CONFIDENTIAL

Study Trial Protocol

PREVESTATGx: A multicentre, controlled, randomised and single-blind adaptive phase IV protocol to evaluate efficacy, safety and cost-efficacy of pre-emptive genotyping strategy in a population at risk of cardiovascular disease susceptible of receiving high or moderate-intensity doses of statins

Protocol Version and Date: 1.0 / 11th December 2023.

Protocol Code: PREVESTATGx

Study Design: Phase IV low-intervention clinical trial

Coordinator: Dr. Alberto M. Borobia.

Sponsor Name: Fundación para la Investigación Biomédica del Hospital Universitario La Paz (FIBHULP).

EU CT number: 2023-509418-12-00

This protocol has been drafted by members pertaining to the iPHARMGx methodology working group.

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ABBREVIATIONS

It is advisable to cross reference the abbreviations hereby present with the iPHARMGx Master Protocol's Abbreviation section.

ALS: amyotrophic lateral sclerosis
DNA: deoxyribonucleic acid
e.g.: *exempli gratia*
FIBHULP: Fundación para la Investigación Biomédica del Hospital Universitario La Paz
GUI: graphical user interface
HDLc: high-density lipoprotein cholesterol
LDLc: low-density lipoprotein cholesterol
MMAS-8: Morisky Medication Adherence Scales
NHS: National Health System
NPRS: Numeric Pain Rating Scale
rsID: Reference SNP cluster identification
SAE: serious adverse event
SAMS: statin-associated musculoskeletal symptoms
SAMS-CI: statin-associated muscle symptom clinical index
SAP: Statistical Analysis Plan
SD: standard deviation
T3: triiodothyronine
T4: thyroxine
TG: triglyceride
TSH: thyroid stimulating hormone

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor:	Fundación para la Investigación Biomédica del Hospital Universitario La Paz (FIBHULP).
Protocol title:	A multicentre controlled, randomised, single-blind adaptive phase IV protocol to evaluate efficacy, safety and cost-efficacy of pre-emptive genotyping strategy in a population at risk of cardiovascular disease susceptible of receiving high or moderate-intensity doses of statins.
Protocol code	PREVESTATGx
Indication:	Patients at risk of cardiovascular disease susceptible of receiving high or moderate-intensity doses of statins.
Hypothesis:	Preemptive genotyping in populations at risk of cardiovascular disease susceptible of receiving high or moderate doses of statin therapy is efficacious, cost-efficacious, and feasible within the Spanish National Health System when compared to the current standard of care.

Study Objectives:	**Study Endpoints:**
<u>Primary objective:</u> To assess the efficacy of a statin preemptive genotyping strategy in reducing statin associated musculoskeletal adverse events.	**<u>Primary endpoints:</u>** A composite variable that includes the incidence of patients with a clinically relevant statin-associated musculoskeletal symptom in the 9-month follow-up period or a serum CPK greater than three times the upper limit of normality prespecified by each centre's laboratory, related to the statin.
<u>Secondary objectives:</u> ○ To assess the efficacy of a statin preemptive genotyping strategy in optimizing dyslipidaemia management when compared to Standard of Care (SoC) treatment/dosing.	**<u>Secondary endpoints:</u>** ○ 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 in order to meet LDLc goals.

○ To assess the pharmacoeconomic feasibility of implementing a preemptive pharmacogenetic strategy to adverse musculoskeletal symptoms.	○ Difference in cost between the intervention combined with the costs derived from the events in the intervention arm and the costs derived from the events in the control arm alone. Additionally, the ratio between cost differences and efficacy differences between both arms may be calculated.
Exploratory objectives: ○ To identify novel prognostic and predictive genetic biomarkers of statin-related adverse events and efficacy. ○ To assess the efficacy of a statin preemptive genotyping strategy in reducing the major ischemic cardiovascular events. ○ To assess the effect of a statin preemptive genotyping strategy in improving patient therapeutic adherence. ○ To assess the effect of a statin preemptive genotyping strategy in reducing perceived pain of SAMS.	**Exploratory endpoints:** ○ Novel prognostic and predictive genetic biomarkers of statin-related adverse events and efficacy will be assessed trough techniques only available at CNIO and genome-wide association studies when applicable. ○ Percentage of participants who experience a 4-component secondary endpoint consisting of cardiovascular death, nonfatal myocardial infarction (MI), resuscitated cardiac arrest, or hospitalization for unstable angina. ○ Difference in Morisky-Green (MMAS-8) questionnaire adherence levels/score between both study arms. ○ Difference in Numeric Pain Rating Scale (NPRS) score between both study arms.
Trial Design Overview:	**Study Design** Phase IV, multicentre, controlled, randomized, parallel and single-blind adaptive clinical trial. **Study population:** All patients, 18 years of age and older, that at risk of requiring intensive or moderate lipid-lowering therapy as either primary or secondary prevention as deemed by their attending physician. Subjects will be eligible for study inclusion if intended statin prescription aligns with both statin type and doses described in this protocol. Statin initiation can be withheld 6 months between signing

	the informed consent form (ICF) and the randomization and beginning of the treatment. All participants included will undergo preemptive genotyping prior statin initiation/dose increase and will be randomly allocated to either one of the following: Intervention arm: statin type and/or statin dose will be adjusted according to the most recent clinical pharmacogenetic guideline treatment/dosing recommendations for their genetic profile. Control arm: will not receive any intervention based on their genetic profile, instead they will receive the SoC statin/statin dose as determined by their healthcare provider. Once the patient is included in the clinical trial their clinical management will be conducted according to standard clinical practice save for some additional procedures, that are considered of minimal added risk for the patient such as: 1. An increase in the frequency of follow-up visits in order to collect relevant data. 2. Biological samples will be obtained (blood) for biochemical and pharmacogenetic analysis.
Participant Population:	All patients deemed susceptible of being prescribed a high or moderate-dose statin-based therapy for either primary or secondary prevention of cardiovascular disease by their attending physician will be offered to participate in this study. **Inclusion Criteria** **1.** Ability of the participant to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations. **2.** Subject has voluntarily signed the ICF. **3.** Subject must be ≥ 18 years old at the time of signing ICF. **4.** Subject is able and willing to take part and be followed-up for the majority of the study duration. **5.** Participants are susceptible to be prescribed any of the following: ○ Atorvastatin ≥40 mg/day *p.o.* ○ Simvastatin ≥20mg/day *p.o.* ○ Pitavastatin≥2mg/day *p.o.*

	○ Rosuvastatin ≥40mg/day *p.o.* ○ Pravastatin ≥40mg/day *p.o.* ○ Lovastatin ≥40mg/day *p.o.* ○ Fluvastatin ≥80 mg/day *p.o.* **6.** Subjects must be naïve to any genotyping test of the following genes: *SCLO1B1, ABCG2, CYP2C9, CYP3A4, CYP3A5* and *HMGCR.* **7.** Subjects must be willing to comply and adhere to any treatment plan modifications established and to the procedures specified in this protocol. **8.** Women of childbearing potential must commit not to become pregnant. These subjects must be willing to use highly effective contraceptive methods or have practiced sexual abstinence during the study. **<u>Exclusion criteria</u>** **1.** Subject is currently taking ubiquinone (Q10). **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 (SmPCs) 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.
Number of participants:	The total number of patients planned to be included is this study is 216 subjects considering a loss to randomize of 20% over a study that required 180 subjects.
Medicinal Product, Dose and Mode of Administration:	Patients participating in this study can receive treatment with any of the statins authorized in Spain for the treatment for the primary and secondary prevention of cardiovascular disease. All forms of administration will be oral (*p.o.*) and dosing schemes will be those specified by the label of each statin or relevant pharmacogenetic guideline when applicable.
Statistical Analysis:	We have established three distinct stages (J=3), each representing a critical point at which data analysis will be conducted. Our objective is

