BMJ Open

Phase IV adaptive randomised clinical trials evaluating efficacy and cost-efficacy of pre-emptive pharmacogenetic genotyping strategies in the Spanish National Health System: iPHARMGx Master Protocol and PREVESTATGx nested clinical trial

Stefan Stewart ,[1] Enrique Seco-Meseguer,[1] Elena Diago-Sempere,[1] Alicia Marín-Candón ,[1] Montserrat Carmona,[2] Miriam Estébanez,[3] Luis A López-Fernández,[4,5] Iñaki Imaz-Iglesia ,[6,7] María del Mar García Saiz,[8] Emilio J Laserna-Mendieta,[9,10] Ana M Peiró,[11] Magí Farré,[12,13] Consuelo Rodriguez-Jimenez,[14,15] Miriam Saiz-Rodriguez,[16] Judith Sanabria-Cabrera,[17] Rocío Rosas-Alonso,[18] Francisco Abad-Santos,[19] Lucia Pedrosa,[6] Antonio J Carcas,[1] Irene García García,[1] Alberto M Borobia ,[1,20] iPHARMGx study group

To cite: Stewart S, Seco-Meseguer E, Diago-Sempere E, *et al*. Phase IV adaptive randomised clinical trials evaluating efficacy and cost-efficacy of pre-emptive pharmacogenetic genotyping strategies in the Spanish National Health System: iPHARMGx Master Protocol and PREVESTATGx nested clinical trial. *BMJ Open* 2024;**14**:e089823. doi:10.1136/bmjopen-2024-089823

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-089823).

SS and ES-M contributed equally.

Received 11 June 2024
Accepted 14 October 2024

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Alberto M Borobia; alberto.borobia@salud.madrid.org

ABSTRACT

Introduction Genetic variations impact drug response, driving the need for personalised medicine through pre-emptive pharmacogenetic testing. However, the adoption of pre-emptive pharmacogenetic testing for commonly prescribed drugs, such as statins, outside of tertiary hospitals is limited due to a lack of pharmacoeconomic evidence to support widespread implementation by healthcare policy-makers. The Spanish Consortium for the Implementation of Pharmacogenetics (iPHARMGx Consortium) addresses this by developing a clinical trial master protocol that will govern multiple nested adaptive clinical trials that compare genotype-guided treatments to standard care in specific drug–gene–population triads, asses their cost-efficacy and identify novel biomarkers through advanced sequencing techniques. The first of these studies aims to assess whether a pre-emptive statin therapy genotyping scheme reduces the incidence of statin-associated muscle symptoms (SAMS) in a population at risk of cardiovascular disease susceptible of receiving high-intensity or moderate-intensity doses of statins: The PREVESTATGx trial.

Methods and analysis the PREVESTATGX trial is a multicentre, adaptive randomised controlled pragmatic phase IV clinical trial nested to the iPHARMGx master protocol with two parallel arms, aiming for superiority. Randomisation will be conducted on an individual basis with a centralised approach and stratification by centre. After inclusion in the trial and genotyping has been performed, subjects will be randomly allocated to experimental group (pharmacogenetic genotype-guided statin prescription) or standard-of-care statin prescription (as deemed by attending physician). The main objective is to assess the efficacy of a statin pre-emptive genotyping strategy in reducing the incidence of SAMS. A total of 225 subjects will be recruited among the 10 participating centres if no futility/efficacy boundary is reached in the prespecified interim analyses. Recruitment will be carried out during a 12-month period and subjects will be followed for a 9-month period.

Ethics and dissemination The PREVESTATGx trial received ethical approval on 24 April 2024. Results will be disseminated via publication in peer-reviewed journals as well as presentation at international conferences. Trial results will be submitted for publication in an open-access peer-reviewed medical speciality-specific publication.

Trial registration number EU CT number: 2023-509418-12-00/Clinical trial Identifier (ClinicalTrials.gov): NCT06262685. Protocol version 1.2 12 April 2024 (includes non-substantial modification number 14 June

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Study will be randomised and stratified by centre minimising selection bias.
⇒ Adaptive trial design allows early efficacy or futility conclusions without full sample size.
⇒ Pragmatic design helps reduce difficulties in recruiting subjects.
⇒ Study is single blinded with a partially subjective primary endpoint.
⇒ Event probability is dependent on *SLCO1B1, CYP2C9* and *ABCG2* variants.

2024). Trial registration of this study can be located at both the EU Clinical Trials Register available from https:// euclinicaltrials.eu/search-for-clinical-trials/?lang=en and https://clinicaltrials.gov. Registration on both websites was done before the enrolment of the first patient complying with European regulations. EU Clinical Trials Register is a primary registry according to the WHO.

INTRODUCTION

Genetic differences can significantly influence drug pharmacokinetics and pharmacodynamics, resulting in variability in individual responses.[1 2] Pre-emptive pharmacogenetic testing is gaining prominence in the rapidly advancing field of personalised medicine as a means of individualising treatment plans, enhancing treatment efficacy and mitigating the occurrence of adverse events (AEs).[3] Multiple studies, including randomised controlled trials, have demonstrated that personalising drug therapy based on pharmacogenetic testing results in better patient outcomes for particular drug–gene combinations.[4] Notably, the Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions study conducted by the Ubiquitous Pharmacogenomics Consortium and the 12-gene pharmacogenetic panel (which included all drugs for which an actionable drug–gene interaction was present in the Dutch Pharmacogenetics Working Group (DPWG) recommendations, with the exceptions of abacavir, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole and drugs containing oestrogen) implementation study have both shown promising results, by significantly reducing the incidence of clinically relevant adverse drug reactions and showcasing the models feasibility across diverse European healthcare system organisations and settings.[5 6]

The growing body of knowledge on the impact of genetic variation on drug response has led to the development of clinical guidelines to assist prescribing clinicians.[7] These guidelines comprehensively assess the associations between over 100 gene–drug pairs, including those created by The DPWG and the Clinical Pharmacogenetics Implementation Consortium. Furthermore, the integration of pharmacogenetic information into clinical practice has been facilitated by the development of more precise, readily available and cost-effective molecular analysis techniques.[7] This has resulted in both the US Food and Drug Administration and the European Medicines Agency including pharmacogenetic information in drug labels provided to prescribers and patients.[8 9]

Despite the potential benefits of pre-emptive pharmacogenomics, there are still limitations hindering its implementation beyond a limited number of tertiary hospitals in healthcare environments.[10]

One major challenge is the lack of pharmacoeconomic studies evaluating the balance between the costs and effects of pre-emptive pharmacogenomics.[10] While pre-emptive pharmacogenetic testing shows promise in improving patient outcomes and reducing the occurrence of adverse drug reactions, the lack of clear efficiency evidence remains a significant challenge for its widespread adoption.[11] Despite the development of comprehensive clinical guidelines and the inclusion of pharmacogenetic information in drug labels, the current state of pharmacogenomic implementation in healthcare systems and communities reveals that most testing is confined to tertiary or highly specialised hospitals, probably due to the patient's characteristics.[12] This highlights the need for further research that better establishes the efficacy, cost-efficacy and feasibility of pre-emptive pharmacogenomic testing for more commonly prescribed drugs in both inpatient and outpatient settings. Such research will enable healthcare policy-makers and regulators to make informed decisions about the broader integration of pharmacogenomics into standard clinical practice and fully endorse it.[11 13]

