Master Trial Protocol

Assessing the Efficacy and Cost-Efficacy of Pre-Emptive Genotyping with Pharmacogenetic Biomarkers in high-risk populations: The iPHARMGx Project - A Multicentre Randomized Controlled Clinical Trial in the Spanish National Health System

Sponsor

Fundación para la Investigación Biomédica del Hospital Universitario La Paz (FIBHULP)

Principal Coordinator Investigator:

Alberto Manuel Borobia Pérez, MD PhD

EudraCT number: n/a, specific to subprotocols

Version 1.0

The Master Protocol has been drafted by members pertaining to the iPHARMGx methodology working group.

I. Signatures

Refer to subprotocols for details and signatures of relevant contributors including principal coordinating investigator, medical contact (as applicable) and statistician.

II. Synopsis

Sponsor	Fundación para la Investigación Biomédica del Hospital Universitario La Paz (FIBHULP).
Funder	This study has been funded by Instituto de Salud Carlos III (ISCIII) through the project PMP22/00055 and co-funded by the European Union.
Principal Coordinator Investigator	Alberto M. Borobia Pérez, MD, PhD.
Title of the clinical trial	Assessing the Efficacy and Cost-Efficacy of Pre-Emptive Genotyping with Pharmacogenetic Biomarkers in high-risk populations: The iPHARMGx Project - A Multicentre Randomised Controlled Clinical Trial in the Spanish National Health System.
Indication	Pre-emptive pharmacogenetic testing.
Phase	Phase IV clinical trial.
Type of trial, trial design, methodology	This is a nation-wide, multicentre, randomised, controlled, and adaptive phase IV clinical trial that aims to assess the efficacy and cost-efficacy of pre-emptive pharmacogenetic testing strategies, including those impacted by genetic variants associated with adverse drug reactions (ADRs) or limited efficacy. Populations at high-risk of developing clinically relevant outcomes will be enrolled in nested trials within this master protocol. The clinical trials will evaluate the efficacy and cost-efficacy of pre-emptive genotyping by defining a drug-gene-endpoint triad. Study subjects will be pre-emptively genotyped and, if found to have an actionable gene variant, randomly allocated to either a test group where guideline-based treatment modifications will be initiated or a control group that will be managed according to healthcare provider standard of care (SoC). Subsequently, subjects will be prospectively followed at prespecified timepoints. Detailed information on drug-gene-endpoint triads, allocation schemes, and follow-up visits will be provided in each of the subprotocols. A Data Monitoring Committee (DMC), composed of physician experts, will be appointed for each nested trial to review the data on an ongoing basis, ensuring the safety of participants and scientific validity of the study.
Number of subjects	The number of subjects to be included in each sub-protocol will be estimated and justified in the corresponding sub-protocol.
Trial objectives	**Overarching primary objective:** • The overarching primary objective of this master protocol is to assess whether genotyping in high-risk populations susceptible to receiving certain targeted treatments is both efficacious and cost-efficacious. **Overarching secondary objectives:** • To assess whether pre-emptive genotyping strategies are feasible within the Spanish National Health System.

	• To identify new potential genetic biomarkers associated with drug response variability. **Overarching safety objectives:** • To assess the safety and tolerability of targeted treatments identified through pre-emptive genotyping, including the incidence and severity of treatment-related adverse events (AEs). • To identify potential predictors of treatment-related AEs, such as genetic or clinical factors. • Other objectives may be defined in each protocol under this master protocol as appropriate.
Study endpoints	**Overarching primary endpoint:** Primary endpoints will vary between each of the different nested studies. Overall, all endpoints will be geared towards assessing efficacy of pre-emptive genotyping schemes of the various actionable genes. The cost of preventing events will be a common endpoint that will govern all nested studies. **Secondary endpoints:** The time frame for the possible secondary endpoints will be defined in each of the respective subprotocols: - Unsolicited AEs until the end of trial. - Solicited AEs at prespecified time points defined in each of the subprotocols. - Rate of serious adverse events (SAEs) Grade ≥3 according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 until end of study or treatment discontinuation. - Physician and patient adherence to pharmacogenomic practical clinical guidelines: defined as adhering to the guidelines or not adhering to the guidelines. - Healthcare expenditure related to predefined events of interest: Any costs made as a result of an AE. - Incidence of drug discontinuation due to an AE related to the drug of inclusion. - Incidence of discontinuation or treatment modification due to lack of efficacy related to the drug of inclusion. - Quality of life assessed using a validated questionnaire. **Exploratory endpoints:** - Identification of new actionable genes/relevant variants within the predefined population subsets. - Other endpoints may be defined in each sub-protocol under this master protocol in accordance with the established objectives.
Study eligibility and principal inclusion and exclusion criteria	**Master protocol eligibility criteria:** The following eligibility criteria will be applicable to all trials nested to this master protocol:

	- 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. The following eligibility criteria will be applicable to all subjects participating in all trials nested to this master protocol: - Subject age of inclusion will be prespecified in each subprotocols. Paediatric subject inclusion will be permitted when applicable. - Subject or their legally authorized representative has voluntarily signed the informed consent document. - Subject is able and willing to take part and be followed-up for the majority of the study duration. - Subjects must be naïve to any genotyping test of the genes studied in each of the nested subprotocols, meaning they have no prior 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. The following constitute exclusion criteria that will be applicable to all subjects participating in all trials nested to this master protocol: - Subject has previous (direct-to-consumer, or clinical) genetic testing for a gene important to the drug of inclusion. - Subject has a life expectancy estimated to be less than three months. - Duration of the treatment of studied drug is expected to be less than seven consecutive days. - Subject or their legally authorized representative does not sign the informed consent document. - Subject has no fixed address. - Subject is, in the opinion of the Investigator, not suitable to participate in the study. **Stratification and subpopulations:** Randomization may be stratified according but not limited to: - Trial Site. - Sex (Man/Women).
Study intervention	In all studies nested to this master protocol, there will be two arms: an intervention arm and a control arm. All participants will undergo pre-emptive genotyping and will be allocated, according to sub-protocol specific schemes, to receive either the most recent clinical pharmacogenetic guideline treatment/dosing recommendations for their genetic profile or the healthcare provider standard of care (SoC).

<table>
<tr><td>Adaptive intervention</td><td>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 not yet established in practical clinical guidelines at the time of trial initiation become available in subsequent guideline updates, they will be incorporated into the study.
This adaptive approach will ensure that the study is able to incorporate emerging biomarkers and treatment options that may have clinical relevance, even if they are not currently established in clinical practice.</td></tr>
<tr><td>Control arm</td><td>Participants in the control arm will not receive any intervention based on their genetic profile, instead the SoC treatment/dosing as determined by their healthcare provider will be administered.</td></tr>
<tr><td>Duration of treatment</td><td>The duration of the intervention in each of the subprotocols nested to this master protocol will be specified based on the specific research question and clinical outcome being studied. The duration may vary between studies depending on the pharmacogenetic biomarker and the treatment being evaluated. The study protocol for each subprotocol will clearly outline the length of time the intervention will be administered and how it will be monitored. Additionally, the duration of the intervention may be adjusted based on safety and efficacy assessments during the study period.</td></tr>
<tr><td>Time schedule</td><td>Refer to sub-protocols for specific details.
<table>
<tr><td>First patient first visit (FPFV):</td><td>Refer to specific sub-protocol for respective details.</td></tr>
<tr><td>Last patient first visit (LPFV):</td><td>Refer to specific sub-protocol for respective details.</td></tr>
<tr><td>Last patient last visit (LPLV):</td><td>Refer to specific sub-protocol for respective details.</td></tr>
<tr><td>Interim analysis (planned):</td><td>Refer to specific sub-protocol for respective details.</td></tr>
<tr><td>End of Study Definition:</td><td>The end of study will be on the day of database lock.</td></tr>
<tr><td>End of trial:</td><td>Refer to specific sub-protocol for respective details.</td></tr>
<tr><td>Final study report:</td><td>Refer to specific sub-protocol for respective details.</td></tr>
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Statistician	Refer to specific sub-protocol for the responsible statistician.
Statistical methods	Detailed statistical methods will be specified in each sub-protocol under this master protocol. All trials nested within this master protocol will be adaptive in nature. As such, prespecified efficacy and futility assessments will be performed as per described in each subprotocols. If either assessment exceeds the prespecified threshold, study termination is warranted. In adaptive clinical trials, sample-size re-estimation (SSRE) is permitted. SSRE enables the increase of sample sizes by leveraging interim data analysis in randomized trials, whether conducted in a blinded or unblinded manner. If differences between both arms are not greater that the prespecified thresholds a SSRE will be performed and the study will continue until the next interim analysis or end of study analysis.
GCP compliance	The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognised Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.
Financing	Public funding. All nested studies are funded by the project PMP22/00055, it is contemplated that new clinical trials with other funding, can be nested in the future.

