vehicle and with reference active compound in adult patients with mild to moderate atopic dermatitis.
- Secondary: To assess the dose-response relationship of three growing concentrations of the product in atopic dermatitis. To assess safety and local tolerability of the experimental treatments.

Design: Double blind randomized active and controlled study. The intended sample size is 150 subjects, randomized to 5 groups (30 per group) (see figure below).



Methods

- Subjects:

Inclusion Criteria:

- Male or female patients aged 18 years or older
- Patients with a diagnosis of AE according to UK Working Party's Diagnostic Criteria for Atopic Dermatitis and with SCORAD value between 8 and 30
- Patients giving written informed consent

Exclusion Criteria:

- Pregnant or lactating women;
- Use of any topical atopic dermatitis therapy in selected areas within two weeks of the study entry and during the study.
- Use of any systemic atopic dermatitis therapy (including phototherapy) within 8 weeks prior to the study entry and during the study.
- Subject receiving topical or systemic medical treatment:
    - anti-inflammatory, antihistamines drugs, or antibiotics in the week preceding the study and during the study,
    - immuno-suppressors and/or corticoids in the month preceding the study and during the study (stabilized treatment with inhaled corticosteroids for asthma and/ or nasal topical steroids for rhinitis are allowed),
    - Systemic retinoids in the six months preceding the study and during the study,
    - any other treatment stabilized likely to interfere the results since less than one month before the study.
- Patients, who in the opinion of the investigator, have clinically relevant history or presence of any disease, any other skin disorder or chronic medical condition which may interfere with the conduct and assessments of the trial
- Patients who have used any study drug (including experimental biologics) and/or participated in any clinical trial within the last 60 days before the day of randomization

- Treatment

Patients will be assigned randomly to be treated with one of the study treatments. Study medication will be prepared in identical tubes and labeled with the number of patients. Study medication will be given every week to the patients. Patients will be instructed to apply a layer of the study treatment to all affected body areas (up to a maximum of 20% of body surface area) twice daily. To monitor the treatment compliance and the amount of product applied, the patient will fill out a patient's diary with the administrations and tubes returned will be weighed. Treatment duration will be 4 weeks.

- Endpoints:

Main endpoint: Change from baseline in EASI at week 4

Secondary endpoint: Success rate at different time points (week 1, 2, 3 and 4): % of patients with a score of clear or almost clear on the 6 point categorical measure investigator's global assessment. Change from baseline in EASI at week 1, 2 and 3.

Safety assessments: Once a week, the Investigator will examine the skin of the subject and will assess local tolerability taking as reference the pre-treatment measures and according to categorical (0 to 4) dermatoxicity, itching and dermal atrophy scales.

Planning

First patient in: October/November year 2 of clinical development

Last patient out: End of April/end of May year 3 of clinical development

Final report: End of August/end of September year 3 of clinical development

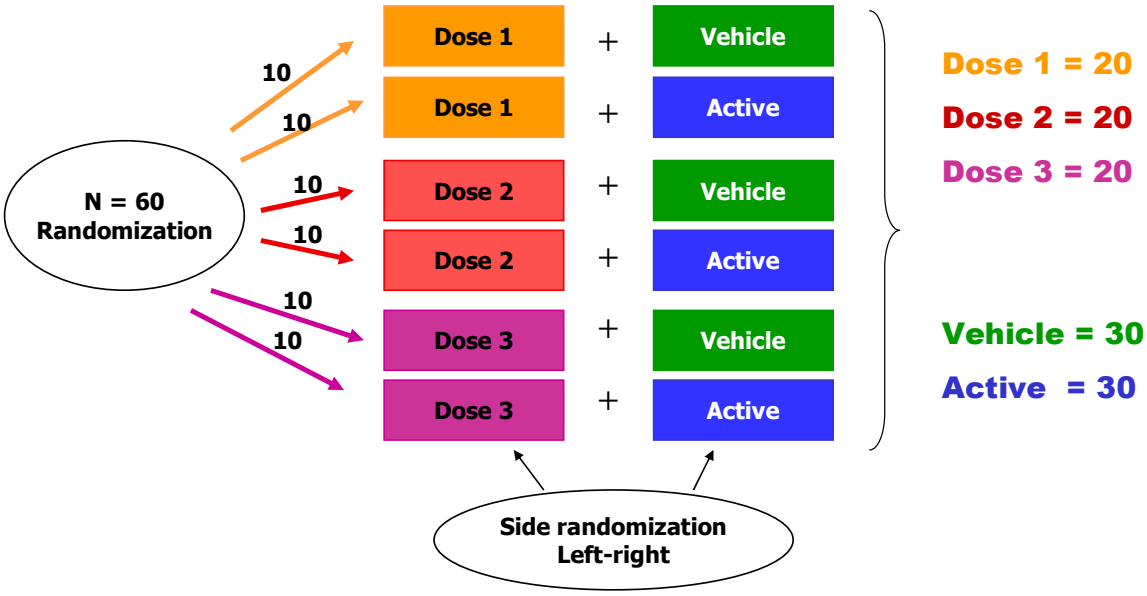
5.4 Proof of concept parallel intra-patient comparison 4 week study (scenario 2)

Description: Phase IIa, intra-patient active and vehicle controlled study, to assess the clinical efficacy and skin tolerability of the product at three different strengths in adult patients with mild to moderate atopic eczema.

Objectives

- Primary: To compare the clinical efficacy of the product at low strength, medium strength and high strength, applied once daily for 4 weeks with that of product vehicle and with reference active compound in adult patients with mild to moderate atopic eczema.
- Secondary: To assess the dose-response relationship of three growing concentrations of the product in atopic eczema. To assess safety and local tolerability of the experimental treatments.

Design: Double blind randomized active and controlled intra-patient study. The intended sample size is 60 subjects, randomized to 6 groups (6 intra-subject comparison). Each subject will be randomized to receive either low strength, medium strength and high strength in one eczema area, and either vehicle or active reference in the other area. (randomization ratio 1:1:1:1:1) (see figure below).