Additionally, many clinicians have limited expertise to determine when pharmacogenetic testing is appropriate, and professional organisations often fail to provide clear recommendations or policy support.[2] Discrepancies between different pharmacogenetic guidelines, perceived conflicts of interest among guideline authors, ambiguity in applying biomarker information from drug labels, and a general lack of acceptance by both physicians and patients further hinder implementation.[14] Concerns about privacy, genetic discrimination, and costs also contribute to patient hesitancy.[14 15]

To address these challenges, the iPHARMGx Consortium has been formed, comprising 11 hospitals across the Spanish National Health System (NHS): Gregorio Marañón General University Hospital, Central Defense Hospital Gomez Ulla, General Hospital of Tomelloso, General University Hospital of Alicante, University Hospital of Burgos, University Hospital of the Canary Islands, University Hospital Germans Trias i Pujol, University Hospital Marqués de Valdecilla, University Hospital Virgen de la Victoria, University Hospital La Princesa and University Hospital La Paz; the Autónoma de Madrid University and the Health Technologies Assessment Agency of Instituto de Salud Carlos III. Both the Consortium framework as well as the PREVESTATGx study have been funded by the Instituto de Salud Carlos III (ISCIII) through the project code PMP22/00055 and by Next Generation EU funds, which finance the actions of the Recovery and Resilience Facility (RRF).

The iPHARMGx framework

To efficiently and effectively achieve the ambitions outlined by the iPHARMGx Consortium, the creation of a stable adaptive phase IV clinical trial infrastructure that would lay the foundational principles that would govern all studies carried out by the consortium was required. To this end, an adaptive clinical trial approach was agreed on, and the development of a clinical trial master protocol commenced.

By means of the master protocol (see iPHARMGx Master Protocol, online supplemental material 1), the iPHARMGx Consortium would provide a common structure that would anchor all trials nested within the

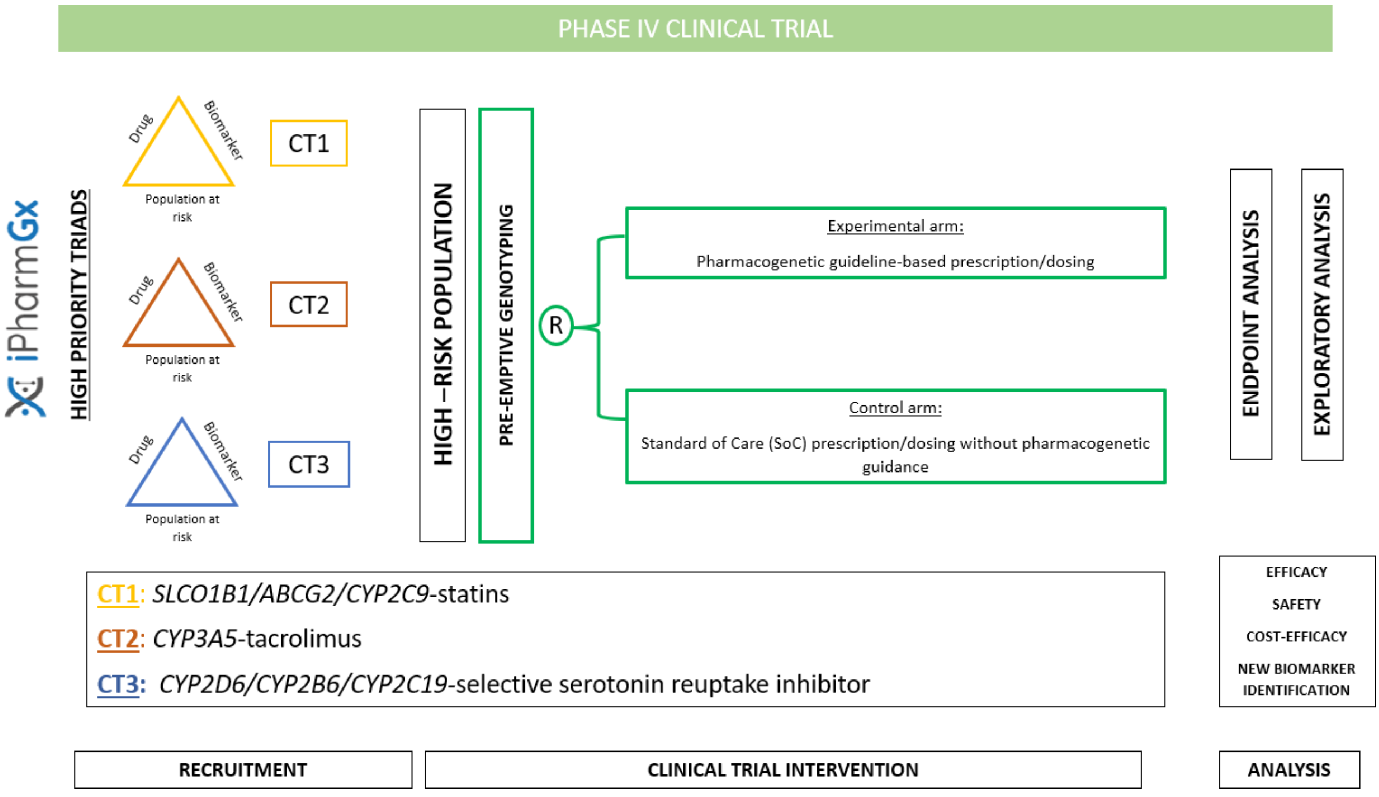

Figure 1 High priority clinical trials nested within the iPHARMGx Consortium: PREVESTATGx clinical trial (CT1), TRANSPGx (*CYP3A5*-tacrolimus) clinical trial (CT2) and Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions clinical trial (CT3).

iPHARMGx Consortium, both in terms of design, objectives and endpoints. All nested studies will be pragmatic phase IV multicentre randomised parallel clinical trials, where all study participants will undergo pre-emptive genotyping. Each of these studies will evaluate a different drug–gene–population triad. Among them, the consortium established three high-priority triads that included different actionable genes (figure 1).

Subjects will then be allocated, according to subprotocol-specific schemes, to receive either the most recent clinical pharmacogenetic guideline treatment/dosing recommendations for their genetic profile (intervention arm) or the healthcare provider standard of care (SoC) (control arm).

The adaptive nature of all trials performed within the iPHARMGx framework will serve a dual purpose. On one hand, it will allow for intermediate analysis to be performed at subprotocol specific timepoints. Furthermore, each nested study will have predefined efficacy and futility thresholds that if met, will warrant study termination. This approach allows for a more efficient sample size usage, decreasing participants exposure to a potentially ineffective or unsafe intervention. On the other hand, genes, variants or biomarkers may be analysed *ad hoc* if their association with a specific outcome is unknown at the time of trial initiation but later deemed relevant. Similarly, if treatment adjustments are not yet established in practical clinical guidelines at the time of trial initiation and become available in subsequent guideline updates, they will be incorporated into the study. This adaptive approach will ensure that the studies carried out under the iPHARMGx framework are able to incorporate emerging biomarkers and treatment options that may have clinical relevance, even if they are not currently established in clinical practice.

The overarching goal of the trials nested to the iPHARMGx platform is to assess the efficacy, safety and cost-efficacy of pre-emptive pharmacogenetic testing. All trial populations will consist of individuals highly susceptible to presenting outcomes with a clearly defined pharmacogenetic substrate (high-risk populations). Widespread implementation of large-scale patient genotyping is not currently feasible, that is the reason why we propose this strategy of genotyping in high-risk populations, which must be evaluated in terms of efficacy and cost-efficacy. Demonstrating its feasibility and efficacy will be the first milestone towards broadening its application beyond its current scope and facilitating its adoption in the Spanish NHS, all the while enhancing the efficiency and safety of prescribed drugs, promoting treatment adherence, improving patient's quality of life and ultimately contributing to a more sustainable NHS.