III. Table of contents

Contents

III.a) List of tables

Refer to corresponding sub-protocols for specific tables.

III.b) List of figures

Refer to corresponding sub-protocol for specific figures.

IV. Abbreviations

Abbreviation	Meaning
ADR	Adverse Drug Reaction.
AE	Adverse Event.
AR	Adverse Reaction.
ADL	Activities of daily living.
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios.
CRF	Case Report Form.
DIBD	Development International Birth Date.
CIOMS	Council for International Organizations of Medical Sciences.
DMC	Data Monitoring Committee.
DSUR	Development Safety Update Report.
EC/IEC	Ethics Committee/ Independent Ethics Committee.
ECG	Electrocardiogram.
eCRF	Electronic Case Report Form.
GCP	Good Clinical Practice.
ICF	Informed Consent Form.
ICH	International Council for Harmonisation.
IRB	Institutional Review Board.
ISCIII	Carlos III Health Institute.
LCC	Local Clinical Centres.
ISF	Investigator Site File.
ITT	Intention-to-Treat.
IWRS	Interactive Web Response Systems.
NCA	National Competent Authority.
NGS	Next Generation Sequencing.
PCI	Principal Coordinating Investigator (Alberto M. Borobia, MD PhD).
PD	Pharmacodynamic.
PI	Principal Investigator.
PK	Pharmacokinetic.
PP	Per-protocol.
SAE	Serious Adverse Event.
SAR	Serious Adverse Reaction.
SCReN	Spanish Clinical Research Network.
SDV	Source Data Verification.
SmPC	Summary of Product Characteristics.
SoC	Standard of Care.
SUSAR	Suspected Unexpected Serious Adverse Reaction.
TMF	Trial Master File.

1. Introduction

Variations in genes responsible for encoding drug-metabolising enzymes, drug transporters, and drug targets can significantly impact the disposition and action of drugs, ultimately leading to variability in response (Wang et al., 2011). 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 (AEs) (Bielinski et al., 2014). 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 (Bottorff et al., 2017). Notably, the Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study conducted by the Ubiquitous Pharmacogenomics Consortium and the 12-gene pharmacogenetic panel implementation study have both shown positive results (Swen et al., 2023; van der Wouden et al., 2020).

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 (Weitzel et al., 2014). These guidelines comprehensively assess the associations between over 100 gene-drug pairs, including those created by The Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC). 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 (Weitzel et al., 2014). This has resulted in both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) including pharmacogenetic information in drug labels provided to prescribers and patients (European Medicines Agency, 2020; Schuck & Grillo, 2016).

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 (Borobia et al., 2018). One major challenge is the lack of pharmacoeconomic studies supporting the positive economic impact of pre-emptive pharmacogenomics (Borobia et al., 2018). While pre-emptive pharmacogenetic testing shows promise in improving patient outcomes and reducing the occurrence of adverse drug reactions, the lack of clear pharmacoeconomic evidence remains a significant challenge (Sukri et al., 2022a). Despite the development of comprehensive clinical guidelines (Sociedad Española de Farmacogenética y Farmacogenómica, 2023) and the inclusion of pharmacogenetic information in drug labels, the limited implementation of this approach outside of tertiary hospitals highlights the need for further research to establish its cost-efficacy and feasibility (Wong et al., 2010). Future studies evaluating the economic impact of pre-emptive pharmacogenomics in clinical practice are needed to bridge the knowledge gap currently precluding its widespread adoption (Sukri et al., 2022b).

The overarching goal of the trials nested within this master protocol is to assess the efficacy, safety, and cost-efficacy of preemptive pharmacogenetic testing in 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.

By demonstrating its feasibility and efficacy, we aim to broaden its application beyond its current scope and facilitate its widespread use in the Spanish National Health System (NHS). This approach has the potential to enhance the efficiency and safety of prescriptions, promote treatment adherence, improve patient quality of life, and ultimately contribute to the sustainability of the NHS.

2. Objectives of the clinical trial

2.1. Description of the clinical trial

This is a randomised, controlled, adaptive, multicentre, phase IV master protocol evaluating the cost-efficacy and efficacy of different preemptive genotyping strategies in high-risk populations susceptible to receiving certain targeted treatments.

This master clinical trial allows the testing of different pre-emptive genotyping strategies in order to assess their efficacy and cost-efficacy. Different trial populations, different genotyping strategies, additional genes/variants, and extended follow-up visits can be added throughout amendments of this master protocol and the corresponding sub-protocol.

Primary objective

The overarching primary objective of this master protocol is to assess whether genotyping in high-risk populations susceptible to receiving certain targeted treatments is both efficacious and cost-efficacious.

The sub-protocols under this master protocol will detail the specific objectives within this overarching primary objective.

2.2. Secondary and other objectives

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

- To assess whether preemptive genotyping strategies are feasible within the Spanish National Health System.
- 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.

Other objectives may be defined in each protocol under this master protocol as appropriate.

2.2.1 Exploratory objectives

Exploratory objectives include the identification of new actionable genes within predefined population subsets in cases where no evidence-based variation is identified. Novel prognostic and predictive genetic biomarkers pertaining to each of the different studies nested within this master protocol 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.

The duration and scope of this exploratory analysis will depend on the research question being studied and the availability of resources.

Each nested subprotocol may include drug-specific exploratory objectives and outcomes, such as pharmacokinetic (PK) or pharmacodynamic (PD) analysis when feasible/applicable.

3. Organisational and administrative aspects of the trial

In the following text responsibilities assigned to the sponsor may to some extent be delegated to the PCI or other persons, institution and/or service providers. Details are fixed in a separate document or contract. In general, for readability reasons only the sponsor and not its delegate is named throughout the text.

3.1. Sponsor

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

3.2. Principal Coordinator Investigator

Principal Coordinator: Alberto M. Borobia Pérez. MD, PhD

Principal Investigator (PI): Refer to specific sub-protocols.

3.3. Statistics

Refer to the respective sub-protocol under this master protocol for details on the responsible statistician.

3.4. Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) of experts will be set up for each trial nested, consisting of statistician and at least two physicians or specialist professionals in the area with ample expertise on both the underlying pathology, treatment management, clinical research methodology and ethics and pharmacogenomics. The DMC will meet periodically at prespecified time points. The task of the DMC is to monitor the well-being of the trial subjects by periodically assessing the safety and efficacy of the trial therapy, and to monitor the integrity and validity of the data collected and the conduct of the clinical trial. Details will be described in sub-protocol specific DMC charters.