Methods

- Subjects:

Inclusion Criteria:

- Male or female patients aged 18 years or older.
- Patients with a diagnosis of AE according to UK Working Party's Diagnostic Criteria for Atopic Dermatitis and with SCORAD value between 8 and 30.
- Patient with at least two atopic dermatitis areas on equivalent topographic areas (arms, legs or trunk). The sum of the size of each of the 2 areas selected will not exceed 20% of the body
- Patients giving written informed consent.

Exclusion Criteria:

- Pregnant or lactating women;
- Use of any topical atopic dermatitis therapy in selected areas within two weeks of the study entry and during the study.
- Use of any systemic atopic dermatitis therapy (including phototherapy) within 8 weeks prior to the study entry and during the study.

- Subject receiving topical or systemic medical treatment:
    - anti-inflammatory, antihistamines drugs, or antibiotics in the week preceding the study and during the study,
    - immuno-suppressors and/or corticoids in the month preceding the study and during the study (stabilized treatment with inhaled corticosteroids for asthma and/ or nasal topical steroids for rhinitis are allowed),
    - Systemic retinoids in the six months preceding the study and during the study,
    - any other treatment stabilized likely to interfere the results since less than one month before the study.
- Patients, who in the opinion of the investigator, have clinically relevant history or presence of any disease, any other skin disorder or chronic medical condition which may interfere with the conduct and assessments of the trial
- Patients who have used any study drug (including experimental biologics) and/or participated in any clinical trial within the last 60 days before the day of randomization
- A total of 60 patients are planned (twenty intra-individual comparisons for each experimental treatment vs control)
- <u>Treatment</u>

Patients will come to the study site every day for being treated with the study medication. A study technician will be in charge of preparing the necessary amount of the study medication for each patient administration, according to the patient number and side of the body to receive each of the treatments, and in a way that the patient will not see the immediate packaging. The technician will apply the respective products in a thin layer on the specified psoriatic plaque. The amount of ointment to be applied will be roughly the size of a pea for each product.

Because the treatment will be applied to each of the selected patient lesions daily by a technician at the study site, the compliance of the treatment will be measured according to the dispensation log records for each patient.

- Endpoints:

Main endpoint: The main end-point will be the intra-subject difference in the percent change from baseline in the local EASI (sum of values of scores in redness, thickness, scratching and lichenification) as assessed by clinical examination by the dermatologist after 28 days of treatment.

Secondary endpoint: Success rate at different time points (week 1, 2, 3 and 4): % of lesions assigned to each treatment with a score of clear or almost clear on the 6 point categorical measure investigator's global assessment for the studied area.

Safety assessments:

Once a week, before and after product use, the Investigator will examine the skin of the subject and will assess local tolerability taking as reference the pre-treatment measures and according to categorical (0 to 4) dermatoxicity, itching and dermal atrophy scales and independently for each of the symmetrical areas selected for the study.