	to maintain a desired level of statistical rigor, with a type I error rate set at 0.05 and a type II error rate fixed at 0.2. The third and final stage corresponds to the final analysis. In order to power this trial for a meaningful effect size (δ= 0.42), we have calculated an estimated total sample size of 180 subjects, with 30 subjects allocated to each arm within each stage. This figure has been increased to 216 subjects considering a non-negligible percentage of pre-randomization loss (20%) of subjects that may be deemed susceptible of receiving a statin but end up not being prescribed one, for whatever reason. Since these subjects will be genotyped, they will be considered for the pharmacoeconomic endpoint. 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. If either assessment exceeds the prespecified threshold, study termination is warranted. Additionally, a sensitivity analysis is contemplated in the event of high rates of subjects being prescribed additional lipid-lowering therapy within the intervention arm, to assess possible impact on primary endpoint analysis. Further information on the statistical analysis will be included in the Statistical Analysis Plan (SAP).
Trial Duration:	Each patient will be followed for a maximum of 36 weeks (roughly nine months). The end-of-study visit for patients who, for whatever reason, do not continue follow-up until week 36 will be the last visit. The end of study is considered as the last visit for the last participant in the study.

1.2. Schedule of assessments

Month	Screening: 0-6 months	Baseline=Randomization Day 1	Month 1 (1,5)	Month 3 (1,5)	Month 6 (1,5)	Month 9 (1)
	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
Randomization and start of treatment		X				
Vital signs (2)	X	X				X
Pharmacogenetics blood draw	X					
Laboratory determinations (3)	X					X
SAMS-CI NPRS MMAS-8 questionnaires (4)	X	X	X	X	x	X
Adverse Events evaluation			X	X	x	X

Table 1: Schedule of study assessments

(1) All visits performed after treatment administration have a +/-7-day window to be performed.
(2) Blood pressure and heart rate.
(3) 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 one month prior to randomization visit. Additional laboratory determinations can be done following local guidelines.
(4) Scale assessment will include a SAMS-CI questionnaire, NPRS scale when applicable and MMAS-8 adherence questionnaire.
(5) Visits to be performed remotely.

1.3. Flowchart

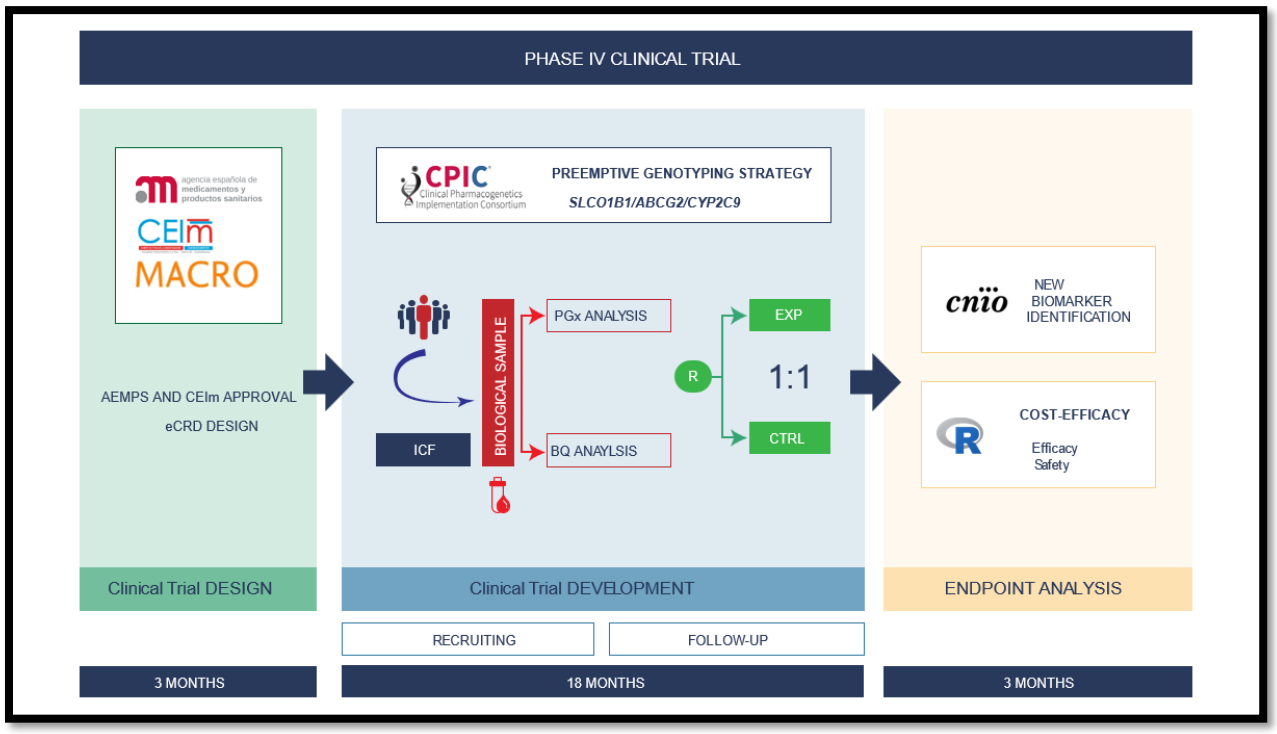

Figure 1: Overall duration of the clinical trial. Follow-up period will last 9 months since subject inclusion, with a recruitment phase that will last a maximum of 12 months since first subject inclusion or until desired sample sized is recruited. Abbreviations are as follow: PGx pharmacogenetic analysis. BQ-biochemistry analysis. EXP: Experimental arm. CTRL: Control arm.

2. GENERAL INFORMATION

2.1. Disclosure

The PREVESTATGx study protocol is an integral component of the broader iPHARMGx master protocol, which serves as the overarching framework that guides the present study. As such, it is imperative that the PREVESTATGx study protocol is assessed in conjunction with the master protocol to ensure a comprehensive understanding of its research approach.

It's important to acknowledge that the iPHARMGx master protocol encompasses certain common elements that are applicable to all individual protocols nested within it. These shared elements have been intentionally omitted from the PREVESTATGx study protocol for the sake of brevity and clarity. Instead, they are explicitly detailed and outlined solely within the master protocol.

Therefore, researchers and stakeholders involved in the PREVESTATGx study are strongly encouraged to reference and cross-reference the master protocol to ensure a comprehensive grasp of the overarching research framework and the specific procedures and guidelines that pertain to this study.

2.2. Study identification

Protocol code: PREVESTATGx
Full Title: "A multicentre controlled, randomised, single-blind adaptive phase IV protocol to evaluate efficacy, safety and cost-efficacy of pre-emptive genotyping strategy in a population at risk of cardiovascular disease susceptible of receiving high or moderate-intensity doses of statins."

EU CT number: 2023-509418-12-00

2.3. Development phase

This is a Phase IV low-intervention clinical trial nested within the iPHARMGx project framework. For further information regarding iPHARMGx, refer to the master protocol.

2.4. Treatment

Patients in this study will receive treatment according to local clinical practice, with any of the authorized statins available as lipid-lowering primary or secondary prevention. Treatment will be administered according to the drug's product labelling in control arm and according to pharmacogenetic clinical guidelines in the intervention arm. The intervention in this study is predicated on the specific type and dosage of statins recommended by the Clinical Pharmacogenetics Consortium's genotype guidelines.