Throughout this process of surveillance, the DMC provides the sponsor with recommendations on trial continuation (including termination, temporary suspension or *ad hoc* genes or polymorphisms analysis) based on the data collected and emerging evidence. The data necessary for the DMC to fulfil this function is provided by the sponsor as determined in the DMC charter (which will be provided annexed to each sub-protocols). Amongst other datasets, these must include listings providing information on serious adverse events and further variables that the DMC considers necessary.

Meetings of the DMC will be conducted through video conference, by phone, or in-person as deemed necessary. If scheduling problems prevent a timely meeting, review and comment may alternatively be conducted by e-mail. One member will be appointed chair of the DMC and be responsible for summarising DMC meetings, inform the PCI and sponsor about meetings, and provide in writing any recommendations involving trial adaptations and/or operational settings. The frequency of the committee data review meetings and other working procedures will be detailed in a separate charter.

3.5. Central Coordinating Office (CCO)

A Central Coordinating Office (CCO) will be established for all nested trials and will oversee the coordination of all the following aspects:

i. Study planning and organisation of DMC meetings.
ii. Ensuring necessary regulatory and ethics committee approvals.
iii. Development of Standard Operating Procedures and computer systems.
iv. Monitoring overall progress of the study.

v. Provision of study materials to local clinical centres (LCCs).
vi. Monitoring and reporting safety information in line with the protocol and regulatory requirements.
vii. Dealing with technical, medical, and administrative queries from LCCs.

3.6. Local Clinical Centres (LCC)

LCC will aid on all relevant tasks regarding the totality of nested clinical trials. The LCC lead investigator and LCC clinic staff are responsible for:

i. Obtaining all relevant local permissions (assisted by the CCO).
ii. All trial activities at the LCC, including appropriate training and supervision for clinical staff.
iii. Executing nested clinical trials as well as conducting trial procedures at the LCC in line with all relevant local policies and procedures.
iv. Dealing with enquiries from participants and others.

3.7. Study laboratories and other technical services

Samples will be analysed as specified in the respective sub-protocols. All sample analysis, including pharmacogenetic testing, will be performed locally or centrally as specified in subprotocols. A laboratory manual specific to each of the subprotocols will specify preparation, handling, storage and shipment of samples.

The exploratory biomarker analyses will be conducted in all cases at the one of the nodes of IMPACT genomics. Novel prognostic and predictive genetic biomarkers 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.

The duration and scope of these analyses will vary depending on the specific research question and study design of each subprotocol, as outlined in the study protocol. The IMPACT genomics nodes will work closely with the study investigators to ensure that the biomarker analyses are conducted in a rigorous and standardised manner, in accordance with best practices in the field. The results of the biomarker analyses will be carefully evaluated and integrated into the overall study findings to provide insights into the mechanisms of action of the drugs being studied and the potential impact of pharmacogenetic biomarkers on drug efficacy and safety.

3.8. Central organisation units

Project management:	Refer to specific sub-protocol.
Monitoring:	Refer to specific sub-protocol.
Data management:	Refer to specific sub-protocol.
SAE management:	Refer to specific sub-protocol.
Scientific advice:	Refer to specific sub-protocol.

3.9. Principal investigators and trial sites

The evaluation of pharmacogenetic biomarkers and their implementation in clinical practice is the main research line of the Coordinating Investigator of this master protocol (Alberto M. Borobia, MD PhD), who in 2012, launched the Clinical Pharmacogenetics Unit at La Paz Hospital, for which he is responsible.

The participation of different centres in the various studies nested within this master protocol may vary depending on the specific aims and objectives of each study, the centre's capacity for subject accrual, study design, and other logistical considerations. As such, some sites may be

involved in multiple studies, while others may only participate in a single study. Nonetheless, all sites will be required to follow the same rigorous protocol guidelines to ensure the integrity of the data collected and the validity of the study results.
The following table displays the principal investigators and all participating centres (LCC) within the iPHARMGx framework. It should be noted that not all centres will participate in all trials. Subprotocols will specify which centres will participate in each of the nested studies. Nested trials will have their own PIs who must be medical doctors with clinical expertise on both the trial population and the treatment being prescribed.

Principal Investigators (PI)	Centres (LCC)
Luis Andrés López Fernández.	University General Hospital Gregorio Marañón.
Miriam Estébanez Muñoz.	Defense Central Hospital Gomez Ulla.
Emilio José Laserna Mendieta.	General Hospital of Tomelloso.
Ana María Peiró Peiró.	General University Hospital of Alicante.
Miriam Saiz Rodríguez.	University Hospital of Burgos.
Consuelo María Rodríguez Jiménez.	University Hospital of the Canary Islands.
Magín Farré Albaladejo.	Germans Trias i Puyol University Hospital.
María del Mar García Sáiz.	Marqués de Valdecilla University Hospital.
Pablo Zubiaur Precioso.	La Princesa University Hospital.
Judith Adriana Sanabria Cabrera.	Virgen de la Victoria University Hospital.
Iñaki Imaz Iglesia.	Institute of Health Carlos III (ISCIII).
Antonio Carcas Sansuán.	Autonomous University of Madrid (UAM).
Alberto M. Borobia.	University Hospital La Paz (HULP).

3.10. Requirements for principal investigators and trial sites

For each clinical trial nested within this master protocol, the appropriate number of centres will be selected based on the specific requirements of each protocol. While prior experience in conducting clinical trials with pharmacogenetic intervention is encouraged, it will not be a mandatory requirement for principal investigators and trial sites participating in these trials. They must also have access to appropriate equipment, trained staff, the target population, and necessary testing capabilities. Documentation certifying the clinical trial team's qualifications will be kept in the sponsor's Trial Master File (TMF) as well as the Investigator Site File at the local site (ISF). All selected centres will undergo validation by an approved process to ensure compliance with standard operating procedures for pharmacogenetic trials.

3.11. Financing

All trials nested within the iPHARMGx framework will be financed through a competitive research grant awarded to the Principal Investigator for Personalized Medicine Projects (grant

number PMP22/00055; ISCIII). The first clinical trials are funded by the PMP project, but future nested clinical trials may secure their own independent funding sources.

A detailed financial plan does not form part of the scope of this master trial protocol. The financial plan is archived separately and all sources of financing must be listed here; it may be needed to gain approvals or to accompany contracts or it may be requested for submission to the ethics committee.

3.12. General aspects of trials design

This is a randomised, controlled, adaptive, multicentre, Phase IV master protocol evaluating different preemptive genotyping strategies in high-risk populations susceptible to receiving certain targeted treatments. This protocol allows testing of different drug-gene-outcome triads to assess the efficacy and safety of implementing a pre-emptive genotyping scheme. Different trial populations, different drugs, different genes, polymorphisms and follow-up visits can be added throughout amendments of this master protocol.

All participants will undergo pre-emptive genotyping and will be allocated, according to sub-protocol specific schemes, to receive either the most recent clinical pharmacogenetic guideline treatment/dosing recommendations (experimental arm) for their genetic profile or the healthcare provider SoC (control arm). Patients in the control arm will be managed according to the healthcare provider (SoC) and will not undergo any treatment modifications based on genotyping results. The control arm will provide a basis for comparison to evaluate the efficacy and cost-efficacy of pre-emptive pharmacogenetic testing strategies. Both cohorts will be followed through time until the predefined event of interest (such as adverse drug reaction or a limited efficacy) occurs.

The study will enrol populations at high-risk of developing clinically relevant outcomes in nested trials within this master protocol, and both subject cohorts will be prospectively followed at prespecified timepoints to assess outcomes.

Detailed information on drug-gene-endpoint triads, allocation schemes, and follow-up visits will be provided in each of the subprotocols to ensure consistency and standardisation across sites.

By comparing outcomes between the test and control groups, this trial will provide valuable insight into the potential benefits of pre-emptive pharmacogenetic testing in improving patient outcomes and reducing healthcare costs.