Planning

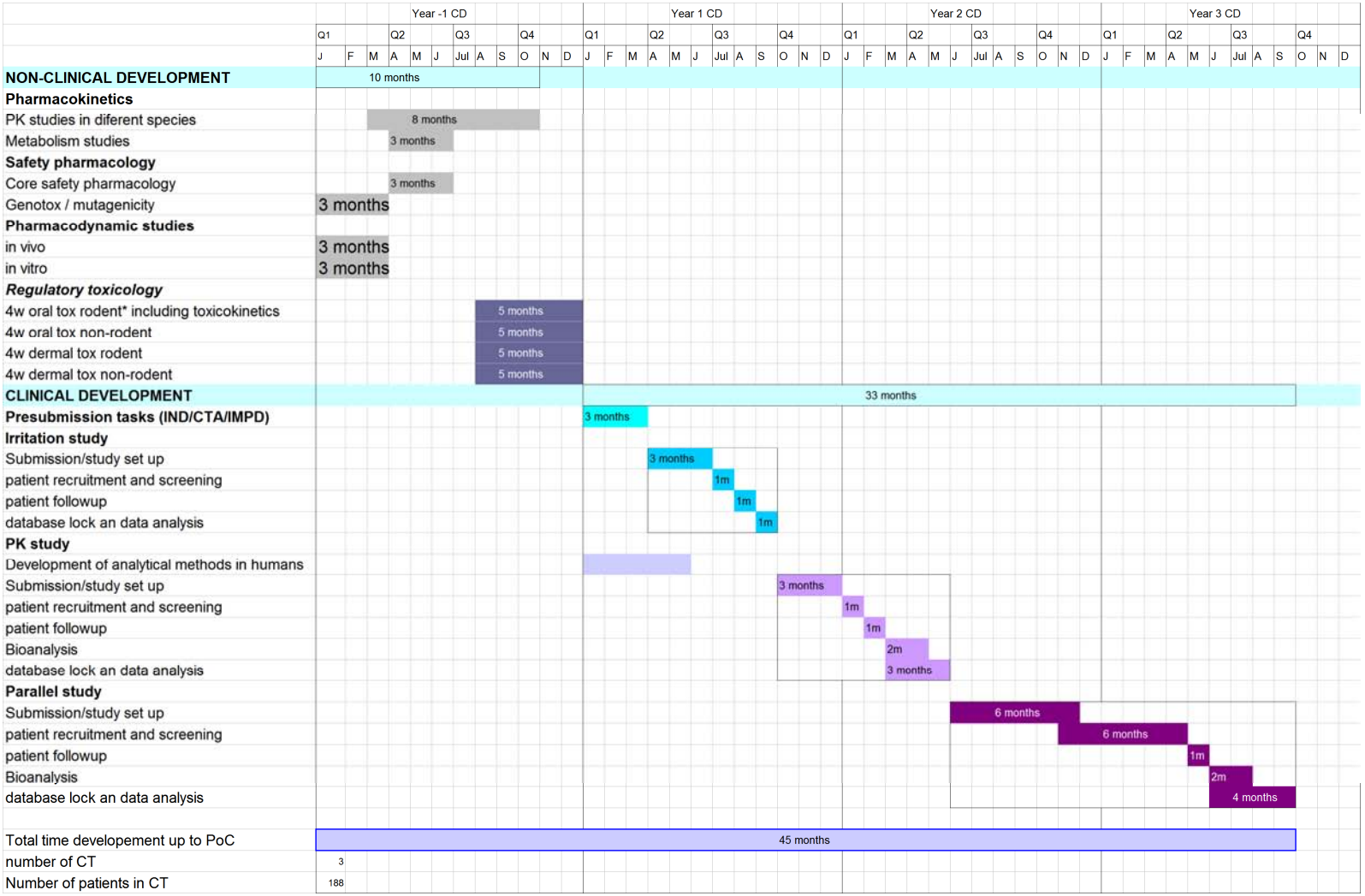
First patient in: October/November

Last patient out: End of April/end of May

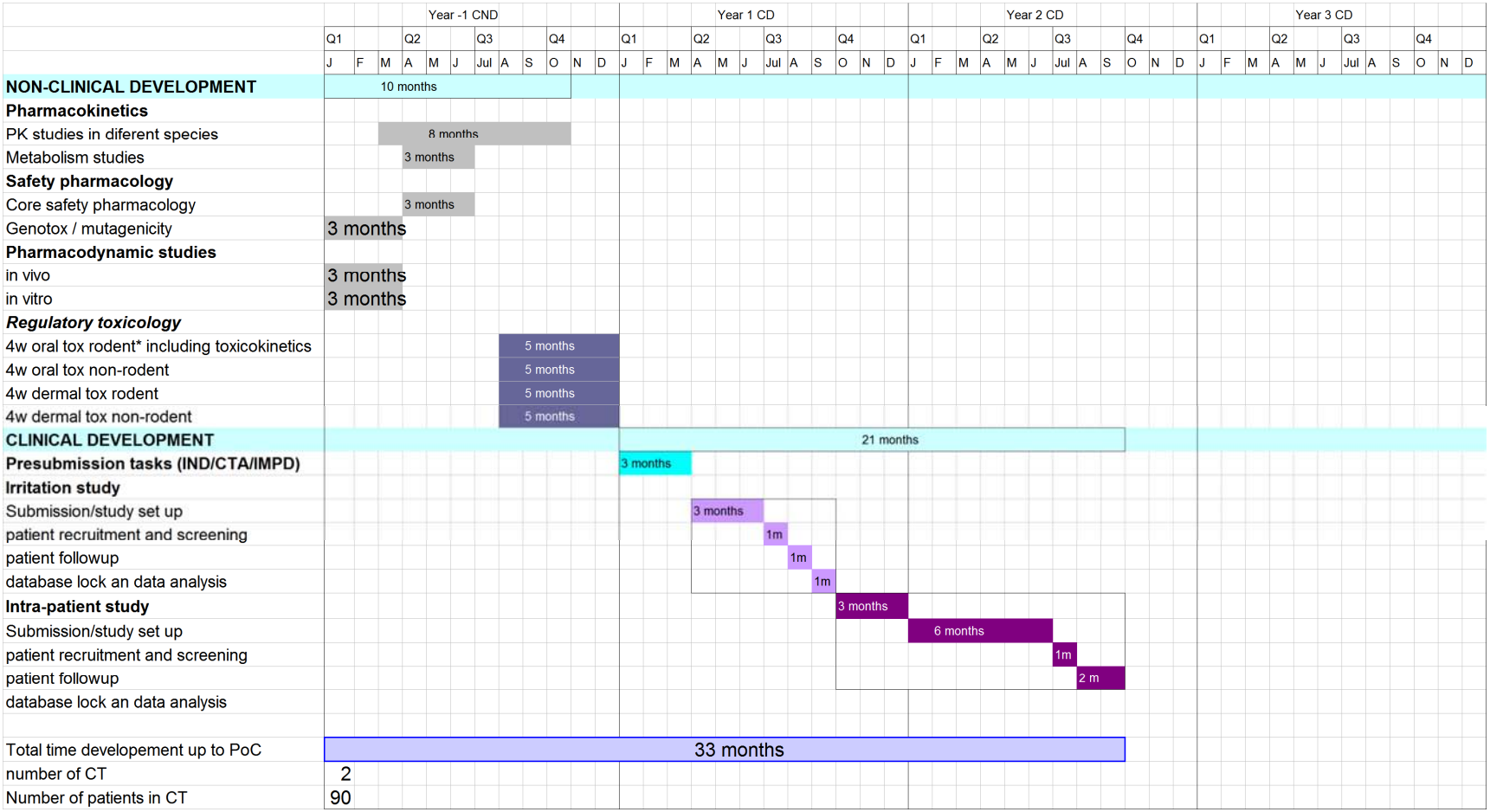
Final report: End of August/end of September

6 Summary of timelines and estimated costing of development

6.1 Scenario 1: parallel comparison



6.2 Scenario 2: parallel intra-subject comparison



Annex II. Clinical Development Plan

Product- exploratory development in:

Psoriasis

1 Table of contents

2 Introduction

2.1 Background

2.1.1 Disease and currently available alternatives

To be tailored to the product

2.2 Rationale for the development

To be tailored to the product

2.3 Scope of development

The product is currently intended for the treatment of psoriasis.

The scope of development is from candidate selection to clinical proof of concept, and consistent with the Target Product Profile

2.3.1 Target product profile

Indication	Short term and intermittent long term treatment of mild to moderate plaque-type psoriasis
Route of administration	Topical dermal
Pharmaceutical form	Ointment
Posology	Aimed to once daily – two daily could be acceptable
Main target population	Adults
Claims to be supported through the clinical development.	1) Similar efficacy to vitamin D3 derivative. About 60% of the patients should show at least 'marked improvement' after 8 weeks of treatment based on PASI scale. 2) Clinically relevant improvement, as assessed by both investigator and patients, in less than 2 weeks of treatment. 3) Safety profile superior to topical corticosteroids, with no dermal atrophy 4) Topical tolerability (mainly irritation) better than vitamin D derivatives. 5) No teratogenicity warnings (to differentiate from retinoids) 6) No lymphoma warnings (to differentiate from calcineurin inhibitors) 7) Systemic absorption from skin not clinically relevant 8) Neither photo allergy nor photo toxicity properties
Regions where the product should be marketed:	Global (or EU + USA)
Regulatory agencies that will be involved	EMA, Local national agencies within EU FDA

3 General investigational plan

3.1 Objective (s) of the development

The objective of the development is to explore the activity of the product by investigation of dose-response or superiority to placebo in mild to moderate psoriasis.