The PREVESTATGx Trial

Statins belong to a class of prescribed medications that primarily function by inhibiting the activity of hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme responsible for regulating the rate of cholesterol

synthesis specifically targeting low-density lipoprotein (LDL) cholesterol reducing the risk of cardiovascular disease (CVD).[16] The increasing utilisation of statins has led to around 25% of individuals aged 65 years or older worldwide being treated long-term with statin therapy, either for primary or secondary prevention of CVD.

The population treated with statin therapy is likely to increase as more patients at risk of CVD are identified, such as HIV-infected individuals who experience a high prevalence of dyslipidaemia primarily attributed to antiretroviral therapy, notably protease inhibitors.[17] This is worsened by the heightened immune activation and inflammation resulting from HIV infection itself, significantly increasing the risk of CVD within this population.[17] As such, recent studies have highlighted the role of pitavastatin as primary prevention of cardiovascular events in HIV populations.[18] Additionally, the potential benefits of statin therapy in HIV-infected population extends beyond lipid reduction. Statins also possess anti-inflammatory and immunomodulatory properties that may offer specific advantages in terms of CVD risk reduction and attenuation of other HIV-associated complications further justifying their prescription in these patients.[17]

Given the common use of statin therapy, careful assessment of the safety and potential side effects of statins is crucial, especially in patients taking multiple medications and facing a risk of drug–drug interactions. The most notable of them being SAMS, a term that encompasses a wide range of symptomatic muscle complaints, with or without detectable biochemical evidence of muscle damage[19] with a reported incidence that ranges from 10% to 29%.[20] SAMS commonly manifest as proximal, symmetric (although less frequently asymmetric) muscle weakness and/or soreness which can be accompanied by serum CK elevation.[21] Symptoms may include muscle tenderness, cramping, stiffness and tendon pain which can cause functional impairments that can lead to treatment discontinuation increasing their CVD risk.[20]

Various pharmacogenetic variants have been identified to influence both the bioavailability of statins and the occurrence of SAMS.[22 23] The *SLCO1B1* gene encodes a transporter responsible for facilitating the hepatic uptake of all statins.[24] *ABCG2,* encodes a transporter that modulates the absorption and disposition of rosuvastatin, and *CYP2C9* encodes an enzyme involved in the oxidation of certain statins.[23] Genetic variations within these genes can result in increased systemic exposure to statins, including simvastatin, rosuvastatin, pravastatin, pitavastatin, atorvastatin, fluvastatin and lovastatin, hence increasing the risk of SAMS.[23]

As such, SAMS stand as a deterrent to patient adherence and persistence with statin therapy, often leading to withdrawal or abandonment while posing a considerable challenge to long-term CVD risk management. Beyond its clinical implications, the economic burden associated with statin discontinuation places strain on national health services. The costs incurred in managing SAMS, be it by patients presenting to clinic, admitted to hospital or by rotating costly lipid-lowering alternatives are added to those derived from the complications that result from inadequate lipid control. To ameliorate such a pressure on healthcare systems, the need for affordable effective strategies that mitigate SAMS with an emphasis on increasing patient compliance is essential to improve public health outcomes.

To meet these challenges, the iPHARMGx Consortium devised the PREVESTATGx trial: a phase IV pragmatic trial nested within the iPHARMGx framework that aims to optimise the treatment of patients susceptible of receiving high-intensity statin lipid-lowering therapy by reducing the incidence of SAMS. It does so while sharing the same paradigms outlined in the iPHARMGx master protocol: to advocate for a feasible, efficacious and cost-efficacious personalised medicine scheme, in this case for statin management; to provide in vivo evidence of the influence of various genotypes on statin efficacy beyond the current research landscape; to potentially unveil novel prognostic biomarkers that further our understanding of statin response and statin AEs that could help explain the often-encountered outliers in routine clinical practice and all in all, deepen our knowledge of statin pharmacogenetics.

METHODS AND ANALYSIS

This study protocol in conjunction with the iPHARMGx master protocol follows the Standard Protocol Items: Recommendations for Interventional Trials guidelines (online supplemental material 2).[25]

iPHARMGx: hypothesis and design

The overall goal of all trials nested within the iPHARMGx framework is to evaluate pre-emptive genotyping strategies in high-risk populations susceptible of receiving certain targeted treatments in terms of both efficacy and cost-efficacy. Our hypothesis is that pre-emptive genotyping in populations at risk is efficacious, cost-efficacious and feasible within the Spanish NHS when compared with the current SoC. Nested studies will be pragmatic, adaptive, phase IV, multicentre, randomised, parallel clinical trials. The following eligibility criteria will be applicable to all trials nested to iPHARMGx Platform:

- All nested trials must have at least one clearly defined pharmacogenetic biomarker present in high-risk populations with an IA level of evidence.
- All nested trial populations must have a target genetic biomarker that has been demonstrated as actionable according to clinical practice guidelines for the treatment of the medical condition being investigated in the study.
- All nested trials must have a clearly defined efficacy outcome or a validated efficacy surrogate outcome.

Overarching iPHARMGx study objectives

The overarching primary objective of the studies nested within the iPHARMGx Platform is to assess whether

genotyping in high-risk populations susceptible to receiving certain targeted treatments is both efficacious and cost-efficacious.

The subprotocols of the studies nested within the iPHARMGx Platform will detail the specific objectives within this overarching primary objective.

Secondary objectives will be detailed comprehensively in each of the subprotocols. The following provides a common frame that will encompass all subprotocols nested.

- To assess whether pre-emptive genotyping strategies are feasible within the Spanish NHS.
- To identify new potential genetic biomarkers associated with drug response variability.
- To assess the safety and tolerability of targeted treatments identified through pre-emptive genotyping, including but not limited to the incidence and severity of treatment-related AEs.
- To identify potential predictors of treatment-related AEs, such as genetic or clinical factors.

iPHARMGx study population and eligibility criteria

The following two eligibility criteria will be applicable to all subjects participating in all trials nested to the iPHARMGx master protocol:

- Subjects must be naïve to any genotyping test of the genes studied in each of the nested subprotocols, meaning they have no history of genetic testing or analysis of their genotype regarding said gene.
- Subjects must be willing to comply and adhere to any treatment plan modifications established in the respective study subprotocols.

Subjects included in studies nested to the iPHARMGx Platform will be predominantly adults (ie, aged 18 or older); however, paediatric populations will be included in some instances and will be stated as such in the inclusion criteria of those specific nested trials.

PREVESTATGx study objectives

Primary objectives

To assess whether a statin pre-emptive genotyping strategy reduces the incidence of clinically relevant SAMS when compared with the current SoC.

Secondary objectives

- To assess the efficacy of a statin pre-emptive genotyping strategy in optimising dyslipidaemia management when compared SoC treatment/dosing.
- To assess the efficiency of implementing a pre-emptive pharmacogenetic strategy to avoid adverse musculoskeletal symptoms.

Exploratory objectives

- To identify novel prognostic and predictive genetic biomarkers of statin-related AEs and efficacy.
- To assess the efficacy of a statin pre-emptive genotyping strategy in reducing the major ischaemic cardiovascular events.
- To assess the effect of a statin pre-emptive genotyping strategy in improving patient therapeutic adherence.
- To assess the effect of a statin pre-emptive genotyping strategy in reducing perceived pain of SAMS.