2.5. Principal Investigators and Participating Centres

Principal Investigators (PI)	Participating Centres
Carlos Ortiz Bautista.	University General Hospital Gregorio Marañón.
Miriam Estébanez Muñoz.	Defense Central Hospital Gomez Ulla.
Modesto Maestre Muñoz.	General Hospital of Tomelloso.
Vicente Ignacio Arrarte.	General University Hospital of Alicante.
Esther Cubo.	University Hospital of Burgos.
Daniel Rodríguez Díaz.	University Hospital of the Canary Islands.
Nuria Alonso.	Germans Trias i Pujol University Hospital.
Zaida Salmón González.	Marqués de Valdecilla University Hospital.
Inmaculada Coca Prieto.	Virgen de la Victoria University Hospital.
José Ignacio Bernardino.	University Hospital La Paz (HULP).

2.6. Data Monitoring Committee

Unidad Central de Investigación Clínica y Ensayos Clínicos (UCICEC).
Fundación para la Investigación Biomédica del Hospital Universitario La Paz.
C.I.F.: G83727057
Paseo de la Castellana, 261. 28046. Madrid.
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2.7. Independent Ethics Committee

CEIC del Hospital Universitario La Paz. Área Sanitaria 5 de la CCAA de Madrid .
Paseo de la Castellana, 261, 28046 Madrid
e-mail: ceic.hulp@salud.madrid.org

2.8. Study Duration

The planned total study duration will be 24 months. Duration of the recruitment period will be 12 months since first inclusion. Duration of the follow-up will be 9 months since subject inclusion. The data analysis, preparation of final report and results publication will last 3 months.

End of study date: The end of study date will be the date of the last visit of the last patient included.

2.9. Study design

2.9.1. Study Design

A multicentre controlled, randomised, adaptive phase IV protocol to evaluate efficacy, safety and cost-efficacy of pre-emptive genotyping strategy in a population at risk of cardiovascular disease susceptible of receiving high or moderate-intensity doses of statins.

2.9.2. Study population

All patients, 18 years of age and older, that require either moderate or high intensity lipid-lowering therapy as either primary or secondary prevention by their attending physician are deemed eligible to participate. Subjects will be eligible for study inclusion if intended statin prescription aligns with both statin type and doses described in this protocol.

2.9.3. Sample size

It is estimated to recruit approximately 216 patients within a one-year period. This calculation is based on clinical considerations, recruitment feasibility, and investigational drugs, and appropriate statistical considerations.

2.9.4. Definition of the intervention

Refer to the Master Protocol for an overview of the intervention. For the purpose of this trail, preemptive genotyping strategies will be evaluated for statin therapy.

3. BACKGROUND AND RATIONALE

3.1. Overview Of Disease and Current Treatment

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 (Brunham et al., 2018). These medications were developed with the objective of lowering cholesterol levels in the bloodstream, specifically targeting LDL cholesterol, as accumulating evidence established that elevated cholesterol was a significant risk factor for the onset of coronary heart disease (CHD) (Brunham et al., 2018). Overall, they have demonstrated efficacy in reducing the risk of cardiovascular (CV) morbidity and mortality in patients with CHD. With the expanding use of statins, approximately 25% of individuals worldwide aged 65 years or older are on long-term statin therapy for primary or secondary prevention of cardiovascular disease (CVD).

Another at-risk demographic are HIV-infected individuals, who experience a high prevalence of dyslipidaemia primarily attributed to antiretroviral therapy (ART), notably protease inhibitors (PIs) (Eckard & McComsey, 2015). This dyslipidaemia, coupled with heightened immune activation and inflammation resulting from HIV infection itself, significantly contributes to an elevated risk of CVD within this population (Eckard & McComsey, 2015). In this context, statins are increasingly being used in HIV patients to mitigate cholesterol levels, particularly LDL, with the aim of reducing CVD risk. Moreover, the potential benefits of statin therapy in the HIV-infected population extend 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 warranting its use in these patients (Eckard & McComsey, 2015). Additionally, a recently published results highlight the role of pitavastatin as primary prevention of cardiovascular events in HIV-populations (Grinspoon et al., 2023).

Consequently, the safety profile and potential adverse effects of statins, particularly in patients taking multiple medications and at risk of drug-drug interactions (DDIs), warrant special attention.

For numerous years, the manifestation of muscle-related symptoms caused by statins has been referred to as "*statin myopathy*". However, "*statin myopathy*" specifically describes muscular weakness of a neuro-muscular nature. In 2014, the National Lipid Association Task Force recommended the adoption of precise terminology to encompass the spectrum of adverse muscle events. This revised terminology was developed based on symptomatology and underlying pathophysiological mechanisms. Therefore, the term "SAMS" (Statin-Associated Muscle Symptoms) encompasses a wide range of symptomatic muscle complaints, with or without detectable biochemical evidence of muscle damage. In this context, we intentionally employ "SAMS" to encompass the entire spectrum of muscle-related complaints and, where

relevant, specify the specific phenotype employed in various studies described herein. However, it is important to note that there is considerable heterogeneity and uncertainty in the definitions of SAMS.

While statin monotherapy is generally well-tolerated, patients concurrently using multiple medications face an elevated risk of adverse events, including SAMS.

3.2. Trial Rationale

The development of this study would help optimise the treatment of patients at high-risk of cardiovascular disease 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 National Health System (SNHS). The establishment of comprehensive pharmacoeconomic evidence serves a dual purpose. Firstly, it contributes to the expanding body of evidence that advocates for the viability of a personalized medicine strategy in statin management, thereby facilitating its broader adoption within the healthcare system. Secondly, 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.

3.3. Pharmacogenetic rationale

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	N/A	c.421C>A
CYP2C9	rs1799853	*2	3608C>T
CYP2C9	rs1057910	*3	42614A>C

Table 2: SNPs deemed mandatory to interrogate in all recruited subjects.

3.3.1. *SLCO1B1*

In this protocol, we use the term *SLCO1B1* (solute carrier organic anion transporter family member 1B1) to refer to the protein product encoded by the *SLCO1B1* gene. This protein, also known by alternative names such as OATP1B1 and OATP-C, plays a crucial role in the liver's uptake of statins, as well as various other substances, both naturally occurring and externally introduced (e.g., bilirubin and 17-beta-Glucuronosyl oestradiol) (Cooper-DeHoff et al., 2022).

A decrease in the function of this transporter can occur due to genetic variations or as a result of drug-induced inhibition. Such reduction can significantly elevate the levels of statins circulating in the bloodstream, which is thought to be a potential root cause of SAMS.

The *SLCO1B1* gene locus is located on chromosome 12 (Chr 12p12.2) and spans a region of 109 kilobases (kb). Although numerous single nucleotide variants (SNVs) have been identified within this gene, only a select few are known to exert clinically significant functional effects (Cooper-DeHoff et al., 2022).

One common variant, namely c.521T>C (rs4149056), results in a substitution of p.V174A and is associated with the SLCO1B1 *5 and *15 haplotypes. It's important to note that the SLCO1B1 *17 haplotype, which also carries the c.521T>C variant, is no longer recognized as a separate allele; it has been merged with SLCO1B115 by the Pharmacogene Variation Consortium (PharmVar). The presence of the minor C allele at c.521T>C has been linked to reduced transport function in laboratory experiments and increased systemic exposure to several drugs in real-world clinical settings (Cooper-DeHoff et al., 2022; Li et al., 2006). Variant 35230A>G (rs2306283) has been linked with low response to pravastatin in regards to LDLc levels, with mixed evidence when it comes to statin induced myopathy (Akao et al., 2012) .

3.3.2. *ABCG2*

ABCG2, the gene responsible for encoding the adenosine triphosphate (ATP)–binding cassette G2 transporter, commonly referred to as the breast cancer resistance protein (BCRP), exhibits a broad tissue distribution, including expression in the liver, blood-brain barrier, and intestine. ABCG2 plays a pivotal role in expelling various compounds into the extracellular environment (Cooper-DeHoff et al., 2022).