Once there will be evidences to support the product activity in the indication, further development will be focused in refining dose selection and obtaining confirmation of such activity for regulatory purposes, as well as to generate any needed supporting information on the product to apply for a new drug authorization in EU and USA. This second phase of development is out of the scope of the present document.

3.2 Milestones of the development:

The main milestones, as relevant for the exploratory clinical development plan, are summarized below for each of the three main development areas.

3.2.1 Chemical- Pharmaceutical

1. First milestone: gram scale and pre-formulation. Obtain product and preliminary formulations for early testing, a formulation that has acceptable release properties with at least 3 months stability and a range of concentrations to be tested in clinical setting.
2. Second milestone: scale to kg and clinical samples. Obtain an improved final formulation with emollient properties appropriate for the treatment of psoriasis, which has acceptable release properties, at least 6 months stability and supports the relevant range of concentrations required for the clinical development of the product.

3.2.2 Non-clinical

1. First milestone: Activity data. Provide the minimum evidence necessary for supporting the product activity.
2. Second milestone: 28 days data. Provide the necessary safety, pharmacokinetic and toxicological information to allow proof of concept up to 28 days with preliminary formulations.

3.2.3 Clinical

1. First milestone: Tolerability. Demonstrate that the product can be applied locally to the skin, with no substantial local irritation potential and with no systemic effects.
2. Second milestone: Proof of activity. Demonstrate that the product has an effect in mild to moderate PSO in adults, without substantial local adverse effects and with no systemic effects.

4 List of studies required to support the clinical proof of concept

Only listings are included; full study information including results of completed studies can be cross-referred to the product investigator's brochure.

CMC development and listing of studies is not included in the present document. Unless otherwise specified, it is assumed that production has been escalated to Kg scale, that a preliminary pharmaceutical development has selected a clinical formulation with a minimum stability of 6 months and appropriate release properties that is available for toxicology and clinical trials, and that analytical methods have been developed and validated for application to biological matrices.

4.1 Scenario 1

4.1.1 Non clinical development

- Pharmacodynamic studies supporting activity and proposed mechanism of action of the compound. In vitro target/receptor profiling and appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model that allows to support human dose selection.
- Core battery of safety pharmacology (CV, CNS and respiratory system)
- Genotoxicity: Ames assay (Bacterial mutation assay) and mammalian cell assays (in vitro/in vivo)
- Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to animals.
- Acute toxicity and toxicities up to 28 days by the oral route in two species (one non-rodent).
- Cutaneous route toxicology up to 28 days, including tolerability assessment.
- Toxicokinetic supportive studies.

4.1.2 Clinical development

4.1.2.1 Safety and tolerability

- Study of the irritation potential of the product at low strength, medium strength and high strength.
- Phase I maximal use pharmacokinetic study to determine the bioavailabilty of the product in healthy volunteers.

4.1.2.2 Proof of activity

- Double-blind randomized parallel groups proof of concept study comparing the product at low strength, medium strength and high strength, placebo (vehicle) and reference active product when applied for 28 days to patients with mild to moderate plaque psoriasis.

4.2 Scenario 2

4.2.1 Non clinical development

- Pharmacodynamic studies supporting activity and proposed mechanism of action of the compound. In vitro target/receptor profiling and appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model that allows to support human dose selection.
- Core battery of safety pharmacology (CV, CNS and respiratory system)
- Genotoxicity: Ames assay (Bacterial mutation assay) and mammalian cell assays (in vitro/in vivo)
- Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to animals.
- Acute toxicity and toxicities up to 28 days by the oral route in two species (one non-rodent).
- Cutaneous route toxicology up to 28 days, including tolerability assessment.
- Toxicokinetic supportive studies.

4.2.2 Clinical development

4.2.2.1 Safety and tolerability

- Study of the irritation potential of the product at low strength, medium strength and high strength.

4.2.2.2 Proof of activity

- Double-blind randomized within subject proof of concept study comparing the product at low strength, medium strength and high strength, placebo (vehicle) and reference active product when applied for 28 days to lesions of patient-volunteers with mild to moderate plaque psoriasis affecting symmetrical flexural areas.

4.3 Scenario 3

Slightly lower CMC requirements may apply in this scenario, so that requirements on toxicology are lower and thus the kilo scale might not be necessarily in place. Also, the final formulation might not be still completely defined; alternatively, solution of active principle or preliminary raw formulations may be used for the proof of concept, which can even be used for choosing between final candidate formulations.

4.3.1 Non clinical development

- Pharmacodynamic studies supporting activity and proposed mechanism of action of the compound. In vitro target/receptor profiling and appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model that allows to support human dose selection.
- Core battery of safety pharmacology (CV, CNS and respiratory system) (may be waived if product absorption is negligible)
- Genotoxicity: Ames assay (Bacterial mutation assay) and mammalian cell assays (in vitro)
- Pharmacokinetic studies of the product given by the iv, the oral and the cutaneous route to animals

- 2-week repeated dose toxicology by topical route in rodent
- Confirmatory toxicology study by non-topical route in non-rodent (at the anticipated NOAEL exposure in rodent), 2 weeks.
- Toxicokinetic supportive studies.

4.3.2 *Clinical development*

4.3.2.1 Proof of activity

- Phase I, randomized trial to assess the antipsoriatic effect of three strengths of the product, vehicle and an active control using a psoriasis plaque test.

5 Study outlines

5.1 Patch test cumulative irritation phase 1 study

Description: A phase I randomized, vehicle-controlled, within subject study, double-blind for the study preparations and observer-blind for the controls, to assess cumulative irritation potential of the product when applied to healthy skin.

Objective: To assess nonspecific, local irritating reactions of the study preparations on intact skin in subjects with healthy skin.

Design: Single-center, randomized, controlled, double-blind, intra-individual comparison of treatments. The determination of the sample size is based on experience with similar studies

Methods:

- Subjects:

33 male or female volunteers, giving written informed consent, aged 18 years or older, with healthy skin in the area of the test fields are randomized to get at least 30 evaluable cases.