Trials under this master protocol follow this general design and overarching primary and secondary objectives. At this time two trials have been designed:

1. A multicentre, controlled, randomised, adaptive phase IV protocol to evaluate efficacy, safety and cost-efficacy of pre-emptive genotyping strategy in a population at high risk of cardiovascular disease susceptible of receiving statins (The PREVESTATGx Trial).
2. A multicentre, controlled, randomised, adaptive phase IV protocol to evaluate efficacy, safety and cost-efficacy of pre-emptive genotyping strategy to optimise tacrolimus dosage in a pretransplant chronic kidney disease population cohort (The TRANSPGx).

Prespecified efficacy and futility assessments will be performed as per described in each subprotocols. If either assessment exceeds the prespecified threshold, study termination is warranted. In adaptive clinical trials, sample-size re-estimation (SSRE) is permitted, and will be performed if futility/efficacy thresholds are not met in the interim analyses.

Decisions on the incorporation of new trials under this master protocol and adding in each trial will be fully justified and decided by the sponsor and PI based on the recommendations of the DMC.

3.12.1. Trial schematic

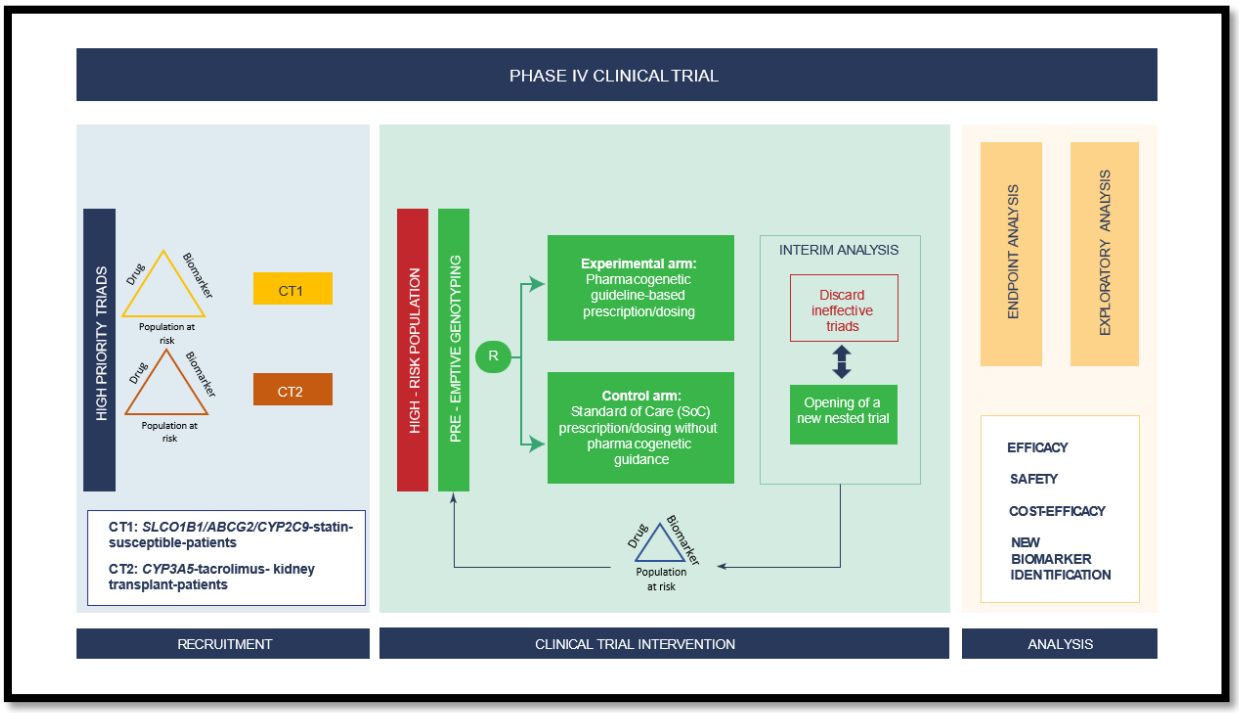

Figure 1. Master protocol trial schematic

3.12.2. Time schedule

At this moment, this master protocol foresees the development of two trials encompassing two high priority drug-gene-population triads. These first trials are subject to a time schedule laid out in the respective sub-protocol. Other sub-protocols may be included under this master protocol with their own time schedule.

Table 1: Time schedule of the trial

First patient first visit (FPFV):	refer to the respective sub-protocol.
First Interim analysis:	refer to the respective sub-protocol.
Second Interim analysis:	refer to the respective sub-protocol.
Last patient first visit (LPFV):	refer to the respective sub-protocol.
Last patient last visit (LPLV):	refer to the respective sub-protocol.
End of trial:	refer to the respective sub-protocol.
Final analysis:	refer to the respective sub-protocol.
Final study report:	refer to the respective sub-protocol.

End of study will be defined at database lock, planned 30 days after the last patient's last visit.

3.13. Discussion of trial design

This is a randomised, controlled, adaptive, multicentre, Phase IV master protocol evaluating different pre-emptive genotyping strategies in high-risk populations susceptible to receiving certain targeted treatments. Trials conducted under this master protocol are designed to

evaluate the efficacy, cost-efficacy and safety of drug-gene-outcome triads while taking into consideration the constant emergence of new genetic variants associated with the targeted outcomes.

Sample-size calculations performed before the start of a trial require assumptions about the hypothesized treatment effect and the outcomes in each arm. Incorrect assumptions can result in a trial being underpowered or even overpowered (FDA, 2019). This can in turn preclude a potentially efficacious intervention from demonstrating differences during a study. The adaptive design of each of the subprotocols will establish at least two predefined intermediate analysis that allow to adapt the sample size and to optimize the duration of the study (Edwards et al., 2020).

The design also allows for the incorporation of newly identified genetic variants and adjustments to the study design as necessary and in a timely fashion. This approach ensures that the study results remain relevant and informative as well as adequately powered, providing valuable insights into the impact of genetic variation on the response to the studied drugs. The use of this flexible master protocol enables researchers to adapt to the rapidly evolving landscape of genetic research, allowing for a more comprehensive evaluation of the targeted drug-gene-outcome triads.

3.14. Risk-benefit assessment

3.14.1. Known potential risks

Potential risks will be detailed in each sub-protocol for all the drug-gene-population triads included. The risks will be based on the SmPC (Summary of Product Characteristics) of each treatment and any risk described in the literature, as well as the potential risks inherent to any standard of care deviation.

3.14.2. Known potential benefits

At present, the treatment management based on pre-emptive genotyping strategies is widely implemented for a limited number of drugs, despite the increasing amount of evidence that warrants its use. The study intervention has the potential to provide significant benefits to the subjects by making available a personalised medicine tool that may not have been possible otherwise, thereby improving patient outcomes and overall healthcare. Additionally, conducting a cost-efficacious analysis as part of this study can provide valuable evidence to support the implementation of pre-emptive pharmacogenetic testing schemes on a larger scale, potentially extending their benefits beyond their current scope. Trial-specific benefits will be described in the respective sub-protocol.

3.14.3. Risk-benefit assessment

The study aims to evaluate the efficacy of preemptive pharmacogenotyping strategies, which could potentially lead to personalised treatment plans and improved clinical outcomes for high-risk populations.