The *ABCG2* gene occupies a chromosomal region spanning over 66 kb and is located on chromosome 4 (Chr 4q22.1). A frequently studied variant, p.Q141K (c.421C>A, rs2231142), has been extensively investigated. This variant features a minor A allele that has been associated with a notable 30–40% reduction in protein expression when compared to the reference allele. Furthermore, this genetic variation has been linked to elevated plasma levels of rosuvastatin (Cooper-DeHoff et al., 2022).

3.3.3. *CYP2C9*

CYP2C9, also known as cytochrome P450 2C9, is a vital enzyme involved in the phase I metabolism of numerous drugs. It belongs to the *CYP2C* gene cluster, situated within a 500kb region on chromosome 10q24 (Chr 10q23.33). The *CYP2C9* gene exhibits significant polymorphism, with a documented presence of at least 71 variant alleles (Cooper-DeHoff et al., 2022).

Among the multitude of variants, two have received extensive scrutiny in research: *CYP2C92* (p.R144C; rs1799853) and CYP2C93 (p.I359L; rs1057910). These two variants are known

to reduce CYP2C9 enzyme function by approximately 30–40% and 80%, respectively. Consequently, they result in increased systemic exposure to Fluvastatin, a drug metabolized by *CYP2C9*. These genetic variations underscore the importance of understanding *CYP2C9* polymorphism, as it can significantly influence drug metabolism and individual responses to medications, emphasizing the need for personalized medicine approaches (Cooper-DeHoff et al., 2022).

Justification for low-intervention clinical trial

Refer to the iPHARMGx Master Protocol.

4. HYPOTHESIS OBJECTIVES AND ENDPOINTS

4.1. Hypothesis

A widespread adoption of a preemptive genotyping scheme in populations at high risk of cardiovascular disease susceptible of receiving statin therapy is cost-efficacious and feasible within the SNHS when compared to the standard of care statin type and dosing. This will improve efficacy, avoid therapy toxicity, and save costs for the national healthcare system, contributing to its overall sustainability.

4.2. Objectives

Primary objectives:

To assess the efficacy of a statin preemptive genotyping strategy in reducing statin associated musculoskeletal adverse events.

Secondary objectives:

- To assess the efficacy of a statin preemptive genotyping strategy in optimizing dyslipidaemia management when compared to Standard of Care (SoC) treatment/dosing.
- To assess the pharmacoeconomic feasibility of implementing a preemptive pharmacogenetic strategy to adverse musculoskeletal symptoms.

Exploratory objectives:

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

4.3. 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 a NPRS score ≥3) in the 9-month follow-up period or a serum CPK greater than three times the upper limit of normality prespecified by each centre's laboratory, related to the statin.

4.4. 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 in order 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 to the costs derived from the events in the control arm alone over the 9-month follow-up period. Additionally, the ratio between cost differences and efficacy differences between both arms may be calculated.

4.5. Exploratory endpoints

- Novel prognostic and predictive genetic biomarkers of statin-related adverse events 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 CNIO as well as genome-wide association studies when applicable. Aforementioned techniques may vary at CNIOs criteria and may include (but are not limited to) assays and/or next generation sequencing techniques.
- Percentage of participants who experience a 4-component exploratory endpoint consisting of cardiovascular death, nonfatal myocardial infarction (MI), resuscitated cardiac arrest, or hospitalization for unstable angina.
- Difference in Morisky-Green (MMAS-8) questionnaire adherence levels/score between both study arms.
- Difference in Numeric Pain Rating Scale (NPRS) score between both study arms. Categories will be as follow: 0-3 no pain; 3-5 moderate pain; 5-7 intense pain; 7-9 very intense pain; 9-10 extreme pain.

4.6. Data to be collected

The following must be cross-referenced with the iPHARMGx Master Protocol:

- Demographic and clinical history endpoints:
  - Age, race, sex.
  - Date of diagnosis of dyslipidaemia.
  - Previous treatments for dyslipidaemia.
- Other clinical situation data throughout the study:
  - Blood pressure.
  - Presence of intercurrent diseases that can modify the activity of the enzymes responsible for the metabolism of statins.
- Analytical data and biomarkers:

- Basic biochemistry profile, liver and kidney profile, ionogram. Cholesterol profile and CPK.
- Genotyping.

- Data related to pharmacological treatment:
  - Treatment selected and its formulation, dose and schedule.
  - Concomitant treatment with other drugs (namely other lipid-lowering therapy):
    - Ezetimibe.
    - PCSK9 inhibitors (e.g: evolocumab).
    - Citrate lyase inhibitors (e.g: bempedoic acid).
    - Bile acid sequestrants e.g: cholestyramine).
    - Fibrates (e.g: gemfibrozil, fenofibrate).
  - Appearance of adverse events derived from treatment.
  - Statin treatment changes or withdrawal.
- Data related to clinical events
  - Outpatient medical visits related to SAMS together with all the interventions and procedures performed during the admission.
  - Hospital admissions related with SAMS together with all the interventions and procedures performed during the admission.
  - Any of the endpoints that compose the exploratory composite endpoint.

4.7. STUDY POPULATION

All patients deemed at high risk of cardiovascular disease by their attending physician and that may require high to moderate-intensity lipid-lowering therapy as either primary or secondary prevention and have never experienced a SAMS are eligible for study inclusion. Subjects receiving statis at low doses but are susceptible to dose titration to moderate-higher intensity statins are also eligible.

4.7.1. Inclusion Criteria:

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

1. Ability of the participant to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.
2. Subject has voluntarily signed the ICF.
3. Subject must be ≥ 18 years old at the time of signing ICF.
4. Subject is able and willing to take part and be followed-up for the majority of the study duration.
5. Participants are susceptible to be prescribed any of the following:
   a. Atorvastatin ≥40 mg/day *p.o.*

b. Simvastatin ≥20mg/day *p.o.*
c. Pitavastatin≥2mg/day *p.o.*
d. Rosuvastatin ≥40mg/day *p.o.*
e. Pravastatin ≥40mg/day *p.o.*
f. Lovastatin ≥40mg/day *p.o.*
g. Fluvastatin ≥80 mg/day *p.o.*

6. Subjects must be naïve to any genotyping test of the following genes: *SCLO1B1, ABCG2, CYP2C9, CYP3A4, CYP3A5* and *HMGCR.*
7. Subjects must be willing to comply and adhere to any treatment plan modifications established and to the procedures specified in this protocol.
8. Women of childbearing potential must commit not to become pregnant. Subjects must be willing to use highly effective contraceptive methods or have practiced sexual abstinence during the study.

4.7.2. 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 (SmPCs) 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.

5. STUDY MEDICATION AND CONCOMITANT THERAPY

Investigational drug: Patients in this study will any of the drugs authorized statins available as lipid-lowering primary or secondary prevention.

Patients in the **control group** will receive the statins according to clinical practice and the drug's product labelling, and never exceeding the already authorized dosages.

Patients in the **experimental group** will receive the dose the specific type and dosage of statins recommended by the Clinical Pharmacogenetics Consortium's genotype guidelines (view Appendix 13.4), using the pharmacogenetic information and characteristic of the patient.

5.1. Concomitant Therapy and prohibited medication

At the time of study initiation, patients will continue to receive all concomitant medications prescribed by their physicians. If a subject is currently taking any prohibited medications during the screening process, they may still be eligible for inclusion after successfully undergoing a washout period, which must span a duration of no less than five times the medication's half-life of elimination. Failure to adhere to this mandatory washout period will lead to a screening failure.

Any medication at the time of enrolment or received during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Prohibited medication, due to the nature of this study is as follows:

- Ubiquinone (Q10) supplements.