- Treatment:

Occlusive application of the study preparations and controls to test fields with intact skin on the back will be performed once daily, from Mondays to Saturdays during a 21-day treatment period (18 treatments). Altogether 6 test fields on the back will be examined: 3 different strengths of the product, vehicle without active ingredients, negative control (Aqua demin.) and a positive control (0,1% sodium dodecyl sulfate (SDS). Approximately 200 µl of each study preparation or control will be applied to the respective test fields (approximately 2.5 cm^2) using Finn Chambers® of 18 mm inside in diameter. The individual test chambers will be filled daily in accordance with the permutation in the randomization list. The test chambers will be fixed with adhesive patches. The outline of the test field will be drawn on the skin using a stencil. The chambers and adhesive patches will be removed daily before the next application.

- Endpoints

Main endpoints: Erytema assessment for the test fields will be performed on study days 2 - 6, 8 - 13, 15, 20 and on study day 22 and graded according to an ordinal scale (0 to 4). A cumulative irritation score (CIS) will be calculated by day, adding up all previous assessment scores including day X. Also, a cumulative irritation index (CiII) Will be calculated dividing the CIS by 4 (maximum value for the scoring system) multiplied by the number of evaluable patients and the number of evaluations, expressed as a percentage.

Safety variables: Medical history physical examination incl. vital signs and laboratory parameters at screening and final clinical examination, recording of adverse events.

Planning

First patient in: Day 0

Last patient out: + 2 months from day 0

Final report: + 3 months from day 0

5.2 Phase I maximal use pharmacokinetic study to determine the absorption and excretion of the product in healthy volunteers.

Description: This is a dedicated pharmacokinetic study aimed to qualify if any systemic exposure occurs. It is required prior to a parallel comparison for 28 days in PSO patients.

Objectives: The main objective is to obtain pharmacokinetic data of the product administered topically after single and repeated applications.

Design: Phase I open label study.

Methods:

- Patients/volunteers: eight healthy male or female volunteers aged over 18 and less than 65, with phototype I to IV are planned.
- Treatment: The product will be applied at the highest intended dose to a broad skin area (double of the intended surface in clinical studies) during 7 days. The treatment applications will be performed daily at the study site.
- Outcome measures: Levels of the product in plasma and urine. Plasma levels will be measured at day one, day 4 and day 7. Cmax, Tmax, T1/2, AUC0-t at day one and at day 4 and 7.

Planning:

First patient in: Day 0

Last patient out: + 1 month from day 0

Final report: + 5 months from day 0

5.3 Proof of concept parallel controlled 4 weeks study (scenario 1)

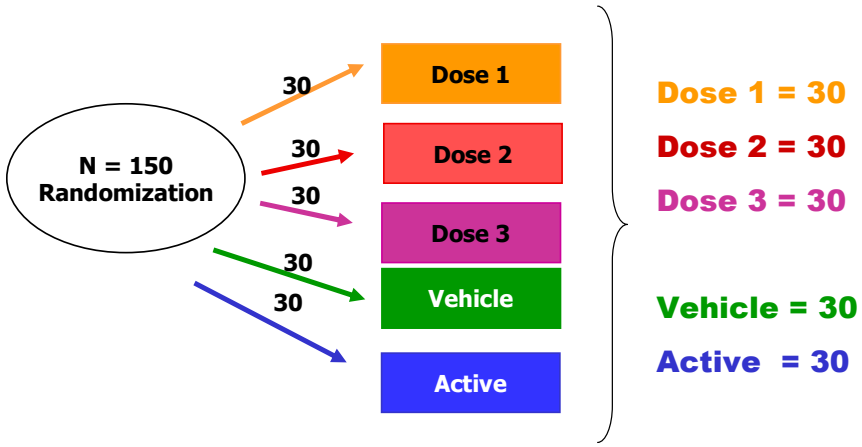
Phase IIa, active and placebo parallel controlled study, to assess the clinical efficacy and skin tolerability of the product at three different strengths in adult patients with mild to moderate chronic plaque psoriasis.

Description: Double-blind randomized parallel groups proof of concept study comparing the product at low strength, medium strength and high strength, placebo and reference active product when applied for 28 days.

Objectives

- Primary: To compare the clinical efficacy of the product at low strength, medium strength and high strength, applied once daily for 4 weeks, with that of product vehicle and with reference active compound in adult patients with mild to moderate plaque type psoriasis.
- Secondary: To assess the dose-response relationship of three growing concentrations of the product in plaque type psoriasis. To assess safety and local tolerability of the experimental treatments.

Design: Double blind randomized active and controlled study. The intended sample size is 150 subjects, randomized to 5 groups (30 per group) (see figure below).



Methods

- Subjects:

Inclusion Criteria:

- Male or female patients aged 18 years or older
- Patients with mild-moderate plaque psoriasis with up to 20% affected body surface area (BSA) (not including face or scalp) suitable for topical therapy
- Patients giving written informed consent

Exclusion Criteria:

- Pregnant or lactating women.
- Patients who have been treated with topical steroids, topical immunosuppressive/ immunomodulative drugs, topical vitamin D3 derivative, topical retinoids, anthralin, coal tar (except when used as shampoo) salicylic acid within 14 days of randomization.
- Patients, who in the opinion of the investigator, have clinically relevant history or presence of any disease, any other skin disorder or chronic medical condition which may interfere with the conduct and assessments of the trial.
- Patients who have used any study drug (including experimental biologics) and/or participated in any clinical trial within the last 60 days before the day of randomization.
- Patients who have been treated with any biologics for their psoriasis within 30 days or 5 half-lives (whichever is longer) of the biologic before the day of randomization the longest documented half-life of the biologic should be used to calculate the 5 half-lives.
- Patients who have been treated with phototherapy (laser, oral steroids, oral retinoid, oral immunosuppressive/immunomodulative drugs, cytostatics, cyclosporine or methotrexate within 30 days of randomization.

- Treatment

Patients will be assigned randomly to be treated with one of the study treatments. Study medication will be preapred in identical tubes and labeled with the number of patients. Study medication will be given every week to the patients. Patients will be instructed to apply a layer of the study treatment to all affected body areas (up to a maximum of 20% of body surface area) twice daily. To monitor the treatment compliance and the amount of product applied, the patient will fill out a patient's diary with the administrations and tubes returned will be weighed. Treatment duration will be 4 weeks.