By identifying genetic markers that may impact drug response, patients can be prescribed medications that are most likely to be effective and safe for them, potentially reducing the risk of adverse events and improving overall treatment outcomes (Turner et al., 2020). The study could contribute to a better understanding of pharmacogenetic testing and personalised medicine in clinical practice, which may have broader implications for healthcare. As with any clinical trial, there are potential risks associated with participation. These may include adverse reactions to study medications or procedures, such as blood draws for genetic testing. There is

a risk that pharmacogenetic testing results may be misinterpreted or not fully understood by healthcare providers, which could lead to inappropriate treatment decisions. There may be additional time and resources required for genetic testing and interpretation, which could result in increased healthcare costs or burdens on patients. However, these are considered minimal when compared to standard clinical care. There is a risk of potential privacy breaches or genetic discrimination, although appropriate safeguards will be put in place to protect patient privacy and confidentiality.

Overall, we consider the potential benefits of personalised treatment plans and improved clinical outcomes outweigh the risks associated with participation in the study. All potential risks will be thoroughly explained to patients during the informed consent process, and appropriate measures will be taken to minimise any potential harms.

3.15. Selection of trial population

The high prevalence of clinically relevant polymorphisms among the priority genes to be included, combined with the large number of drugs commonly prescribed in our environment, suggests that recruitment of trial participants will be rapid and efficient. Specific characteristics pertaining to specific subprotocol populations will be detailed in their respective document.

Reasons for sex distribution

Subjects included in this trial are expected to be similar to the general population that is susceptible to being prescribed the study drug given their pharmacogenetic profile. Sex distribution will therefore be similar to said population and no restrictions will be made in relation with sex, unless included in the selection criteria for reasons specified in the respective subprotocol.

3.15.1. Inclusion under master protocol: trial eligibility criteria

The following eligibility criteria will be applicable to all trials nested to this master protocol:

- All nested trials must have at least one clearly defined pharmacogenetic biomarker present in at 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.

3.15.2. Inclusion criteria

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

- Subject age of inclusion will be prespecified in each subprotocols. Paediatric subject inclusion will be permitted when applicable.
- Subject or their legally authorized representative has voluntarily signed the informed consent document.
- Subject is able and willing to take part and be followed-up for the majority of the study duration.
- Subjects must be naïve to any genotyping test of the genes studied in each of the nested subprotocols, meaning they have no prior 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.

Refer to sub-protocols for more trial-specific exclusion criteria.

3.15.3. Exclusion criteria

The following constitute exclusion criteria that will be applicable to all subjects participating in all trials nested to this master protocol:

- Subject has previous (direct-to-consumer, or clinical) genetic testing for a gene important to the drug of inclusion.
- Subject has a life expectancy estimated to be less than three months.
- Duration of the treatment of studied drug is expected to be less than seven consecutive days.
- Subject or their legally authorized representative does not sign the informed consent document.
- Subject has no fixed address.
- Subject is, in the opinion of the Investigator, not suitable to participate in the study.

Refer to sub-protocols for more trial-specific exclusion criteria.

3.16. Withdrawal of trial subjects after trial start

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance/adherence reasons. This is expected to be uncommon. When a participant withdraws before study completion, the reason for withdrawal is to be documented in the electronic case report forms (eCRF) and in the source document pertaining to said study. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed. The participant will be permanently discontinued from the study intervention and the study at that time. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study site records.

3.17. Lost to Follow-Up

To minimize the likelihood of a participant being classified as lost to follow-up, efforts should be made to collect comprehensive contact information from each participant, including their home, work, and mobile telephone numbers, as well as email addresses for both the participant and their relevant family members.

A participant will be classified as lost to follow-up if they cannot be reached by the study site through direct telephone contact with the patient or their relatives on at least two separate occasions, or if written correspondence goes unanswered. However, a participant cannot be officially designated as lost to follow-up until all reasonable attempts made by the study site personnel to establish contact with the participant are deemed unsuccessful.

3.18. Closure of trial sites/Premature termination of the clinical trial

3.18.1. Closure of trial sites

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has

been performed. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

3.18.2. Premature termination of trial

The sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under study intervention at the time of termination shall undergo a final examination which must be documented. The sponsor must be informed without delay if any principal investigator has ethical concerns about continuation of the trial.

Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial subject changes markedly.
- It is no longer ethical to continue the study intervention.
- The sponsor considers that the trial must be discontinued for safety reasons (e.g., on the advice of the DMC).
- It is no longer practicable to complete the trial.
- Interim analysis yields results that exceed either the futility or efficacy thresholds predefined for each subprotocol.

The sponsor decides on whether to discontinue the trial in consultation with the PCI, DMC and trial statistician, as applicable.

3.19. Intervention

3.19.1. Intervention to be given.

All participants will undergo preemptive genotyping and will be randomly allocated, according to sub-protocol specific schemes, to receive either standard of care treatment/dosing (control arm) o pharmacogenetic guideline-based treatment/dosing (experimental arm). All protocols nested under this master protocol will allow for the incorporation of treatment adjustments based on newly identified genetic variants or polymorphisms as necessary and in a timely fashion if these are documented on updated iterations of the current clinical guidelines. Description of intervention, details of genotyping techniques, drug-gen variants explored, and guideline-based treatment modifications used will be described in each sub-protocol.

3.19.2. Assignment of trial subjects to treatment groups

Subject fulfilling selection criteria will be randomised to the different arms in the trial through a central procedure. Randomization may be stratified according but not limited to:

- Trial site.
- Sex.

The participants will be randomised into the study arms as defined in each sub-protocol. Allocation schemes will also be detailed in each subprotocol. Randomisation will be implemented through an Interactive Web Response Systems (IWRS) software and will be detailed in full in each of the pertaining subprotocols.

3.19.2.1. Blinding

Studies under the iPHARMGx will be single-blind and as such allocation to either intervention or controlled arm will be concealed from participants. A double-blind design, although always preferable, was not considered feasible due to the methodological difficulty in assessing certain endpoints if the prescribing clinician is blinded. It has been deemed sufficiently appropriate to blind only subjects since the primary endpoint will be either a single validated

surrogate endpoint for a clinical outcome or a composite of validated surrogate endpoint with a relevant clinical variable. Blinding procedures will be described as applicable in concerned subprotocols.

3.19.2.2. Previous and concomitant medication

There are no *a priori* previous or concomitant medication prohibited in this protocol for the trials initially planned. Any medication at the time of enrolment or received during the study must be recorded along with:

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

Further trial-specific details may be described in the respective sub-protocols.

3.19.2.3. Rescue therapy for emergencies

Specified in the corresponding subprotocol, as applicable.

3.19.3. Continuation of treatment after the end of the clinical trial

Not applicable.

3.20. Efficacy and safety variables

Main overarching efficacy endpoints will vary between each of the different nested studies. Overall, all endpoints will be geared towards assessing efficacy, cost-efficacy and feasibility of preemptive genotyping strategy of the various actionable genes. A common cost-efficacy endpoint will govern all nested studies, as described below.

Overarching safety variables of interest may include unsolicited and solicited AEs at prespecified time-points, as applicable.

3.20.1.1. Primary target endpoint

Primary cost-efficacy endpoint will govern all nested studies. A primary efficacy endpoint may also be included in cases when applicable, and in a similar way, a primary safety outcome may be included in specific sub-protocols. All nested studies will share a target endpoint that is the cost of preventing an event. The definition of what constitutes an event will be disclosed in each of the nested-studies and will vary among drug-gene-endpoint triad.

3.20.1.2. Secondary and other target variables

As mentioned earlier, certain nested trials may have secondary outcomes that could serve as primary outcomes in other trials; the following list represents the commonly anticipated secondary outcomes across all nested trials.

Safety

- Unsolicited AEs until the end of trial.
- Solicited AEs at prespecified time points defined in each of the subprotocols.
- Rate of (SAEs) Grade ≥3 according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 until end of study or treatment discontinuation.
- Physician and patient adherence to pharmacogenomic practical clinical guidelines: defined as adhering to the guidelines or not adhering to the guidelines.
- Healthcare expenditure related to predefined events of interest: Any costs made as a result of an AE.
- Incidence of drug discontinuation due to an AE related to the drug of inclusion.