5.2. Pregnancy, breastfeeding and contraception disclosure

Evidence on whether statins are safe during pregnancy, excreted in breastmilk or genotoxic is not clearly established in the scientific literature. SmPC's for most marketed statins contraindicate the administration of them during pregnancy/breastfeeding. For the sake of participants safety, the sponsor concurs with these recommendations. Therefore, subjects must be willing to comply with contraception and pregnancy measures established in this protocol. Once the subject's participation in this study is completed or subject ends participation for whatever reason, any recommendation on contraception and pregnancy will not be performed on the sponsors behalf, being sole responsibility of the subject's regular healthcare provider.

6. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1. Discontinuation of Study Medication

The criteria for discontinuation of study medication are described below:

A) Lack of efficacy or excess of risk as defined by two prespecified interim analysis performed at week 12 and week 24 that test for both efficacy and futility. Both analyses align with the framework described in the iPHARMGx master protocol.
B) Any situation that precludes the subject from continuing statin therapy as assessed by the investigator team (e.g., unforeseen pregnancy).

6.2. Patient Discontinuation/Withdrawal Criteria:

Detailed in Master Protocol.

6.3. Lost to Follow-Up

Detailed in Master Protocol.

7. STUDY ASSESSMENTS AND PROCEDURES

All patients deemed susceptible to receive a statin treatment at high-moderate dose will be offered to participate in this study.

They will also be asked for their consent to store an aliquot of their DNA for future studies that allows for novel biomarker discovery (e.g., next generation sequencing to be performed as disclosed in the master protocol).

7.1. General instructions

Study procedures and their timing are summarized in Schedule of Assessments (section 1.2). Protocol waivers or exemptions are not allowed. Safety concerns should be discussed with the sponsor or sponsor representative immediately upon notice, to determine if the participant should continue or discontinue the study intervention. Adherence to the study design requirements, including those specified in the flow chart, is essential and required for study conduct. The recruitment period will last up to 12-months after the first subject is included (see Flowchart in section 1.3). Screening visit can potentially last up to 6-months after subject signs ICF. It is mandatory that subject has been genotyped before being randomized to either arm or blinding would be compromised. At the time that the patients agree to be recruited for the study, all the information deemed appropriate and relevant for the study will be recorded. The patients included in the study will undergo the visits and procedures detailed in this protocol.

7.2. Study visits and procedures

Study visits and procedures.

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

- Eligibility check:
- Medical history.
- Physical examination.
- Concomitant medication.
- Scales to assess the likelihood of SAMS (SAMS-CI).
- NPRS: Visual Analog Scale.
- MMAS-8: Morinsky-Green 8-item therapeutic adherence questionnaire.

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 meticulously documented, including any relevant pre-existing conditions and medications. Any new information must be recorded in de medical history.
    - Physical examination will encompass a comprehensive physical examination 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 (e.g., myalgia or myopathy) were caused or worsened by statin use. A complete scale assessment with all items must be done at every visit. 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 (*i.e* a SAMS-CI score ≥7), a NPRS will be performed to assess pain encumbrance and burden. Clinically relevant pain encumbrance will be defined as a NPRS score greater or equal to 3.
6. 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. 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 6-8 medium adherence and a score of 8 high adherence.

7.2.1. Screening visit

The inclusion and exclusion criteria for this study are described in Section 4.7. 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 -20ºC for quality control purposes and/or further genetic analysis by techniques only available at CNIO.

Subject must have a mandatory screening laboratory analysis that includes all safety and efficacy parameters described in this study (View 14. Clinical Laboratory Tests) 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. In other words: screening laboratory determination will not be required if subject has a lab determination including all required parameters performed for whatever reason up to one month prior to randomization visit.

7.2.2. Baseline: Up to 6 months after first screening visit

A baseline assessment of SAMS-CI scale to assess possible SAMS confounders will be performed. Baseline MMAS-8 and NPRS scales will also be performed.

Subject will be randomized to receive either standard of care treatment (control arm) or pharmacogenetic guideline-based treatment (experimental arm). Prior to treatment initiation, in cases where subject is allocated to experimental arm, a dose/treatment recommendation will be made available to the prescribing clinician by a Clinical Pharmacologist or a or by a Pharmacist with expertise in Pharmacogenetics.

A urine pregnancy test will be performed if subject is female and of childbearing potential. Upon completion of visit subject will be initiate treatment to comply with 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.

7.2.3. Visit 3: 30 days after treatment initiation (+/- 7 days window)

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

7.2.4. Visit 4: 90 days after treatment initiation (+/- 7 days window)

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

7.2.5. Visit 5: 180 days after treatment initiation (+/- 7 days window)

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

7.2.6. 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 adverse events must be recorded and appropriate questionnaires be completed.

7.3. Efficacy and futility boundaries and end-of-study visit

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 rigor, with a type I error rate (alpha) set at 0.05 and a type II error rate fixed at 0.2. The third and final stage corresponds to the ultimate analysis.

In order to power this trial for a meaningful effect size (δ= 0.42), we have calculated an estimated total sample size of 180 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 216 to factor in possible pre-randomization loss of subjects (20%) that despite being genotyped do not receive statin for whatever reason. Therefor in order to adequately assess the pharmacoeconomic feasibility of the intervention, they must be included in the pharmacoeconomic endpoint analysis (Wason, 2015).

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 Statin-Associated Muscle Symptoms (SAMS) ranging from 7% to 29%(Stroes et al., 2015). Furthermore, studies have established approximately a 2.5-fold increased risk (OR: 2.35; 95% CI: 1.08–5.12) of myopathy among individuals carrying the c.521C allele of the *SLCO1B1* gene (Hou et al., 2015). 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.

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. If either assessment exceeds the prespecified threshold, study termination is warranted. These boundaries were calculating using the graphical user interface (GUI) is built upon (and in to) v.2.2.0 of the R package OptGS (Wason, 2015).

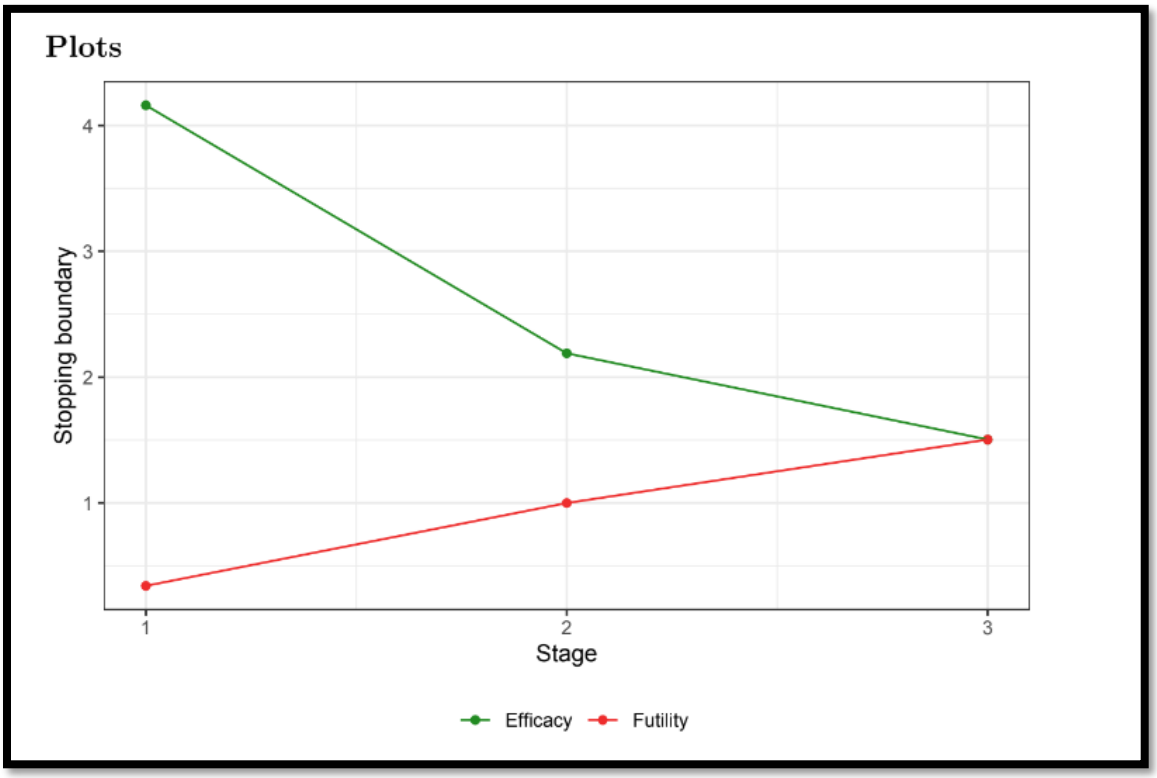

Figure 2: futility and efficacy thresholds plot that must be met in order to warrant study termination.