Inclusion criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

- Ability of the participant to understand the purpose and risks of the study, to provide informed consent, and to authorise the use of confidential health information in accordance with national and local privacy regulations.
- Subject has voluntarily signed the informed consent form (ICF).
- Subject must be ≥18 years old at the time of signing ICF.
- Subject is able and willing to take part and be followed up for the majority of the study duration.
- Participants are susceptible to be prescribed any of the following:
  - Atorvastatin ≥40 mg/day *p.o.*
  - Simvastatin ≥20 mg/day *p.o.*
  - Pitavastatin ≥2 mg/day *p.o.*
  - Rosuvastatin ≥40 mg/day *p.o.*
  - Pravastatin ≥40 mg/day *p.o.*
  - Lovastatin ≥40 mg/day *p.o.*
  - Fluvastatin ≥80 mg/day *p.o.*
- Subjects must be naïve to any genotyping test of the following genes: *SCLO1B1, ABCG2, CYP2C9, CYP3A4, CYP3A5* and *HMGCR*.
- Women of childbearing potential must commit not to become pregnant. Subjects must be willing to use highly effective contraceptive methods or have practised sexual abstinence during the study.

Exclusion criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Subject is currently taking ubiquinone (Q10) supplements.
2. Known personal or family history of statin-associated autoimmune myopathy or HMG-CoA reductase disorder.
3. Pregnant or breastfeeding women.
4. Subject has a personal history or analytical evidence of one of the following disorders:
   a. Any contraindications to statin administration as revealed in the summary of product characteristics for statins.
   b. Prior SAMS if subject is not statin naïve.
5. Any condition or situation deemed by the investigator precluding or interfering with the present study.

Study procedures

All study procedures and the schedule of assessments are summarised in table 1.

Table 1 Summary of procedures and schedule of assessments

Month	Screening: 0–6 months	Baseline=randomisation Day 1	Month 1* †	Month 3*†	Month 6* †	Month 9*
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (EOS)
Eligibility check	X					
Informed consent	X					
Medical history/baseline medication	X	X				X
Physical examination	X	X				X
Randomisation and start of treatment		X				
Vital signs‡	X	X				X
Pharmacogenetics blood draw	X					
Laboratory determinations§	X					X
SAMS-CI[20] ** NPRS MMAS-8 questionnaires¶	X	X	X	X	X	X
Adverse events evaluation			X	X	X	X

*All visits performed after treatment administration have a ±7 day window to be performed.
†Visits to be performed remotely. During the course of the study, additional remote contacts can be performed by the investigators to ensure patient's well-being within as per routine medical practice.
‡Blood pressure and heart rate.
§Laboratory determinations will include serum biochemistry, cell blood count, complete renal, liver and LDLc and total cholesterol and triglycerides panel, thyroid hormone panel, serum calcidiol and serum CK. Urine pregnancy tests may be performed at the investigator's discretion. Screening laboratory determination will not be required if subject has a lab determination including all required parameters performed for whatever reason up to 1 month prior to randomisation visit. Additional laboratory determinations can be done following local guidelines.
¶Scale assessment to be performed at every visit will include a Numeric Pain Rating Scale (NPRS) when applicable and Morisky Medication Adherence Scale (MMAS-8) questionnaire (MMAS 2006 www.adherence.cc used with permission).
**Statin-Associated Muscle Symptoms Clinical Index questionnaire (SAMS-CI) will be performed on every visit after visit 2.

The following list of procedures will be performed at all visits after inclusion:

1. Eligibility check:
   - This assessment will involve a comprehensive review of specific inclusion/exclusion criteria outlined in the protocol to ensure that participants can continue to participate.
2. Medical history and physical examination
   - Participants' medical histories will be documented, including any relevant pre-existing conditions and medications. Any new information must be recorded in the medical history.
   - Physical examination will encompass a comprehensive physical examination which will be conducted to assess participants' overall health and monitoring changes throughout the study. This examination will include an evaluation of vital signs, such as blood pressure, heart rate, respiratory rate and body temperature and a full systems and organs exploration.
   - In cases when visit is performed remotely, an overall health assessment over the telephone by the investigator will be considered sufficient.
3. Concomitant medication
   - Any new medication or change in previously recorded medication must be recorded.
4. SAMS-CI scale assessment:
   - The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) is a method for assessing the likelihood that a patient's muscle symptoms (eg, myalgia or myopathy) were caused or worsened by statin use. A complete scale assessment with all items must be done at every visit in all visits after visit 2. This is due to the fact that SAMS-CI questionnaire cannot be completed if subject is not taking statin. Scale is added as an appendix to this protocol and will be used to assess causality whenever a subject is suspected to have SAMS.
5. A Numeric Pain Rating Scale (NPRS):

- A quick tool for assessing pain severity and its impact on functioning. In cases where muscle symptoms have been deemed to be caused by statin therapy (ie, a SAMS-CI score ≥7), an NPRS will be performed to assess pain encumbrance and burden. Clinically relevant pain encumbrance will be defined as an NPRS score greater or equal to 3.

6. Morisky Medication Adherence Scale (MMAS-8): Morinsky-Green 8-item therapeutic adherence questionnaire:
   - The MMAS-8 consists of eight questions, seven of which are dichotomous (yes or no), and one of which is scored on a 5-point Likert-type scale.[26 27] The questions are designed to assess the patient's behaviour and beliefs about taking medication. The MMAS-8 has been used in several studies to assess adherence to medication in chronic diseases. The scale has been translated into several languages and has been validated in different populations. A score below 6 indicates low adherence, a score between 6 and 8 medium adherence and a score of 8 high adherence.

Screening visit

The study will be explained to the participant and informed consent will be obtained prior to any study procedure.

After checking the selection criteria, informing the patient and signing the ICF, a pharmacogenetic analysis sample will be extracted. The pharmacogenetic sample will be collected preferably at the screening visit but it can be collected at any point prior to statin therapy initiation. An aliquot of DNA sample will be stored at −20°C for quality control purposes and/or further genetic analysis by techniques available at a central laboratory affiliated with the Precision Medicine Infrastructure associated with Science and Technology (IMPaCT).

Subject must have a mandatory screening laboratory analysis that includes all safety and efficacy parameters described in this study that can be performed between 30 to 1 day before baseline/randomization visit. Screening laboratory analysis can be performed for whatever reason, just as long as it does not exceed the aforementioned window and can in theory date from before ICF signing. Therefore, screening laboratory determination will not be required if subject has a lab determination including all required parameters performed for whatever reason up to 1 month prior to randomisation visit.

Baseline: up to 6 months after first screening visit

If the subject has successfully completed the screening visit and is eligible based on compliance with all inclusion criteria and none of the exclusion criteria, randomisation and baseline procedures may be delayed for up to 6 months after screening. This means that the prescription of any of the specified doses of statins in inclusion criterion 5 can be withheld for a maximum of 6 months in subjects who may not require high-intensity lipid-lowering therapy at the time of screening but are likely to require it in the foreseeable future.

Prior to randomisation, a baseline assessment of MMAS-8 and NPRS scales will be performed to assess for any possible confounders.