- Incidence of discontinuation or treatment modification due to lack of efficacy related to the drug of inclusion.
- Quality of life assessed using a validated questionnaire.

3.20.1.3. Exploratory endpoints

All accrued subjects will have an aliquot stored that may be used to analysed to explore possible novel prognostic and/or predictive genetic biomarkers in outlier (i.e, the presence or absence of a predefined event in response to drug administration does not align with the currently described pharmacogenetic knowledge) 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.

In a similar way, in studies where it may be applicable, PK/PD endpoints may be analysed.

3.21. Description of visits

Procedures and activities to perform during the visits will be thoroughly described in each sub-protocol.

3.21.1. Rationale for assessment procedures

The assessment procedures in all studies encompassed within this master protocol will be designed to evaluate the efficacy of pre-emptive pharmacogenetic testing in high-risk populations. The genotyping test will be performed before initiating the pharmacological treatment and in those subjects allocated to the experimental arm, individualise treatment based on current clinical guidelines. Genotyping will be performed by various techniques depending on the performing LCC, and foreseeable samples required are limited to total blood samples (maximum volume will not exceed that required for routine blood analysis and is anticipated to be of 6mL). Efficacy and safety assessments will be performed at different timepoints based on the drug-gene-population triad studied and will be specified accordingly in each subprotocol; in all cases these procedures will not exceed in an unacceptable way those performed during standard clinical practice. Efficacy and safety assessments are anticipated to be conducted simultaneously.

3.21.2. Pharmacokinetics/Determination of drug levels

In studies where it may be applicable, PK/PD endpoints may be analysed either as a surrogate for a primary endpoint (for example serum CK concentration in the cases of statin-induced rhabdomyolysis or out-of-target trough tacrolimus concentration in the case of renal transplant failure).

3.22. Data quality assurance

3.22.1. Monitoring, pharmacovigilance, data management and statistical analysis

SCReN (Spanish Clinical Research Network) is part of the ISCIII PLATFORMS TO SUPPORT R&D IN BIOMEDICINE AND HEALTH SCIENCES Support Platform and is funded by the PTC20/00018 grant with co-financing from the FEDER (European Regional Development Fund) funds and will be tasked with the following functions:

Clinical Trial Monitoring: SCReN will actively oversee and monitor trials nested under the iPHARMGx framework, at nodes prespecified in each subprotocol. Ensuring that they are conducted in adherence to both this master protocol as well as specific subprotocols and meet the appropriate regulatory requirements.

The exact extent of the monitoring procedures is described in a separate monitoring manual. All principal investigators agree that the monitor regularly visits the trial site and assure that the monitor will receive appropriate support in their activities at the trial site, as agreed in separate contracts with each trial site. The declaration of informed consent (see section 5.5) includes a statement allowing the monitor to compare the case report forms (CRFs) with the trial subject's medical records (doctor's notes, ECGs, laboratory printouts etc.).

The PI will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:

- To check the declarations of informed consent.
- To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs).
- To check the completeness and accuracy of entries on the CRFs.
- To validate the entries on the CRFs against those in the source documents (source data verification, SDV).
- To evaluate the progress of the trial.
- To evaluate compliance with the trial protocol.
- To assess whether the trial is being performed according to GCP at the trial site.
- To discuss with the principal investigator aspects of trial conduct and any deficiencies found.

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems. The principal investigator will reasonably consider the corrective and preventive measures suggested by the monitor. All participant data relating to the study will be recorded on electronic CRFs. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF. Guidance on completion of eCRFs will be provided in the Trial Master File. The investigator must permit study-related monitoring, audits, REC/NCA review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan. The sponsor or designee is responsible for the data management of this study, including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organisations).

Data Management: SCReN will also be responsible for proper data management and storage. The trial sites will be monitored to ensure the quality of the data collected. The trial database will be developed and validated before data entry based on standard operating procedures at the. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed up daily. After completion and cleaning of data, the database is locked, and the data are exported for statistical analysis.

The data will be entered online at the trial sites via the Internet. Plausibility checks are run during data entry, thereby detecting many discrepancies immediately. The Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the trial sites electronically via the trial software. These electronic queries have to be answered by the trial site without unreasonable delay. Further details will be specified in the data management manual. A guidance document and web-based training for data entry in the eCRF will be provided.

All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data) via secure platform transfer or encrypted e-mail. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation. The trial database will be developed and validated before data entry based on standard operating procedures. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed up daily. After completion and cleaning of data, the database is locked, and the data are exported for statistical analysis.

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All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data) via secure platform transfer or encrypted e-mail. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period, this applies to both the investigator and sponsor part of the TMF. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Digitisation of paper-based documentation must meet regulatory requirements, especially concerning quality assurance, completeness and correctness. Paper-based documentation must not be destroyed after digitisation and must be archived according to applicable regulations.

Pharmacovigilance: SCReN assumes responsibility for pharmacovigilance activities. That will be carried out in accordance with the current applicable legislation at a centralised node in Hospital La Paz. This includes the collection, analysis, and reporting of AEs as well as the

responsibility of elaborating and submitting Development Safety Update Reports (DSUR). Adverse drug reactions that must be reported are detailed in Section 6.

3.23. Documentation

Principal Investigators will oversee and coordinate data collection, entry, and protection. Trial-specific data will be collected by the clinical trial staff using designated source documents. Standard GCP practices will be followed to ensure accurate, reliable, and consistent data collection. Any correction to source documentation needs to ensure a valid correction trail, including leaving original entries legible and signed or initial dated corrections. If source documents involve electronic patient files, then an audit trail of changes to documentation must be available.

All trial data must be verifiable to the source documentation. All source documents will be kept in a locked facility at the clinical site. Source documents include but are not limited to:

- Informed Consent Forms.
- Reported laboratory results.
- Lists of AEs.
- Lists of concomitant medication.
- Documentations of existing clinical conditions.

Medical records will be archived by the trial site as per local regulations.

All data relevant to the trial are documented by the PI or designees in corresponding (eCRFs). All eCRFs and laboratory reports will be reviewed by the clinical team to ensure that they are accurate and complete.

The Principal Investigators may authorise trial staff members to sign the eCRFs to confirm accuracy of the data. At the completion of the follow-up visits, final sign-off must be performed by the Principal Investigators.

4. Ethical and regulatory aspects

4.1. Ethics committee

The clinical trial will not be started before a favourable opinion of the competent ethics committee and the authorization of the Spanish regulatory agency (AEMPS).

This study will be conducted in accordance with the protocol and with the following:

- Consensus on ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable ICH Good Clinical Practice (GCP) guidelines dated July 1996 and its Addendum E6(R2) of June 2017.
- Applicable laws and regulations.

4.2. Ethical considerations

The protocol, protocol amendments, Informed consent form (ICF), SmPCs and other relevant documents (e.g., advertisements) must be submitted to a Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and National Competent Authority (NCA) by the sponsor and reviewed and approved by the IEC/IRB and NCA before the study is initiated. The present trial protocol and any amendments were and will be prepared in accordance with the principles of the Declaration of Helsinki.

Protocols and any substantial amendments to the protocol will require National Competent Authority (NCA) approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The sponsor will be responsible for the following:

- Providing written summaries of the status of the study to the REC/NCA annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB.
- Notifying the IEC/NCA of SAEs or other significant safety findings as required by IEC/NCA procedures when applicable.
- Providing oversight of the conduct of the study at the sites and adherence to requirements of ICH guidelines, the IEC/NCA, European Regulation 536/2014 for clinical trials on medicinal products, and local regulations in Spain (RD190/2015), which regulates clinical trials with medicines and the Spanish Registry of Clinical Studies.