7.4. Biological samples

Pharmacogenetics:

In alignment with the principles outlined in the iPHARMGx master protocol, our study, as well as all studies pertaining to the priority triads established within the iPHARMGx framework, will employ a proven pharmacogenetic genotyping tool. All centres that will take part in this study will genotype the previously stated level IA relevant SNPs of said genes according to their own available techniques (Table 2). 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 CNIO analysis. This will not be mandatory for all participating laboratories.

In addition, a custom 180-SNP Taqman® assay, purposefully designed to meet the requirements of the iPHARMGx project will be commissioned, to aid the centres with techniques capable of processing it as well as exploring additional variants than the relevant level IA SNPs.

This custom assay has been collaboratively designed with the involvement of all members of the Pharmacogenetics Working Package (GdT-FGx) associated with the iPHARMGx project and is comprised of experts in pharmacogenetics (including Clinical Pharmacologists, Geneticists, and Pharmacists) across 9 different hospitals. It also includes members from the Nation Centre of Oncological Investigations (CNIO) and each participating centre biobank who will participate in sample storage and extended genotyping tasks.

Our custom assay is ensured to encompass a sufficiently broad array of SNPs (Single Nucleotide Polymorphisms) that are pertinent to this research objectives. In particular, it guarantees coverage of all level IA relevant SNPs for the following genes *SCLO1B1, CYP2C9, ABCG2* involved in SAMS and that are described in CPIC Guideline for Statins (January 2022 Revision).

Furthermore, any remaining available SNP slots within the assay will be strategically allocated in a hierarchical fashion. This allocation will adhere to an evidence-based descending order, prioritizing SNPs based on their established relevance and potential impact on our research objectives (as described in PHARMGKB).

Through this comprehensive genotyping strategy, we aim to achieve a thorough and insightful exploration of the genetic landscape, facilitating the generation of robust and clinically valuable insights within the context of the iPHARMGx project.

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 the CEGEN-CNIO Unit using Illumina genotyping (GDA with Enhanced PGx), which evaluates 1,933,117 markers or any other technique they deemed apt, with the aim of conducting an unbiased approach (GWAS) of potential biomarkers that may be associated with the response. 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 CNIO at any given time, to be explored through any technique deemed adequate them .

8. Measures to minimize bias

This is a randomized, single-blind, placebo-control trial which is in accordance with the ICH guideline E8 (R1) on general considerations for clinical studies. To ensure minimized incurrence of bias, special care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant or his/her parent(s)/legal guardian(s) will be the preferred method of inquiry.

8.1. Randomization and blinding

This is a randomized single-blind trial; therefore, blinding will be required for only participating subjects. A single-blind design was not considered feasible due to the methodological difficulty assessing certain endpoints if the prescribing clinician is blinded. 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. Further rationale for blinding scheme may be found in the iPHARMGx master protocol. Randomization 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. The adaptive nature of this study permits modifications of the aforementioned randomization ratio if it is deemed so in the intermedia Interactive Web Response Systems (IWRS) software will be utilised for subject randomization. Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized/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 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.

9. SAFETY ASSESSMENTS

Planned time points for all adverse events assessments are provided in the Schedule of assessments. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the eCRF.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention.

AEs will be documented in the eCRF for each visit as determined in the Schedule.

9.1. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

Detailed in the Master Protocol.

9.2. Time period and frequency for collecting and reporting AE and SAE information

Detailed in the Master Protocol.

9.3. Method of detecting AEs and SAEs

Detailed in Master Protocol.

9.4. Definition of a statin associated musculoskeletal symptoms (SAMS) by the 2014 National Lipid Association Statin Muscle Safety Task Force:

Terminology around statin-associated adverse muscle events is variable and has changed over time. In this topic, where possible, we use the categories of events defined by the 2014 National Lipid Association Statin Muscle Safety Task Force:

- Myalgia: A symptom of muscle discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal creatine kinase (CK)

level. Myalgia symptoms can be described as similar to what would be experienced with a viral syndrome such as influenza.

- Myopathy: Muscle weakness (not due to pain), with or without an elevation in CK level.
- Myositis: Muscle inflammation.
- Myonecrosis: Elevation in muscle enzymes compared with either baseline CK levels (while not on statin therapy) or the upper limit of normal that has been adjusted for age, race, and sex:
    - Mild – Three- to 10-fold elevation in CK.
    - Moderate – 10- to 50-fold elevation in CK.
    - Severe – 50-fold or greater elevation in CK.
- Clinical rhabdomyolysis – Defined by the Task Force as myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of at least 0.5 mg/dL [44 micromol/L]).

9.5. Assessment of AEs and SAEs and Regulatory reporting requirements for serious adverse events

Detailed in the Master Protocol.

10. STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

10.1. Statistical Analyses

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, standard deviation, median and interquartile range). The normality of the variables will be studied using the Kolmogorov-Smirnof normality test.

For the study of the main variable, the Pearson Chi-Square test (or Fisher's exact test for 2X2 tables or likelihood ratio in mXn tables, if necessary) will be used in the case of qualitative variables and the Student's t-test, ANOVA of one factor or its non-parametric equivalents Mann-Whitney U test, Kruskal-Wallis test in the case of 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 (BIC).The statistical software R [R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria] will be used.

The level of statistical significance is set at $p<0.05$. The statistical software R (version 4.3.1, 2023-06-16) [R Core Team (2021)] will be used.

Further details will be included in the SAP.

10.2. Safety analyses

Safety endpoints include serious adverse events (SAEs) leading to study treatment discontinuation and death. SAEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). SAEs leading to study treatment discontinuation and death will be summarized with absolute and relative frequencies (%) with 95% confidence intervals (CIs). More details on the statistical analysis will be provided in the SAP.

11. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1. Regulatory and ethical considerations

Detailed in Master Protocol.

Informed Consent process
Detailed in Master Protocol.

Data protection
Detailed in Master Protocol.

Data quality assurance
Detailed in Master Protocol.

Detailed Source documents
Detailed in Master Protocol.

Insurance
Detailed in Master Protocol.

11.2. Study and site start and closure

Detailed in Master Protocol.

Study/Site Termination

Detailed in Master Protocol.

11.3. Publication policy

Detailed in Master Protocol.

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13. APPENDIX

13.1. Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)

Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)

Instructions:

- Use with patients who have had muscle symptoms that were **new or increased** after starting a statin regimen.
- A **statin regimen** includes any statin at any dose or frequency, including a statin the patient has used previously, at the same or a different dose.
- **Muscle symptoms** may include aches, cramps, heaviness, discomfort, weakness, or stiffness.
- Interpret overall score in light of **other possible causes** of the muscle symptoms, such as:
  - Recent physical exertion
  - Changes in exercise patterns
  - Hypothyroidism
  - Drug interaction with statin
  - Concurrent illness
  - Underlying muscle disease
- **See reverse** for Frequently Asked Questions

How many statin regimens has the patient had that involved new or increased muscle symptoms?