Subject will be randomised to receive either SoC treatment (control arm) or pharmacogenetic guideline-based treatment (experimental arm). Before treatment initiation, for subjects allocated to the experimental arm, a dose or treatment recommendation will be provided to the prescribing clinician by a clinical pharmacologist or a pharmacogenetics-expert pharmacist. This recommendation will take into account the subject's pharmacogenetic profile, clinical background and any potential drug–drug interactions or phenoconversion risks based on their concomitant medications and medical history.

On completion of baseline visit, subject will initiate treatment with the prescribed dose. Study treatment will not be administered at site. Medication must be purchased by the subject, and administration will take place in outpatient environment.

Visit 3: 30 days after treatment initiation (±7 days window)

Visit to be performed remotely. Related and unrelated AEs must be recorded and appropriate questionnaires (SAMS-CI, MMAS-8 and NPRS) be completed.

Visit 4: 90 days after treatment initiation (±7 days window)

Visit to be performed remotely. Related and unrelated AEs must be recorded and appropriate questionnaires be completed.

Visit 5: 180 days after treatment initiation (±7 days window)

Visit to be performed remotely. Related and unrelated AEs must be recorded and appropriate questionnaires (SAMS-CI, MMAS-8 and NPRS) be completed.

Visit 6: 270 days after treatment initiation (±7 days window)

Blood samples for laboratory assessments will be obtained. Vital signs (including blood pressure, heart rate, respiratory rate and body temperature) must be recorded. Related and unrelated AEs must be recorded and appropriate questionnaires be completed.

For safety purposes, additional remote contacts can be performed by the investigators within the context of routine clinical practice. These must be recorded in the electronic medical history.

Sample size calculation: efficacy and futility boundaries

This is an adaptive trial nested within the iPHARMGx protocol. For the purpose of this clinical study protocol, we have established three distinct stages (denoted as J=3), each representing a critical point at which data analysis will be conducted. Our objective is to maintain a desired level of statistical rigour, with a type I error rate (α) set at 0.05 and a type II error (β) rate fixed at 0.2. The third and final stage corresponds to the ultimate analysis.

To power this trial for a meaningful effect size (δ=0.42), we have calculated an estimated total sample size of 180

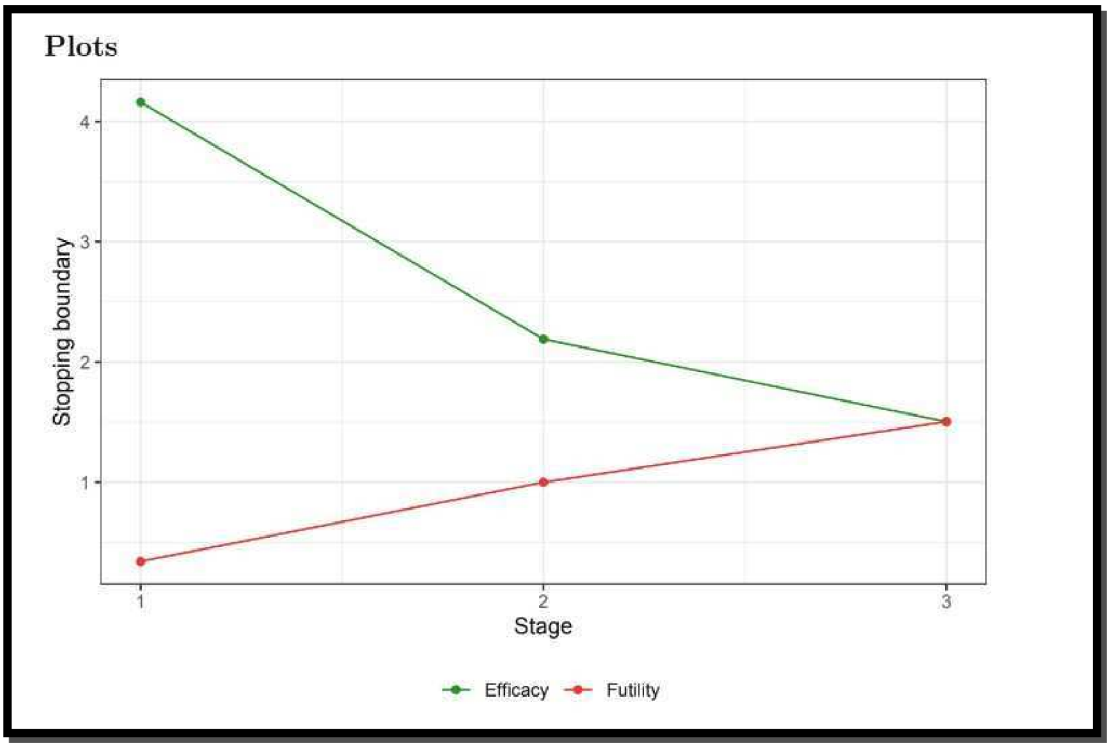

Figure 2 Futility and efficacy thresholds plot that must be met to warrant study termination.

subjects, with 30 subjects allocated to each arm within each stage. This sample size determination is critical for ensuring the statistical robustness of the trial and the ability to detect the intended therapeutic effect. This total number of subjects has been increased to 225 to factor in possible prerandomisation loss of subjects (20%) that despite being genotyped do not receive statin for whatever reason. Therefore, to adequately assess the pharmacoeconomic feasibility of the intervention, they must be included in the pharmacoeconomic endpoint analysis.[28]

The rationale behind the sample size calculation per arm per stage is grounded in existing published data. Research indicates that individuals within the general population who receive statins face an excess risk of developing SAMS ranging from 7% to 29%.[29] Furthermore, studies have established approximately a 2.5-fold increased risk (OR: 2.35; 95% CI 1.08 to 5.12) of myopathy among individuals carrying the c.521C allele of the *SLCO1B1* gene.[30] These insights from the literature help us in estimating the expected effect size and risk within our target population, allowing us to tailor our trial accordingly. Based on these data, and taking the percentages 10% and 26%, respectively, the effect size is calculated in R statistical software being delta=0.42.

To guide our decision-making during the study, we have established specific efficacy boundaries and criteria for evaluating futility. These are as follows: (4.161, 2.189 and 1.504) for efficacy and (0.341, 0.999 and 1.504) for futility (figure 2). If either assessment exceeds the prespecified threshold, study termination is warranted. These boundaries were calculated using the graphical user interface built on (and in to) V.2.2.0 of the R package OptGS.[28]

Through a multi-faceted strategy that includes extensive outreach, collaboration with multiple healthcare centers, leveraging electronic health records to identify eligible participants, and employing dedicated recruitment staff to engage and follow-up with potential participants, we expect to achieve adequate enrollment.

Randomisation and blinding

This is a randomised single-blind trial; therefore, blinding will be required for only participating subjects. A double-blind design was not considered feasible due to the methodological difficulty of assessing certain endpoints if the prescribing clinician is blinded, mainly because it would be impossible to conceal a prescribing clinician of a dose or a statin type he/she would not normally prescribe under routine clinical practice conditions. It has been deemed sufficiently appropriate to blind only subjects since the primary endpoint is a composite of validated surrogate endpoint with a relevant clinical variable. Randomisation may be stratified according to the subject's centre, concomitant treatment with non-statin lipid-lowering therapies and primary or secondary prevention.

Subjects will be allocated to either intervention arm or to control arm at a 1:1 ratio. An intermedia Interactive Web Response Systems (IWRS) software will be used for subject randomisation. Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalised/locked. The investigator may, in an emergency, reveal the identity of the intervention to the subject by contacting the IWRS while the responsibility to break the intervention code to

a third party in emergency situations resides solely with the investigator.

Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. Only the data manager and the statistician will have access to the unblinded randomisation list, under the foreseeable circumstances.

In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their study intervention assignment unblinded should continue to receive scheduled evaluations but will be excluded from primary analysis.

Intervention

Investigational drug: patients in this study will be prescribed any of the authorised statins available as lipid-lowering primary or secondary prevention.

1. Patients in the control group will receive the statins according to clinical practice and the drug's product labelling, and never exceeding the already authorised dosages (see Section 13.4 of PREVESTATGx Study Protocol, online supplemental material 3).
2. Patients in the experimental group will receive the specific type and dosage of statins recommended by the Clinical Pharmacogenetics Consortium's genotype guidelines using the pharmacogenetic information and characteristic of the patient.

Outcomes

Primary endpoint

A composite variable that includes the incidence of patients with a clinically relevant statin-associated musculoskeletal symptom (defined as a combination of a SAMS-CI score ≥7 and an NPRS score ≥3) in the 9-month follow-up period or a serum creatin phosphokinase greater than three times the upper limit of normality prespecified by each centre's laboratory.

Secondary endpoints

The following will be the studies' secondary endpoints:

- 9-month change in percentual LDLc defined as the percentage difference between LDLc values at 9 months minus baseline LDLc.
- Percentage of patients that require either a statin dose modification/withdrawal or additional lipid-lowering therapy after 9 months to meet LDLc goals.
- The difference between the costs of the intervention and all its surrounding procedures combined with the costs derived from the events in the intervention arm when compared with the costs derived from the events in the control arm alone over the 9-month follow-up period. The costs will include but not be limited to: the direct costs of genotyping (which will include the costs of genetic testing, sample collection and processing, technology, infrastructure and personnel costs); direct medical costs (including cost of managing SAMS which could involve additional physician visits or laboratory testing, as well as the cost of switching medications due to the SAMS); cost offsets and savings (such as avoided costs due to genotyping from preventing SAMS such as avoided hospitalisations and reduced need for additional medications). Additionally, the ratio between cost differences and efficacy differences between both arms may be calculated.

Exploratory endpoints

The study includes four exploratory endpoints:

Novel prognostic and predictive genetic biomarkers of statin-related AEs and efficacy will be assessed in outlier subject's/or any given subject for quality control reasons trough techniques not readily available at all centres, and only available at a central laboratory affiliated with the Precision Medicine Infrastructure associated with Science and Technology (IMPaCT) as well as genome-wide association studies when applicable. IMPaCT is constituted of three distinct pillars oriented towards improving R&D research quality in the field of precision medicine. iPHARMGx is aligned with both the Genomic and Precision pillars of IMPaCT. Percentage of participants who experience a 4-component exploratory endpoint consisting of cardiovascular death, non-fatal myocardial infarction, resuscitated cardiac arrest or hospitalisation for unstable angina.

Difference in MMAS-8 questionnaire adherence levels/score between both study arms and difference in NPRS score between both study arms.

Biological samples

After checking the selection criteria, informing the patient and signing the ICF, a pharmacogenetic analysis sample will be extracted. The pharmacogenetic sample will be collected preferably at the screening visit but it can be collected at any point prior to statin therapy initiation. An aliquot of DNA sample will be stored at −20°C for quality control purposes and/or further comprehensive genetic analysis to be performed at a central laboratory affiliated with the IMPaCT.

Subject must have a mandatory screening laboratory analysis that includes all safety and efficacy parameters described in this study (see Section 14 of PREVESTATGx Study Protocol, online supplemental material 3) that can be performed between 30 and 1 day before baseline/randomisation visit. Screening laboratory analysis can be performed for whatever reason, just as long as it does not exceed the aforementioned window and can in theory date from before ICF signing. In other words: in line with the pragmatic nature of this study screening laboratory determination will not be required if subject has a

Table 2 Variants deemed mandatory to interrogate in all recruited subjects

Gene	rsID	Star allele	cDNA
SLCO1B1	rs4149056	*5, *15	c.521T>C/37041T>C
SLCO1B1	rs2306283	*14, *15	c.388A>G/35230A>G
ABCG2	rs2231142	Not Applicable	c.421C>A
CYP2C9	rs1799853	*2	3608C>T
CYP2C9	rs1057910	*3	42614A>C

laboratory determination including all required parameters performed for whatever reason up to 1 month prior to randomisation visit.

In alignment with the principles outlined in the iPHARMGx master protocol, our study will employ a proven pharmacogenetic genotyping tool. All centres that will take part in this study will genotype high-evidence (level 1A) relevant variants of the pertaining genes (table 2) according to their own available techniques. In this regard, and considering that any genotyping tool capable of interrogating the mandatory single nucleotide variants (SNVs) for this trial will be considered acceptable as per protocol, the preferred method for genotyping will be TaqMan™ probes. These can be used either individually or included in an OpenArray® System that simultaneously analyses 120 SNVs. The turnaround time for results may vary depending on the laboratory, but it is expected to be no longer than 15 days from the time of sample collection. All participating local laboratories have reserved rights to analyse the aforementioned SNPs of a subject's sample more than once if the so wish to, for quality control purposes. However, they must ensure sufficient sample volume is preserved for central laboratory analysis. This will not be mandatory for all participating laboratories.

In those subjects that constitute outliers to previously established pharmacogenetic profiles, novel biomarkers will be explored through state-of-the-art techniques as described by the master protocol: genotyping will be performed at a central laboratory using advanced sequencing techniques with the aim of conducting an unbiased approach of potential biomarkers that may be associated with the statin response and SAMS. Additionally, a sample from every genotyped subject will be stored as an aliquot and preserved to serve as a quality control measure. These aliquots can be made available for analysis at said central laboratory at any given time, to be explored through any technique deemed adequate by them.

Statistical analysis

A descriptive-univariate analysis will be carried out for all study variables. Frequency results will be expressed as absolute and relative frequencies. Continuous variables will be expressed with the main measures of dispersion (mean, SD, median and IQR). The normality of the variables will be studied using the Kolmogorov-Smirnof normality test.

For the primary endpoint, the Pearson χ^2 test (or Fisher's exact test for 2X2 tables or likelihood ratio in mXn tables, if necessary) will be used for qualitative variables and the Student's t-test, analysis of variance of one factor or its non-parametric equivalents Mann-Whitney U test, Kruskal-Wallis test for quantitative variables.

To address scenarios where subjects in the intervention arm are prescribed additional lipid-lowering drugs to achieve desired LDLc goals, a sensitivity analysis could be performed to assess the possible impact of an added therapy on the primary endpoint.

Finally, a multivariate model will be fitted with all the variables that were statistically significant in the previous analysis. Different multivariate models will be fitted (logistic regression, unweighted support vector machine, weighted support vector machine, artificial neural networks and partial least square regression). The optimal model will be selected using the Bayesian information criterion.

The level of statistical significance is set at $p<0.05$. The statistical software R (V.4.3.1) will be used.

Further details will be included in the Statistical Analysis Plan.

Economic evaluation

A cost-efficacy evaluation will be conducted from the perspective of the Spanish NHS. Direct costs for each arm of the study will be calculated.

Direct costs will encompass healthcare resources used during the follow-up period, along with their associated unit costs per patient. Additionally, the expenses incurred by the participating centres to implement the intervention will be accounted for.