4.3. Legislation and guidelines

The present clinical trial will be conducted in accordance with the principles of the guidelines for Good Clinical Practice (ICH-GCP) and applicable legislation. All principal investigators and other staff involved in the trial will be informed that local and national competent authorities as well as competent authorities from foreign countries and authorised representatives of the sponsor have the right to review trial documentation and the trials subject´s medical records at any time under confidentiality.

4.4. Notification of the authorities, approval, and registration

Before the start of the clinical trial, all necessary documentation will be submitted to the responsible national competent authority for approval. Local authorities will be notified according to applicable regulations.

4.5. Obtaining informed consent from trial subjects

The investigator or his/her representative will explain in a comprehensible language about the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. This includes consent to data access by representative of the sponsors (e.g., monitors, auditors) and the competent authorities.

Participants must be informed that their participation is voluntary. Participants will be required to give a statement of informed consent that meets the requirements, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the ethics committee. Trial subjects will be informed that withdrawal of consent is possible at any time without giving reasons and without jeopardising the subject´s well-being. Subjects must not be enrolled into the trial unless they have consented to take part in writing.

The medical record must include a statement that informed consent was obtained before the participant was enrolled in the study, the nature of consent (participant), and the date the consent was obtained. The authorised person (investigator or sub-investigator) obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study if relevant. A copy of the ICF(s) must be provided to the participant.

The ICF will contain a separate section that addresses the secondary use of data and remaining samples for optional exploratory research.

The investigator or authorised designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The participant can opt to document their agreement to allow any data and remaining specimens to be used for secondary exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

4.6. Insurance of trial subjects

This is a phase IV low intervention clinical trial. As it is a low-intervention clinical trial, patient’s risk related to the study are covered by the National Health System insurance.

4.7. Data protection

The provisions of data protection legislation will be observed (Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights). It is assured by the sponsor that all investigational materials and data will be pseudonymised in accordance with data protection legislation.

Trial subjects will be informed that their pseudonymised data will be handled in accordance with applicable law. Participants will be assigned a unique identifier number by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. Sponsor staff that require access to personal data will agree to keep confidentiality. Data relevant to fulfil the objectives of the study will be collected only.

The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor and by inspectors from

regulatory authorities. Study participants have the right to request access to their personal data and the right to request rectification of incorrect or incomplete data.

Exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Subjects who do not agree to data handling as described in the informed consent form will not be enrolled into the trial.

The sponsor of each sub-protocol is responsible for data protection. Contact details for the sponsor's data protection officer are described respectively in each sub-protocol and in the trial specific ICF. Data processing and appropriate delegation will be carried out and specified by the sponsor.

5. Statistical methods and sample size calculation

5.1. Statistical and analytical plan

Refer to sub-protocols for respective statistical and analytical plan. A statistical analysis plan will be drafted for each sub-protocol.

5.1.1. Analysis population

Details about analysis population are specified in the respective section of the concerned sub-protocol.

5.1.2. Description of trial subject groups

For the description of trial subject groups, please refer to respective sub-protocols under this master protocol.

5.1.3. Primary target variable

Please refer to respective sub-protocols under this master protocol.

5.1.4. Secondary target variables

Please refer to respective sub-protocols under this master protocol.

5.1.5. Subgroup analyses

Please refer to respective sub-protocols under this master protocol.

5.1.6. Interim analysis

Please refer to respective sub-protocols under this master protocol.

5.2. Sample size calculation

Please refer to respective sub-protocols under this master protocol.

6. Safety

6.1. Adverse event

An AE is any untoward medical occurrence in a trial subject administered an intervention. There does not necessarily have to be a causal relationship with this treatment. The AEs may be, but is not restricted to a new illness, worsening of a sign or symptom following trial-specific treatment, the clinically significant abnormal results of an examination (e.g., laboratory findings, electrocardiogram) or deterioration of a pre-existing medical condition, or a combination of two or more of these factors. Due to the nature of this study, reporting AE to the Regulatory Authorities is not required. AEs must, however, be recorded as such in the eCRF.

6.2. Serious adverse events

Due to the nature of this study, SAEs are not required to be reported to the Regulatory Authority. For purpose of clarification, a SAE is any untoward medical occurrence that at any dose:

1. Results in death.
2. Is life-threatening at the time of the event.
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly or birth defect.
6. Is any other medical important event in the opinion of the investigator.

Inpatient hospitalisation is defined as any stay in hospital that includes at least one night (midnight to 06:00). Admission to hospital as an inpatient planned before the first admission of the intervention is not considered as SAE but must be documented in a proper manner in the trial subject's medical records and CRF.

EXCEPTIONS: the following events are not considered as SAE:

The participant is formally admitted to a hospital for medical reasons with no seriousness criterion and does not require overnight hospitalisation.

- Elective or previously scheduled surgery or medical treatment; hospitalisation for social or administrative reasons.

Pre-existing diseases or present conditions detected prior to start of study drug administration and which do not worsen.

6.3. Definitions of adverse reactions and adverse drug reactions

6.3.1. Pregnancy

Given that all foreseeable drugs included in all nested protocols will be prescribed under label-use and that this is a low-intervention phase IV clinical trial that does not require AE reporting, the occurrence of a pregnancy will not be regarded as a reportable event.

6.3.2. Serious adverse reactions

Given the nature of all trials nested within this protocol, only serious adverse drugs reactions (SAR) will be reported to the regulatory authorities. For clarification purposes, a SAR is any untoward medical occurrence that has a possible causal relationship with the intervention and that:

1. Results in death.
2. Is life-threatening at the time of the event.
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation.
4. Results in persistent or significant disability/incapacity.

5. Is a congenital anomaly or birth defect.
6. Is any other medical important event in the opinion of the investigator.

Inpatient hospitalisation is defined as any stay in hospital that includes at least one night (midnight to 06:00).

If a SAR is suspected trial subjects who develop AEs must be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels.

6.3.3. Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction the nature or severity of which is not consistent with the product information available for the study intervention, is regarded as serious, and has at least a possible causal relationship with the intervention.

If a SUSAR is suspected trial subjects who develop adverse events must be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels.

6.3.4. Adverse drug reactions derived from procedures related to the intervention

In the unlikely event that an AE cannot be explained by the administration of the drug and no other possible cause is identified, yet there is still sufficient causality criteria to establish a relationship between the intervention and the event, this may be related to the procedures surrounding the intervention itself *(e.g.* genotyping) these must be also reported to the regulatory authorities.

6.3.5. Documentation of adverse events and adverse drug reactions

All AEs and ADR will be documented in the eCRF including all information listed below.

AEs occurring will be documented when occurring in time frames prespecified in each of the subprotocols:

The AE is documented in the CRF including the following information:

- AE verbatim.
- Date and time of onset and resolution.
- Severity.
- Causal relationship with IMP/study treatment.
- Seriousness.
- Action taken.
- Outcome.

AEs will be followed up for up to 30 days after the last visit of the trial subject, if applicable.

6.3.5.1. Exceptions from adverse event recording

Preexisting diseases (before study intervention) are not documented as adverse events but as concomitant diseases. New diseases and preexisting diseases that worsen during the trial are documented as AEs.

6.3.6. Severity of the adverse event

The CTCAE (Common Terminology Criteria for Adverse Events) grading table (v5.0) will be used by trial investigators to classify adverse events. It comprises the following categories:

- Grade 1: Mild.
  Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate.

Minimal, local or non-invasive intervention required, limiting age-appropriate instrumental activities of daily living* (ADL).

- Grade 3: Severe or medically significant but not immediately life-threatening. Hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences. Urgent intervention indicated.
- Grade 5: Death related to AE. (Apart from grading methods each death is to be assessed as grade 5).