One — Complete the questions on the left side of this page.

Two or more — Complete the questions on the right side of this page.

Regarding this statin regimen:

A. Location and pattern of muscle symptoms (If more than one category applies, record the highest number.) — **Enter score:**

Symmetric, hip flexors or thighs	3
Symmetric, calves	2
Symmetric, proximal upper extremity	2
Asymmetric, intermittent, or not specific to any area	1

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3
4–12 weeks	2
>12 weeks	1

C. Timing of muscle symptom improvement after withdrawal of statin (If patient is still taking statin, stop regimen and monitor symptoms.)

<2 weeks	2
2–4 weeks	1
No improvement after 4 weeks	0

Rechallenge the patient with a statin regimen, (even if same statin compound or regimen as above) **then complete final question:**

D. Timing of recurrence of similar muscle symptoms in relation to starting second regimen

<4 weeks	3
4–12 weeks	1
>12 weeks or similar symptoms did not reoccur	0

Total: All four scores above must be entered before totaling

Regarding the statin regimen *before* the most recent regimen:

A. Location and pattern of muscle symptoms (If more than one category applies, record the highest number.) — **Enter score:**

Symmetric, hip flexors or thighs	3
Symmetric, calves	2
Symmetric, proximal upper extremity	2
Asymmetric, intermittent, or not specific to any area	1

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3
4–12 weeks	2
>12 weeks	1

C. Timing of muscle symptom improvement after withdrawal of statin

<2 weeks	2
2–4 weeks	1
No improvement after 4 weeks	0

Regarding the *most recent* statin regimen: (even if same statin compound as above)

D. Timing of recurrence of similar muscle symptoms in relation to starting regimen

<4 weeks	3
4–12 weeks	1
>12 weeks or similar symptoms did not reoccur	0

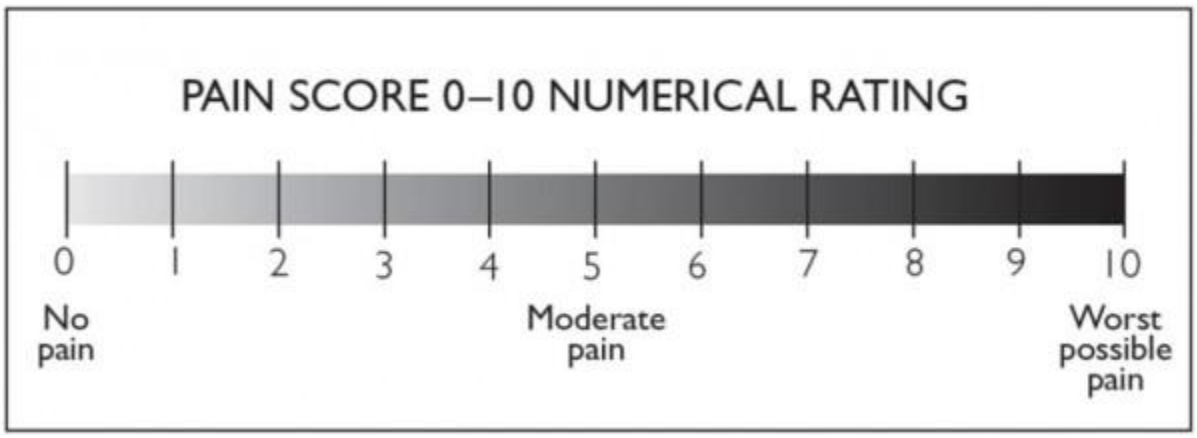
Total: All four scores above must be entered before totaling

Interpretation

Total score:	2–6	7–8	9–11
Likelihood that the patient's muscle symptoms are due to statin use:	Unlikely	Possible	Probable

10 Oct 2016. Based on Rosenson et al. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol.* 2014 May–Jun;8(3 Suppl):S58–71.

13.2. Numerical Pain Score Rating Scale (NPRS)



NPRS scale will be divided into Categories will be as follow: 0-3 no pain; 3-5 moderate pain; 5-7 intense pain; 7-9 very intense pain; 9-10 extreme pain.

13.3. Morisky Medication Adherence Scales (MMAS-8)

Morisky Medication Adherence Scales: MMAS-8	
1	Do you sometimes forget to take your pills?
2	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?
3	Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?
4	When you travel or leave home, do you sometimes forget to bring along your medicine?
5	Did you take all your medicine yesterday?
6	When you feel like your symptoms are under control, do you sometimes stop taking your medicine?
7	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?
8	How often do you have difficulty remembering to take all your medicine? (a) Never/rarely; (b) Once in a while; (c) Sometimes; (d) Usually; (e) All the time.

A score below 6 indicates low adherence, a score between 6 < 8 medium adherence and a score of 8 high adherence.

13.4. CPIC Table of Phenotype-based Dosing Recommendations

Available at: https://cpicpgx.org/guidelines/cpic-guideline-for-statins/

Phenotype	Implications	Dosing recommendations	Classification of recommendations[a]	Considerations
All statins				
SLCO1B1 increased function	Typical myopathy risk and statin exposure	Prescribe desired starting dose and adjust doses based on disease-specific guidelines	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and ancestry should be evaluated prior to initiating a statin
SLCO1B1 normal function	Typical myopathy risk and statin exposure	Prescribe desired starting dose and adjust doses based on disease-specific guidelines	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and ancestry should be evaluated prior to initiating a statin
Atorvastatin				
SLCO1B1 decreased function or SLCO1B1 possible decreased function	Increased atorvastatin exposure as compared with normal function, which may translate to increased myopathy risk	Prescribe ≤40 mg as a starting dose and adjust doses of atorvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for 40-mg dose. If dose >40 mg needed for desired efficacy, consider combination therapy (i.e., atorvastatin plus nonstatin guideline-directed medical therapy)[3]	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
SLCO1B1 poor function	Increased atorvastatin exposure as compared with normal and decreased function, which may translate to increased myopathy risk	Prescribe ≤20 mg as a starting dose and adjust doses of atorvastatin based on disease-specific guidelines. If dose >20 mg is needed for desired efficacy, consider rosuvastatin or combination therapy (i.e., atorvastatin plus nonstatin guideline-directed medical therapy)[3]	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
Fluvastatin				
SLCO1B1 decreased function or SLCO1B1 possible decreased function	Increased fluvastatin exposure as compared with normal function; typical myopathy risk with doses ≤40 mg	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >40 mg per day	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
SLCO1B1 poor function	Increased fluvastatin exposure as compared with normal and decreased function; typical myopathy risk with doses ≤40 mg	Prescribe ≤40 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If patient is tolerating 40 mg per day but higher potency is needed, a higher dose (>40 mg) or an alternative statin (see **Figure 1** for recommendations for alternative statins) or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy)[3] could be considered. Prescriber should be aware of possible increased risk for myopathy with fluvastatin especially with doses >40 mg per day	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy

Phenotype	Implications	Dosing recommendations	Classification of recommendations[a]	Considerations
Lovastatin				
SLCO1B1 decreased function or SLCO1B1 possible decreased function	Increased lovastatin acid exposure as compared with normal function, which may translate to increased myopathy risk	Prescribe an alternative statin depending on the desired potency (see **Figure 1** for recommendations for alternative statins). If lovastatin therapy is warranted, limit dose to ≤20 mg/day	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
SLCO1B1 poor function	Increased lovastatin acid exposure as compared with normal and decreased function, which may translate to increased myopathy risk	Prescribe an alternative statin depending on the desired potency (see **Figure 1** for recommendations for alternative statins)	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
Pitavastatin				
SLCO1B1 decreased function or SLCO1B1 possible decreased function	Increased pitavastatin exposure as compared with normal function, which may translate to increased myopathy risk	Prescribe ≤2 mg as a starting dose and adjust doses of pitavastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >1 mg. If dose >2 mg needed for desired efficacy, consider an alternative statin (see **Figure 1** for recommendations for alternative statins) or combination therapy (i.e., pitavastatin plus nonstatin guideline-directed medical therapy)[3]	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
SLCO1B1 Poor Function	Increased pitavastatin exposure as compared with normal and decreased function, which may translate to increased myopathy risk	Prescribe ≤1 mg as a starting dose and adjust doses of pitavastatin based on disease-specific guidelines. If dose >1 mg needed for desired efficacy, consider an alternative statin (see **Figure 1** for recommendations for alternative statins) or combination therapy (i.e., pitavastatin plus nonstatin guideline-directed medical therapy)[3]	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
Pravastatin				
SLCO1B1 decreased function or SLCO1B1 possible decreased function	Increased pravastatin exposure as compared with normal function; typical myopathy risk with doses ≤40 mg	Prescribe desired starting dose and adjust doses of pravastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy with pravastatin especially with doses >40 mg per day	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
SLCO1B1 poor function	Increased pravastatin statin exposure as compared with normal and decreased function; typical myopathy risk with doses ≤40 mg	Prescribe ≤40 mg as a starting dose and adjust doses of pravastatin based on disease-specific guidelines. If patient is tolerating 40-mg dose but higher potency is needed, a higher dose (>40 mg) or an alternative statin (see **Figure 1** for recommendations for alternative statins) or combination therapy (i.e., pravastatin plus nonstatin guideline-directed medical therapy)[3] could be considered. Prescriber should be aware of possible increased risk for myopathy especially with pravastatin doses >40 mg	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
Rosuvastatin				
SLCO1B1 decreased function or SLCO1B1 possible decreased function	Increased rosuvastatin exposure as compared with normal function; typical myopathy risk with doses ≤20 mg	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >20 mg	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
SLCO1B1 poor function	Increased rosuvastatin exposure as compared with normal function and decreased function; typical myopathy risk with doses ≤20 mg	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines If dose >20 mg needed for desired efficacy, consider combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy)[3]	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
Simvastatin				
SLCO1B1 decreased function or SLCO1B1 possible decreased function	Increased simvastatin acid exposure as compared with normal function; increased risk of myopathy	Prescribe an alternative statin depending on the desired potency (see **Figure 1** for recommendations for alternative statins). If simvastatin therapy is warranted, limit dose to <20 mg/day	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
SLCO1B1 poor function	Increased simvastatin acid exposure compared with normal and decreased function; highly increased myopathy risk	Prescribe an alternative statin depending on the desired potency (see **Figure 1** for recommendations for alternative statins)	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy

Phenotype	Implications	Dosing recommendations	Classification of recommendations[a]	Considerations
Normal function	Typical myopathy risk and rosuvastatin exposure	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated prior to initiating rosuvastatin
Decreased function	Increased rosuvastatin exposure as compared with normal function; unknown risk for myopathy; increased lipid-lowering effects	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific guidelines and population-specific guidelines	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated prior to initiating rosuvastatin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
Poor function	Increased rosuvastatin exposure compared with normal and decreased function; unknown myopathy risk; increased lipid-lowering effects	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy)[3]	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated prior to initiating rosuvastatin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy

Phenotype	Implication	Dosing recommendations	Classification of recommendations[a]	Considerations
CYP2C9 normal metabolizer	Normal exposure	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin
CYP2C9 intermediate metabolizer AS of 1 and 1.5	Increased fluvastatin exposure as compared with normal metabolizer, which may translate to increased myopathy risk	Prescribe ≤40 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If dose >40 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy)[3]	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy
CYP2C9 poor metabolizer AS 0.5 and 0	Increased fluvastatin exposure as compared with normal and intermediate metabolizer, which may translate to increased myopathy risk	Prescribe ≤20 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy)[3]	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy

AS, activity score.
[a]Rating scheme described in the **Supplemental Material**.

	ABCG2 normal function	ABCG2 decreased function	ABCG2 poor function
SLCO1B1 increased function	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. STRONG	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. MODERATE	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).[3] OPTIONAL
SLCO1B1 normal function	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. STRONG	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. MODERATE	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).[3] OPTIONAL
SLCO1B1 decreased function or possible SLCO1B1 decreased function	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >20 mg. STRONG	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >20 mg. MODERATE	Prescribe ≤10 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >10 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).[3] OPTIONAL
SLCO1B1 poor function	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).[3] MODERATE	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).[3] MODERATE	Prescribe ≤10 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >10 mg needed for desired efficacy, consider combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).[3] OPTIONAL

	CYP2C9 normal metabolizer	CYP2C9 intermediate metabolizer	CYP2C9 poor metabolizer
SLCO1B1 increased function	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines. STRONG	Prescribe ≤40 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If dose >40 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy).[3] MODERATE	Prescribe ≤20 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy).[3] MODERATE
SLCO1B1 normal function	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines. STRONG	Prescribe ≤40 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If dose >40 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy).[3] MODERATE	Prescribe ≤20 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy).[3] MODERATE
SLCO1B1 decreased function or possible decreased function	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >40 mg per day. MODERATE	Prescribe ≤20 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy).[3] OPTIONAL	Prescribe an alternative statin depending on the desired potency (see **Figure 1** for recommendations for alternative statins). OPTIONAL
SLCO1B1 poor function	Prescribe ≤40 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If patient is tolerating 40 mg per day but higher potency is needed, a higher dose (>40 mg) or an alternative statin (see **Tables 2–6** and **Figure 1** for recommendations for alternative statins) or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy)[3] could be considered. Prescriber should be aware of possible increased risk for myopathy with fluvastatin especially with doses >40 mg per day. MODERATE	Prescribe an alternative statin depending on the desired potency (see **Table 2** and **Figure 1** for recommendations for alternative statins). OPTIONAL	Prescribe an alternative statin depending on the desired potency (see **Table 2** and **Figure 1** for recommendations for alternative statins). OPTIONAL

14. CLINICAL LABORATORY TESTS

The tests detailed in table will be performed by the local laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10.2.1: Protocol-required Laboratory Tests

Laboratory Tests	Parameters
Haematology	
	Haemoglobin (g/dL)
	Platelet count (x 10^9/L).
	White blood cell count (x 10^9/L)
	Neutrophils (x 10^9/L)
	Lymphocytes (x 10^9/L) and its fractions.
Clinical chemistry	
	K, Potassium (mmol/L)
	Na, Sodium (mmol/L)
	Creatinine (µmol/L)
	Total bilirubin (µmol/L)
	Cholesterol profile: LDLc, HDLc, triglycerides (TG) (all in mg/dl)
	AST, Aspartate aminotransferase or SGOT, serum glutamic-oxaloacetic transaminase (IU/L) ALT, Alanine aminotransferase or serum glutamic-pyruvic transaminase (SGPT) (IU/L) GGT, gamma-glutamyl transferase (IU/L) ALP, alkaline phosphatase (UI/L)
	CPK, creatinine phosphokinase (IU/L)
	Glucose (mg/dL)
	Thyroid Panel: Thyroid Stimulating Hormone (TSH) (µIU/mL) Free Thyroxine (T4) (ng/dL) Free Triiodothyronine (T3) (ng/dL)
	Serum calcidiol (vitamin D) (ng/mL)