- Endpoints:

Main endpoint: Change from baseline in PASI at week 4.

Secondary endpoint: Success rate at different time points (week 1, 2, 3 and 4): % of patients with a score of clear or almost clear on the 6 point categorical measure investigator's global assessment. Change from baseline in PASI at week 1, 2 and 3.

Safety assessments: Once a week, the Investigator will examine the skin of the subject and will assess local tolerability taking as reference the pre-treatment measures and according to categorical (0 to 4) dermatoxicity, itching and dermal atrophy scales.

Planning

First patient in: October/November year 2 of clinical development

Last patient out: End of April/end of May year 3 of clinical development

Final report: End of August/end of September year 3 of clinical development

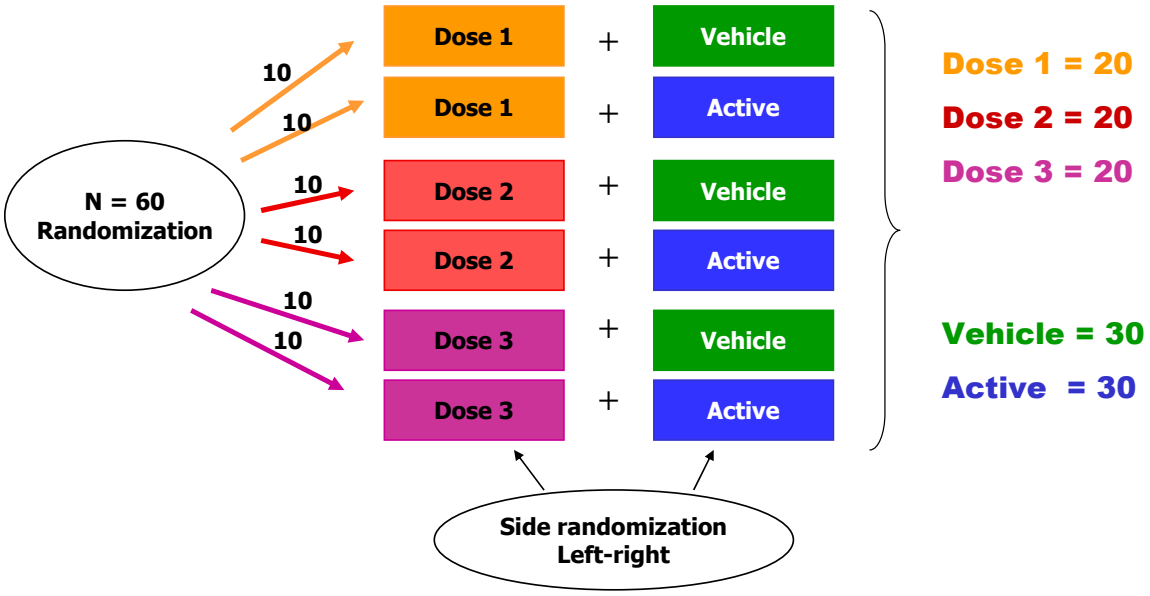
5.4 Proof of concept parallel intra-patient comparison 4 week study (scenario 2)

Description: Phase IIa, intra-patient active and vehicle controlled study, to assess the clinical efficacy and skin tolerability of the product at three different strengths in adult patients with mild to moderate chronic plaque psoriasis.

Objectives

- Primary: To compare the clinical efficacy of the product at low strength, medium strength and high strength, applied once daily for 4 weeks with that of product vehicle and with reference active compound in adult patients with mild to moderate plaque type psoriasis.
- Secondary: To assess the dose-response relationship of three growing concentrations of the product in plaque type psoriasis. To assess safety and local tolerability of the experimental treatments.

Design: Double blind randomized active and controlled intra-patient study. The intended sample size is 60 subjects, randomized to 6 groups (6 intra-subject comparison). Each subject will be randomized to receive either low strength, medium strength and high strength in one psoriasis affected area, and either vehicle or active reference in the other area. (randomization ratio 1:1:1:1:1) (see figure below).



Methods

- Subjects:

Inclusion Criteria:

- Male or female patients aged 18 years or older
- Patient with at least two eligible psoriatic plaques on equivalent topographic areas (arms, legs or trunk), ideally of size about 2%, but in all cases each smaller than 5%, of body surface area.
- Patients giving written informed consent

Exclusion Criteria:

- Pregnant or lactating women;
- Patients who have been treated with topical steroids, topical immunosuppressive/ immunomodulative drugs, topical vitamin D3 derivative, topical retinoids, anthralin, coal tar salicylic acid within 14 days of randomization
- Unstable psoriasis or psoriasis other than plaque-type

- Patients, who in the opinion of the investigator, have clinically relevant history or presence of any disease, any other skin disorder or chronic medical condition which may interfere with the conduct and assessments of the trial
- Patients who have used any study drug (including experimental biologics) and/or participated in any clinical trial within the last 60 days before the day of randomization
- Patients who have been treated with any biologics for their psoriasis within 30 days or 5 half-lives (whichever is longer) of the biologic before the day of randomization the longest documented half-life of the biologic should be used to calculate the 5 half-lives;
- Patients who have been treated with phototherapy (laser, oral steroids, oral retinoid, oral immunosuppressive/immunomodulative drugs, cytostatics, cyclosporine or methotrexate within 30 days of randomization
- A total of 60 patients are planned (twenty intra-individual comparisons for each experimental treatment vs control.
- <u>Treatment</u>

Patients will come to the study site every day for being treated with the study medication. A study technician will be in charge of preparing the necessary amount of the study medication for each patient administration, according to the patient number and side of the body to receive each of the treatments, and in a way that the patient will not see the immediate packaging. The technician will apply the respective products in a thin layer on the specified psoriatic plaque. The amount of ointment to be applied will be roughly the size of a pea for each product.

Because the treatment will be applied to each of the selected patient lesions daily by a technician at the study site, the compliance of the treatment will be measured according to the dispensation log records for each patient.

- Endpoints:

Main endpoint: The main end-point will be the intra-subject difference in the percent change from baseline in the sum of signs and symptoms scores (sum of severity scoring (0-3) of erythema, scaling and induration and pruritus) in each unilateral target lesion as assessed by clinical examination by the dermatologist after 28 days of treatment.