Various resources and their corresponding unit costs, including doctor's visits, medications and any hospital interventions during follow-up, will be recorded. The total costs for each patient in both intervention groups will be aggregated to allow for a comparison of the average cost per event avoided between the intervention and control groups. The findings will be presented in terms of cost per event and avoided events, with efforts made to assess the utility of each intervention whenever feasible.

To gauge the uncertainty surrounding the model and unit costs, particularly if obtained from sources other than the clinical centres, both univariate and probabilistic sensitivity analyses will be conducted. These analyses will provide valuable insights into the robustness of the findings and assist in decision-making processes.

Data collection and outcome measures

The handling, communication and transfer of personal data will be protected, complying with the basic ethical principles of Biomedical Research and applicable regulations: Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing

of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation) and Act 41/2002 of 14 November, regulating patient autonomy and rights and obligations regarding clinical information and documentation. An eCRF form has been designed using MACRO Electronic Data Capture by Elsevier. To ensure the quality of data, data management will be performed by a data manager of the Spanish Clinical Research Network (SCReN), located at University Hospital La Paz. The data management plan has been approved by the principal investigator. Data collection forms will be included in the final report. All demographic data (including subject's gender, age and ethnicity) will be recorded in the eCRF and factored in the analysis plan. On completion of the study, all participants will be informed of their pharmacogenetic profile, regardless of the study arm to which they were allocated. Adverse drug events will be graded according to the Common Terminology Criteria for Adverse Events version 5.0 and are recorded in the electronic eCRF for both reporting and statistical analyses according to the hierarchical structure of the Medical Dictionary for Regulatory Activities (MedDRA), categorising events under the relevant system organ class, and whenever possible the MedDRA Preferred Term.

Coordination, data management, monitoring and statistical analysis of the study will be performed by SCReN.

Patient and public involvement

The development of the research question and outcome measures were based on the clinical experience of internal medicine, cardiology, neurology and endocrinology specialists who treat this profile of patients and have an active desire to optimise statin treatment. Patients and patient advisers were not involved in the design, recruitment or conduct of this study. The patients will be notified of the study results in writing and verbally, and we will invite them to help us develop our dissemination strategy.

Ethics and dissemination

This study follows the principles of the 2013 Declaration of Helsinki. It was designed and shall be implemented, executed and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations on clinical studies and patient data confidentiality. The study was reviewed and approved by the Spanish Regulatory Agency (AEMPS) and by the Clinical Research Ethics Committee of La Paz University Hospital (HULP code: 6625). The researchers will adhere strictly to the provisions of this protocol and will complete the case report forms. The investigators ascertain they will apply due diligence to avoid protocol deviations. If deviations occur, the investigator must inform the monitor, and the consequences of such deviations will be reviewed and discussed by the team. All protocol deviations will be documented/recorded specifying the reason, data, action taken and consequences to patients and the study.

Any protocol amendment will be identified by a consecutive number and must be approved and signed by the sponsor and the principal investigator. If relevant, approval by the Ethics Committee and the Spanish Agency of Medication and Health Products must occur before any changes are implemented.

This clinical trial has been classified by the Spanish Agency for Medicines and Healthcare Products as a 'low-intervention clinical trial'. The additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared with normal clinical practice. If any possible damage that could be suffered by a subject, resulting from the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial, it is covered by the applicable compensation system already in place.

The investigators ascertain that they will apply due diligence to avoid protocol deviations. If deviations occur, the investigator must inform the monitor, and the consequences of such deviations will be reviewed and discussed by the team. All protocol deviations will be documented/recorded specifying the reason, data, action taken and consequences to patients and the study.

Anonymised individual participant data will be made available when the trial is complete, on request to the corresponding authors and approval by the scientific committee. Once a proposal has been approved, data will be shared through a secure online platform. In addition, after study completion and finalisation of the study report, the results of this trial will be submitted for publication in a scientific journal or will be made public, complying with the Declaration of Helsinki.

Access to data

A copy of the database of data collected during the trial will be attached as an appendix to the publication resulting from this clinical trial. Data will be available at the same time as the results are published and will be kept available to everyone without any time limit. Data will be available indefinitely on the publisher's website, as long as it is kept by the publisher, for anyone who wishes to access the data, for non-commercial purposes.

DISCUSSION

Several hurdles are precluding the seamless integration of pharmacogenetic biomarkers into patient care pathways, challenges such as the scarcity of high-level evidence regarding the efficacy, effectiveness and efficiency of genetic markers, as well as a lack of consensus in the field on whether a widespread adoption would be feasible. The iPHARMGx Consortium's pioneering initiative addresses critical barriers to the widespread implementation of pharmacogenetics in routine clinical practice.

The development of the PREVESTATGx study would help optimise the treatment of patients at high risk of CVD by aiming to reduce the impact of SAMS, which has

a great impact on both the quality of life of patients as well as the overall sustainability of the Spanish NHS. The establishment of comprehensive pharmacoeconomic evidence serves a dual purpose. First, it contributes to the expanding body of evidence that advocates for the viability of a personalised medicine strategy in statin management, thereby facilitating its broader adoption within the healthcare system. Second, it will provide in vivo evidence of the influence of various genotypes on statin efficacy beyond the current research landscape. Simultaneously, it will offer insight into uncovering novel biomarkers that could help explain the often-encountered outliers in routine clinical practice, deepening our knowledge of statin pharmacogenetics as a whole.

As of 21 of May 2024, this study has received approval from an Ethics Committee and the AEMPS. The study is expected to commence in June 2024 with the recruitment of the first subject. Recruitment for the last included subject is expected in December 2024, with a predicted end of follow-up on September 2025.

Author affiliations
[1]Clinical Pharmacology Department, Hospital Universitario La Paz, Madrid, Spain
[2]Unidad de Investigación en Telemedicina y e-Salud, Instituto de Salud Carlos III, Madrid, Spain
[3]Internal Medicine Department, Hospital Central de la Defensa Gomez Ulla, Madrid, Spain
[4]Pharmacy Department, Instituto de Investigación Sanitaria Gregorio Marañón, Hospital General Universitario Gregorio Maranon, Madrid, Spain
[5]Plataforma SCReN (Spanish Clinical Research Network), Madrid, Spain
[6]Health Technology Assessment Agency (AETS), Instituto de Salud Carlos III, Madrid, Spain
[7]Red de Investigación en Servicios de Salud en Enfermedades Crónicas, Madrid, Spain
[8]Clinical Pharmacology Service, Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Spain
[9]Department of Gastroenterology, Research Unit, Hospital General de Tomelloso, Tomelloso, Castilla-La Mancha, Spain
[10]Instituto de Investigación Sanitaria de Castilla La Mancha, Toledo, Castilla La Mancha, Spain
[11]Unidad de Farmacología Clínica, Unidad del Dolor, Alicante Department of Health-General Hospital, Alicante, Comunidad Valenciana, Spain
[12]Department of Clinical Pharmacology, Pharmacogenomics Unit, Hospital Germans Trias i Pujol, Badalona, Catalunya, Spain
[13]Department of Pharmacology, Universitat Autonoma de Barcelona, Cerdanyola del Vallès, Catalunya, Spain
[14]Clinical Trials Unit, Pharmacology Department, Hospital Universitario de Canarias, La Laguna, Canarias, Spain
[15]Complejo Hospital Universitario de Canarias, UICEC, La Laguna, Spain
[16]Research Unit, Fundación Burgos por la Investigación de la Salud, Hospital Universitario de Burgos, Burgos, Spain
[17]Servicio de Farmacología Clínica, IBIMA Plataforma BIONAND, Universidad de Málaga, Málaga, Spain, Platform for Clinical Research and Clinical Trials IBIMA, Hospital Universitario Virgen de la Victoria, Malaga, Andalucía, Spain
[18]Pharmacogenetics Laboratory, Genetics Department, Hospital Universitario La Paz, Madrid, Spain
[19]UICEC Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria La Princesa (IP), Hospital Universitario de la Princesa, Madrid, Spain
[20]Pharmacology Department. School of Medicine, Autonomous University of Madrid, Madrid, Spain

Acknowledgements The iPHARMGx study group extends its sincere gratitude to Philip Morisky, MBA, for his invaluable counsel on the optimal use of the MMAS-8 tool in this research.