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Only serious reactions to the intervention must be reported to the Regulatory Authorities. For further clarification on how to establish causality view Section 6.3.6.

6.3.7. Causal relationship between adverse event and investigational intervention

The investigator will assess therefore every AE whether a causal relationship with the study intervention and/or study procedure/s can be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the intervention and/or study procedure/s, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered as a symptom or sign of an underlying disorder, no causal relationship will be assumed.

Every AE will be assessed (eCRF/SAE-Report) according to the causality determinations of CIOMS VI-Group as follows:

- Related: There is a reasonable possibility that the AE may be related to the intervention.
- Not related: There is not a reasonable possibility that the AE may be related to the intervention.

A report on an event which cannot be judged because information is insufficient or contradictory or has not been judged will be regarded as related.

The following remarks might be helpful for the judgement for relatedness.

6.3.7.1. Related

- A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the study intervention administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the intervention (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- A clinical event, including laboratory test abnormality, with a reasonable time sequence to the study intervention administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- A clinical event, including laboratory test abnormality, with a reasonable time sequence to the study intervention administration, but which could also be explained by

concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

- A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
- A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

6.3.7.2. Unrelated

A clinical event, including laboratory test abnormality, with a temporal relationship to the administration of the study intervention which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

6.4. Reporting of adverse events, adverse events of special interest, pregnancy and changes in risk-benefit assessment

Every AE that occurs from the time of study administration up until the last visit, also as specified in the respective subprotocol, must be documented in the appropriate part of the CRF but do not need to be reported to either the sponsor or the Regulatory Authorities. They must, however, be recorded in the eCRF. This is also applicable to pregnancies.

6.4.1. Reports from the investigator to the sponsor

The investigator will inform the sponsor of the occurrence or receipt of knowledge of the occurrence of an SAR without delay, at the latest within 24 hours of being made aware of the event.

The study specific SAR report forms must be completed and submitted by e-mail to the sponsor delegate responsible of SAR management procedures:

SAR Reporting E-Mail: farmacovigilancia.ucicechulp@gmail.com

The investigator will also inform the sponsor without delay within 24 h of being made aware of any pregnancy of a trial subject that occurs during the trial and its outcome. This will be documented on the appropriate separate pregnancy forms. The pregnant trial subject will be asked to give separate informed consent for pregnancy follow up. The parents will be asked to give informed consent to follow-up the child until 4 weeks after birth.

In the interest of participants' safety, follow-up for up to 30 days after the individual participant's study termination (individual study termination is defined as last visit) is required for SAEs that are not sufficiently resolved at the participant's final trial visit.

6.4.2. Assessment of AR by the sponsor

All cases of suspected ARs are assessed by the sponsor with regard to seriousness, causality, and expectedness, regardless of the investigator's assessments.

6.4.3. Notification of ethics committee and competent authority

Every SUSAR that becomes known in a clinical trial will be reported by the sponsor, to the competent authority and the ethics committee.

All reporting requirements are regulated in the appropriate document.

6.4.3.1. Fatal and life-threatening SUSARs

The competent authority and the responsible ethics committee must be informed by the sponsor of all fatal or life-threatening SUSARs. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases,

attempts will be made to obtain further relevant information which will be supplied to the competent authority and the ethics committee within a further 8 days.

6.4.3.2. SUSARs that are not fatal or life-threatening

The competent authority and the responsible ethics committee will be informed without delay by the sponsor of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

6.4.4. Review and reporting of changes in the risk-benefit ratio

The sponsor will inform the competent authority, the responsible ethics committee and the competent authorities of all other member states of the EU or EEA where the trial is being conducted, of any events or factors that mean that the risk-benefit ratio of the study intervention has to be reviewed. This will be done without delay, at the latest within 15 days. This includes, but is not restricted to:

- Individual reports of expected SARs with an unexpected outcome.
- A clinically relevant increase in the rate of occurrence of expected SARs.
- SUSARs in trial subjects who have already completed the follow-up period of the clinical trial (”end-of-trial visit”).
- Events in connection with the conduct of the study or the development of the investigational medicinal product which may affect the safety of the trial subjects.

6.4.5. Informing the Data Monitoring Committee

The DMC will be informed of all safety-relevant events by the sponsor.

An independent data monitoring committee (DMC) consisting of independent scientists not otherwise involved in the trial will be appointed and will review the data regularly during the study for safety and scientific integrity and will make recommendations to the sponsor regarding the stopping of an intervention for harm or for futility. The frequency of the committee data review meetings and other aspects such as stopping rules will be detailed in a separate charter. There will only be one DMC overseeing all trial arms, and this committee will communicate with the DMCs of other corresponding platform trials to exchange information. The level of monitoring will depend on the safety profile of the intervention.

6.4.6. Informing the investigators

The sponsor will inform investigators of all SUSARs including all relevant further information within the periods set by the competent authority.

The sponsor will inform all investigators on any change of information concerning the scientific documents of the trial (SmPC, Investigator’s Brochure, risk-benefit-ratio).

6.4.7. Informing the marketing authorisation holder

The sponsor will also inform the marketing authorisation holder about all SUSARs including information reported to the competent authority and ethics committee in accordance with contractual agreements, if applicable.

6.5. Annual safety report (DSUR)

The sponsor will supply annually a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the competent authorities. This report will also be supplied to the responsible ethics committee.

The annual safety report will be compiled according to the corresponding ICH guideline E2F "Development Safety Update Report – DSUR".
The sponsor will supply the report within 60 days after the reference date (data-lock point) defined as one year from the first authorisation to conduct the clinical trial by the sponsor (the "Development International Birth Date" (DIBD) of the study drug or in this case intervention. The start of the annual period for the DSUR is the month and date of the DIBD. The data lock point of the DSUR should be the last day of the one-year reporting period.

7. Trial results and publication

7.1. Reports

7.1.1. Interim reports

Section 6.5 describes the requirements for annual reports on the safety of trial subjects. Interim reports about the study conduct and results are defined by each sub-protocol as applicable.

7.1.2. Final report

The competent authority and ethics committee will be informed within 90 days after the end of the trial.

Within one year after the end of the trial, the competent authority and the ethics committee will be supplied with the full final study report (competent authority) or the summary of the final study report (ethics committee).

7.2. Publication

Trials under this master protocol will be registered in a public register, in which trial results will be posted. The results of this study will be published in a suitable publication irrespective of findings. Results will also be presented at scientific meetings.

The sponsor will comply with the requirements for publication of trials results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship for each will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Conflicts of interests will be disclosed. The contribution of all partners and others will be fairly described in the acknowledgement section or as co-author, depending on the contribution in the trial design, planning and publication.

In line with the EU data sharing policy, individual patient-level data will be shared with the scientific community (either as anonymised or pseudonymised data sets), while maintaining the integrity and privacy of the trial participants and in compliance with the EU General Data Protection Regulation and national or local rules.

Data and other trial documents should be made available through an appropriate data repository, helping to ensure that the data objects are properly prepared, are available in the longer term, are stored securely and are subject to rigorous governance. The terms and conditions of data transfers to a repository and the data sharing process shall be subject to specific data processing agreements to be established between the concerned parties as well as to a specific data sharing plan, where the details are specified.

8. Amendments to the trial protocol

Changes to this master trial protocol and/or sub-protocols under this master protocol may only be implemented if agreed by the sponsor, sponsor's representative, the PCI and statistician. Any changes to the trial procedures must be made in writing and must be documented with reasons and signed by the sponsor's representative (i.e., the PCI) and the statistician.

Significant changes will be implemented after approval by the competent authority and favourable opinion of the ethics committee, only. Exceptions to this are amendments made to avoid immediate dangers.

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