Secondary endpoint: Success rate at different time points (week 1, 2, 3 and 4): % of lesions assigned to each treatment with a score of clear or almost clear on the 6 point categorical measure investigator's global assessment for the studied area. Intra-subject difference in the percent change from baseline in the sum of signs and symptoms scores in each unilateral target lesion at week 1, 2 and 3.

Safety assessments:

Once a week, before and after product use, the Investigator will examine the skin of the subject and will assess local tolerability taking as reference the pre-treatment measures and according to categorical (0 to 4) dermatoxicity, itching and dermal atrophy scales and independently for each of the symmetrical areas selected for the study.

Planning

First patient in: October/November

Last patient out: End of April/end of May

Final report: End of August/end of September

5.5 Proof of concept plaque assay 2 weeks study (scenario 3)

Description: Phase I, randomized trial to assess the antipsoriatic effect of three strengths of the product, vehicle and an active control using a psoriasis plaque test.

Objectives

- Primary: To assess the antipsoriatic effect of three strengths of the product in paque psoriasis compared to vehicle and active control.
- Secondary: To assess the dose-response relationship of three growing concentrations of the product in plaque type psoriasis. To assess safety and local tolerability of the experimental treatments.

Design: Randomized, intra-patient, single-center, observer-blind, vehicle and active comparator controlled study. The study will allow to assess the dose response relationship of three growing concentration of the product as well as safety and local tolerability when the product is applied under occlusion. A total of 15 patients with single stable plaques in non extensor areas (i ex: thorax, arm or leg not involving skin close to joints or flexures) will receive daily simultaneous applications of the 5 treatments at delimited sites, occluded with a Finn Chamber which will be changed daily, during 2 weeks.

The antipsoriatic effect will be assessed by means of the clinical sum score at each application site after two weeks of treatment, and additionally the thickness of the psoriatic skin infiltrate assessed by ultrasonography twice a week and the pathological assessment by confocal in vivo microscopy will be also measured. Signs of skin irritation after occlusive application will also be monitored daily during the treatment period.

Methods

- Subjects:

Inclusion Criteria:

- Male or female patients aged 18 years or older
- Patients with psoriasis plaques in a chronic stable phase covering a sufficient area to allocate 5 treatment areas in 1 or 2 comparable plaques
- Patients giving written informed consent

Exclusion Criteria:

- Pregnant or lactating women;
- Patients, who in the opinion of the investigator, have clinically relevant history or presence of any disease, any other skin disorder or chronic medical condition which may interfere with the conduct and assessments of the trial
- Patients who have used any study drug (including experimental biologics) and/or participated in any clinical trial within the last 60 days before the day of randomization
- Patients who have been treated with topical steroids, topical immunosuppressive/ immunomodulative drugs, topical vitamin D3 derivative, topical retinoids, anthralin, coal tar (except when used as shampoo) salicylic acid within 14 days of randomization
- Patients who have been treated with any biologics for their psoriasis within 30 days or 5 half-lives (whichever is longer) of the biologic before the day of randomization the longest documented half-life of the biologic should be used to calculate the 5 half-lives;
- Patients who have been treated with phototherapy (laser, oral steroids, oral retinoid, oral immunosuppressive/immunomodulative drugs, cytostatics, cyclosporine or methotrexate within 30 days of randomization
- A total of 15 patients are planned.

- Treatment

Patients will receive daily simultaneous application of all 5 treatments at different skin sites, each randomly assigned a Finn skin chamber (1,4 cm diameter) sealed in holes punched in a hydrocoloid dressing and affixed to the skin. Chambers will be fixed in place with surgical tape and removed before each new application. Patients will return daily to the study centre for removal and reapplication of the treatment. Treatment period will be 2 weeks.

Endpoints:

Main endpoint: Change from baseline in the clinical sum score after 2 weeks of treatment

Secondary endpoint: Change from baseline in thickness of the psoriatic skin infiltrate after 2 weeks of treatment, assessed by ultrasonography twice a week.

Safety assessments: Safety will be assessed by monitoring vital signs, laboratory tests assessments and ECG and by recording and analyzing all adverse events. Signs of skin irritation will be monitored daily during the treatment period at the application site using a 4 point scale.