Collaborators iPHARMGx study group: Ignacio Bernardino, Javier Guijarro-Eguinoa, Arturo Gómez López De Las Huertas, Pedro Arias, Susana Martín-López, Olga Hladun Alvaro, Vicente Arrate, Ana Fries, Esther Cubo, Daniel Rodriguez Díaz, Fernando Marqués García, Núria Alonso Pedrol, Modesto M Maestre Muñiz, Leticia Rodríguez Alcolado, Xandra García-González, Irene Taladriz-Sender, Carlos Ortiz-Bautista, Inmaculada Coca-Prieto, Angela Remesal-Doblado, María Isabel Lucena, Zaida Salmón González.

Contributors Conceptualisation: AMB and AJC. Methodology: SS, ES-M, ED-S, IGG, AM-C, MC, LAL-F, II-I, MF, RR-A, AJC and AMB. Funding acquisition: ME, LAL-F, II-I, MdMGS, EJL-M, AMP, MF, CR-J, MS-R, JS-C F-AS and AMB. Project administration: SS, ES-M, AJC and AMB. Supervision: AJC and AMB. Writing draft: SS, ES-M, ED-S and AMB. AMB is the guarantor. All authors reviewed the manuscript.

Funding This study was funded by the Instituto de Salud Carlos III (ISCIII) through the project code PMP22/00055 and by Next Generation EU funds, which finance the actions of the Recovery and Resilience Facility (RRF).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Stefan Stewart http://orcid.org/0000-0001-7181-7235
Alicia Marín-Candón http://orcid.org/0000-0001-8883-3151
Iñaki Imaz-Iglesia http://orcid.org/0000-0002-7864-4194
Alberto M Borobia http://orcid.org/0000-0002-8584-3263

REFERENCES

1 Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. *N Engl J Med* 2011;364:1144–53.
2 Stewart S, Dodero-Anillo JM, Guijarro-Eguinoa J, *et al*. Advancing pharmacogenetic testing in a tertiary hospital: a retrospective analysis after 10 years of activity. *Front Pharmacol* 2023;14:1292416.
3 Bielinski SJ, Olson JE, Pathak J, *et al*. Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. *Mayo Clin Proc* 2014;89:25–33.
4 Bottorff MB, Bright DR, Kisor DF. Commentary: Should Pharmacogenomic Evidence Be Considered in Clinical Decision Making? Focus on Select Cardiovascular Drugs. *Pharmacotherapy* 2017;37:1005–13.
5 van der Wouden CH, Böhringer S, Cecchin E, *et al*. Generating evidence for precision medicine: considerations made by the Ubiquitous Pharmacogenomics Consortium when designing and operationalizing the PREPARE study. *Pharmacogenet Genomics* 2020;30:131–44.
6 Swen JJ, van der Wouden CH, Manson LE, *et al*. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *Lancet* 2023;401:347–56.
7 Weitzel KW, Elsey AR, Langaee TY, *et al*. Clinical pharmacogenetics implementation: approaches, successes, and challenges. *Am J Med Genet C Semin Med Genet* 2014;166C:56–67.

8 Schuck RN, Grillo JA. Pharmacogenomic Biomarkers: an FDA Perspective on Utilization in Biological Product Labeling. *AAPS J* 2016;18:573–7.
9 European Medicines Agency. EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine, 2020. Available: https://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine [Accessed 20 Jun 2023].
10 Borobia AM, Dapia I, Tong HY, *et al*. Clinical Implementation of Pharmacogenetic Testing in a Hospital of the Spanish National Health System: Strategy and Experience Over 3 Years. *Clin Transl Sci* 2018;11:189–99.
11 Sukri A, Salleh MZ, Masimirembwa C, *et al*. A systematic review on the cost effectiveness of pharmacogenomics in developing countries: implementation challenges. *Pharmacogenomics J* 2022;22:147–59.
12 David SP, Devine B, Palaniappan L, *et al*. Editorial: State of the science of pharmacogenomics implementation in healthcare systems and communities. *Front Pharmacol* 2024;15:1463384.
13 Wong WB, Carlson JJ, Thariani R, *et al*. Cost effectiveness of pharmacogenomics: a critical and systematic review. *Pharmacoeconomics* 2010;28:1001–13.
14 Hippman C, Nislow C. Pharmacogenomic Testing: Clinical Evidence and Implementation Challenges. *J Pers Med* 2019;9:40.
15 Mukerjee G, Huston A, Kabakchiev B, *et al*. User considerations in assessing pharmacogenomic tests and their clinical support tools. *NPJ Genom Med* 2018;3:26.
16 Brunham LR, Baker S, Mammen A, *et al*. Role of genetics in the prediction of statin-associated muscle symptoms and optimization of statin use and adherence. *Cardiovasc Res* 2018;114:1073–81.
17 Eckard AR, McComsey GA. The role of statins in the setting of HIV infection. *Curr HIV/AIDS Rep* 2015;12:305–12.
18 Grinspoon SK, Fitch KV, Zanni MV, *et al*. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. *N Engl J Med* 2023;389:687–99.
19 Feng Q. Approach to clinical and genetic characterization of statin-induced myopathy. *Methods Mol Biol* 2014;1175:67–90.
20 Dicken W, Mehta A, Karagiannis A, *et al*. Statin associated muscle symptoms: An update and review. *Prog Cardiovasc Dis* 2022;75:40–8.
21 Franc S, Dejager S, Bruckert E, *et al*. A comprehensive description of muscle symptoms associated with lipid-lowering drugs. *Cardiovasc Drugs Ther* 2003;17:459–65.
22 Reith C, Baigent C, Blackwell L, *et al*. Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials. *The Lancet* 2022;400:832–45.
23 Cooper-DeHoff RM, Niemi M, Ramsey LB, *et al*. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. *Clin Pharmacol Ther* 2022;111:1007–21.
24 Wilke RA, Ramsey LB, Johnson SG, *et al*. The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. *Clin Pharmacol Ther* 2012;92:112–7.
25 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
26 Berlowitz DR, Foy CG, Kazis LE, *et al*. Effect of Intensive Blood-Pressure Treatment on Patient-Reported Outcomes. *N Engl J Med* 2017;377:733–44.
27 Bress AP, Bellows BK, King JB, *et al*. Cost-Effectiveness of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2017;377:745–55.
28 Wason JMS. OptGS: An R Package for Finding Near-Optimal Group-Sequential Designs. *J Stat Softw* 2015;66.
29 Stroes ES, Thompson PD, Corsini A, *et al*. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J* 2015;36:1012–22.
30 Hou Q, Li S, Li L, *et al*. Association Between SLCO1B1 Gene T521C Polymorphism and Statin-Related Myopathy Risk: A Meta-Analysis of Case-Control Studies. *Medicine (Baltimore)* 2015;94:e1268.