Planning

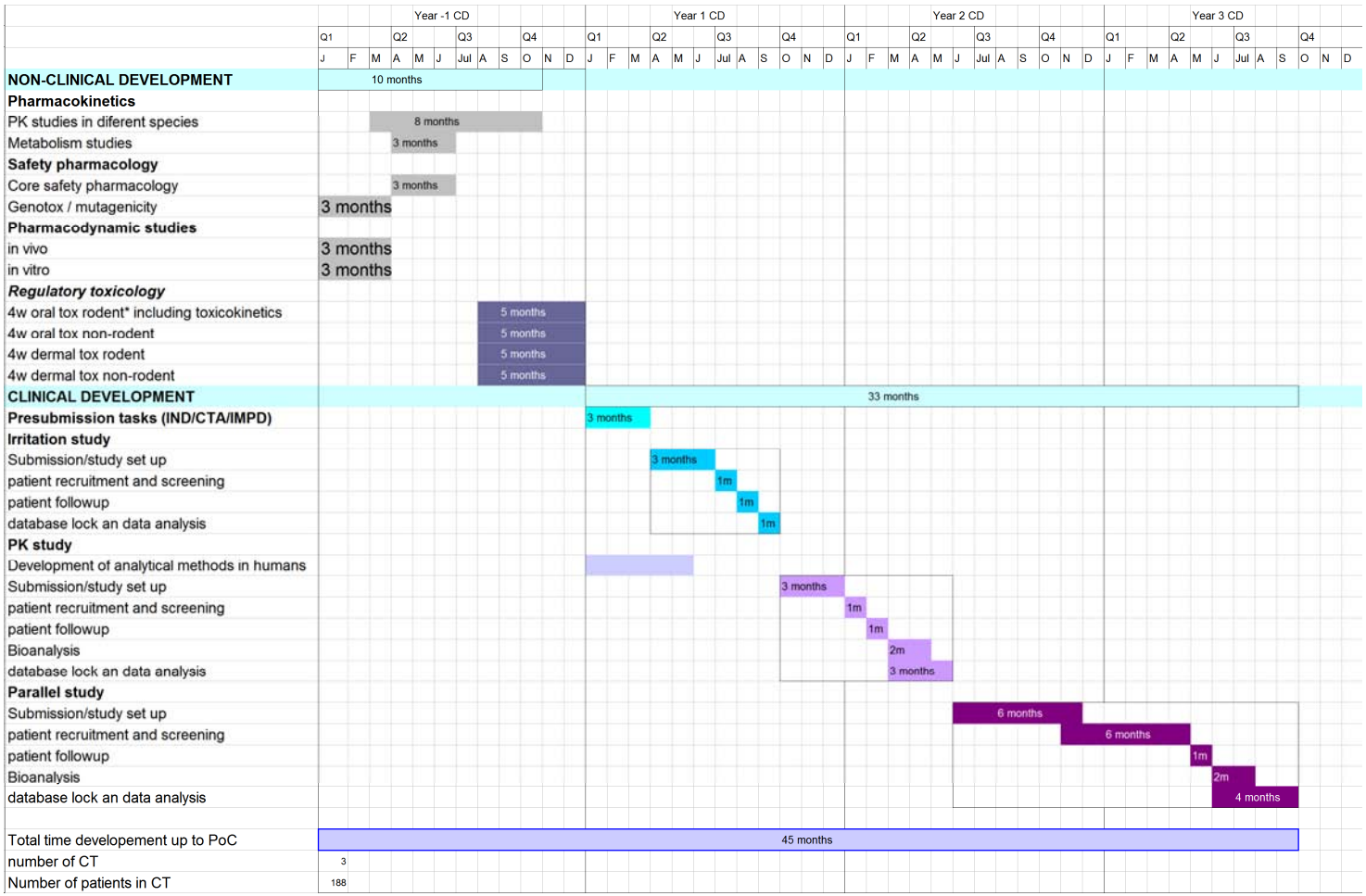
First patient in: October year 1

Last patient out: December year 1

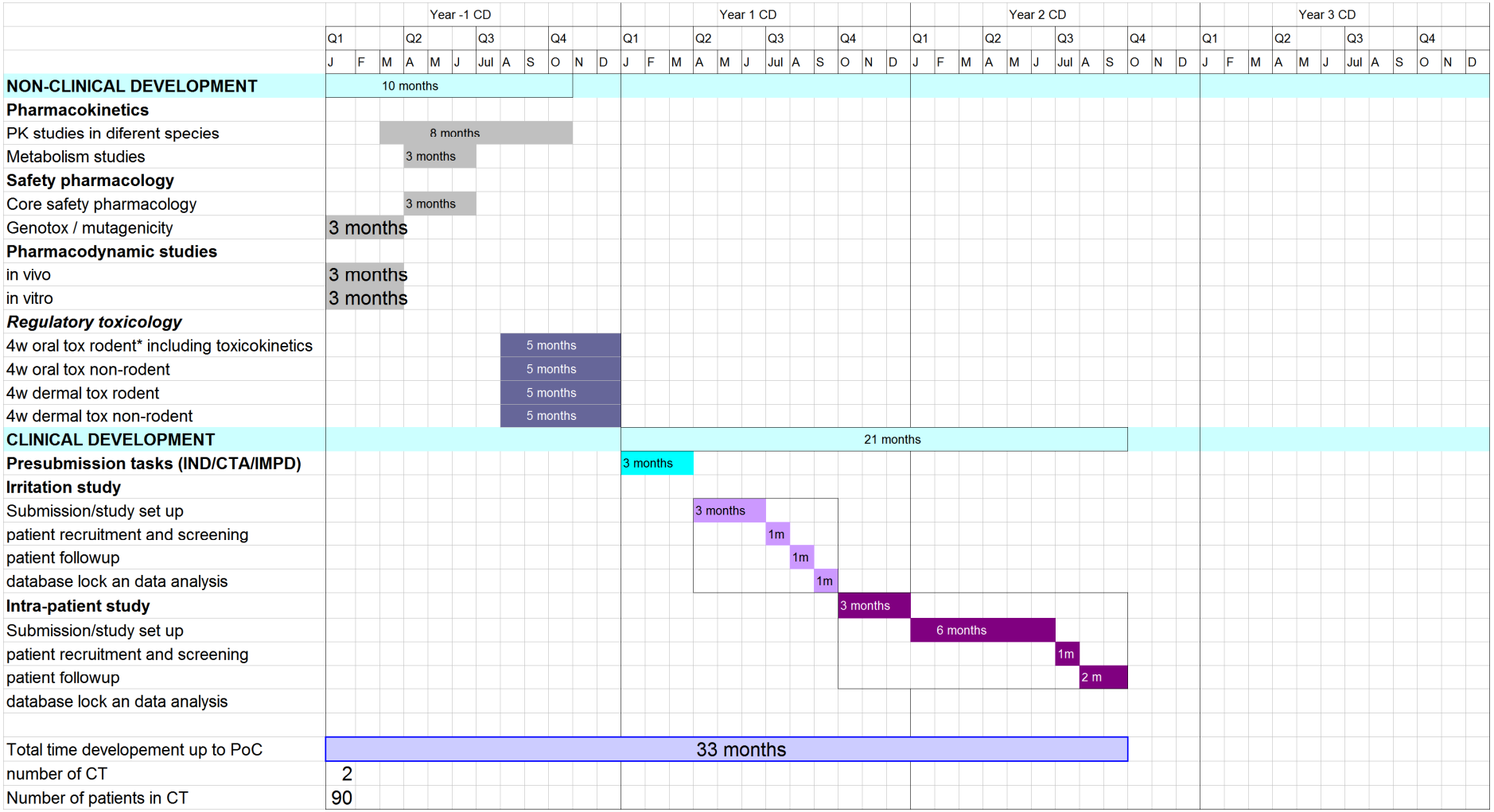
Final report: April year 2

6 Summary of timelines and estimated costing of development.

6.1 Scenario 1: parallel comparison



6.2 Scenario 2: parallel intrasubject comparison



6.3 Scenario 3: parallel intrasubject comparison