EFFECTIVENESS OF HYPERTENSION MANAGEMENT WITH AN AMLODIPINE AND PERINDOPRIL ARGININE-BASED STRATEGY IN MOROCCO

SYNERGIA-MAROC

IC4-05985-014-MAR

PAGE DE SIGNATURE DU PROTOCOLE

Cette étude doit être réalisée conformément au protocole, aux Bonnes Pratiques Cliniques et aux requis réglementaires en vigueur.

Signature du représentant légal du promoteur

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ABREVIATIONS LIST

ACEi : Angiotensin-Converting Enzyme inhibitor

ADR : Adverse Drug Reaction

AE : Adverse event

ARB : Angiotensin-Receptor Blocker

bpm : Beats Per Minute

CCB : Calcium Channel Blocker

CDC : Centers for Disease Control and Prevention

cm : centimeter

CRF : Case Report Form

CVD : Cardiovascular Disease

DBP : Diastolic Blood Pressure

ECG : ElectoCardioGram

GCP : Good Clinical Practise

GFR : Glomerular Filtration Rate

HDL : High Density Lipoprotein

ICH : International Conference on Harmonisation

IEC : Independent Ethics Committee

kg : kilogramm

NCD : Non-Communicable Disease

NYHA : New York Heart Association

SADR : Serious Adverse Drug Reaction

SAE : Serious Adverse Event

SBP : Systolic Blood Pressure

SD : Standard Deviation

WHO : World Health Organsiation

INTRODUCTION

Africa is experiencing a rapid increase in the prevalence of non-communicable diseases (NCDs), with 85% of premature deaths from NCDs occurring in Low- and middle-income countries (WHO, 2018). In North Africa, NCDs are already responsible for over 75% of all deaths, with cardiovascular diseases (CVD) being the leading individual cause of death in countries like Morocco (Africa, 2022).

In Morocco in 2018, ischemic heart disease accounted for 57% of deaths in the country and these numbers keep growing (Chadli S, 2018). Hypertension is the main CVD risk factor, with a prevalence of 29.3% (Elyamani R, 2021). Many patients with hypertension are undiagnosed (Nejjari, et al., 2013) and most patients with hypertension in Morocco (75%) are not on any pharmacological treatment (Elyamani R, 2021). Therefore, early blood pressure control is crucial in preventing both cardiovascular and systemic complications in these patients.

The World Health Organization (WHO) recommends initiating pharmacological antihypertensive treatment no later than 4 weeks after diagnosis with systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Among the first-line antihypertensive medications recommended by WHO, long-acting dihydropyridine calcium channel blockers (CCBs) are recommended in patients of African descent (WHO, 2021).

When additional medication is needed, WHO recommends the addition of an angiotensin-converting enzyme inhibitor (ACEi), an angiotensin-receptor blocker (ARB) or a diuretic, and single-pill combination therapy is recommended for improved medication-taking adherence and persistence as well as blood pressure control (WHO, 2021). Long-acting antihypertensive drugs in single-pill combination therapy are associated with a greater reduction in mean 24h blood pressure (Parati G, 2020). Amlodipine (a CCB) and perindopril (an ACEi) are long-acting antihypertensive drugs that, reduce mean blood pressure as single-pill combinations more than their respective monotherapies (William J. Elliott, 2015).

A recent meta-analysis and systematic review of 10 clinical trials conducted in different countries showing the benefits of the single-pill combination of amlodipine and perindopril in lowering blood pressure, heart rate, improving medication adherence and safety, and reducing adverse events (Mostafa S, 2022).

There is strong evidence to suggest the benefits of fixed combination therapy of amlodipine and perindopril arginine in lowering blood pressure and improving adherence and safety following previous monotherapy regimens. However, there are limited studies on this single-pill combination therapy in populations from Northern Africa (Hammoudi-Bendib N, 2021).

In Morocco, the single-pill combination of amlodipine and perindopril arginine has market authorisation and is indicated as substitution therapy for the treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

This study seeks to evaluate the effectiveness of a perindopril arginine and amlodipine-based strategy in hypertensive patients who were uncontrolled on a monotherapy of amlodipine. Subsequently, the patients were put on amlodipine and perindopril arginine as a free combination treatment regimen, and then switched to the single-pill combination of perindopril arginine and amlodipine when the patient is controlled.

I- STUDY OBJECTIVES AND ENDPOINTS

1. Objectives

1.1. General objective

To evaluate the effectiveness of an amlodipine and perindopril arginine-based strategy in hypertensive patients who were uncontrolled on monotherapy of amlodipine.

1.2. Specific objectives

- To determine whether the addition of perindopril arginine in free combination in hypertensive patients who were uncontrolled on monotherapy of amlodipine would improve blood pressure control
- To assess the short-term safety of a free combination of amlodipine and perindopril arginine-based strategy in hypertensive patients.
- To assess the short-term safety of a single-pill combination of amlodipine and perindopril arginine-based strategy in hypertensive patients

2. Endpoints

2.1. Primary endpoint

- The primary endpoint is a change in supine office systolic blood pressure (SBP) and diastolic blood pressure (DBP) between baseline and the end of the study.

2.2. Secondary endpoints

- Change in supine office SBP and DBP between baseline and the initiation of the single-pill combination therapy with amlodipine and perindopril arginine
- Change in supine office SBP and DBP between the initiation of the single-pill combination therapy with amlodipine and perindopril arginine and the end of the study
- Change in the proportion of patients whose blood pressure is controlled (SBP < 140 mmHg and DBP < 90 mmHg) between baseline and the end of the study
- Difference in the proportion of participants who report side effects between the initiation of the single-pill combination therapy with amlodipine and perindopril arginine and the end of the study.

II- STUDY DESIGN AND DESCRIPTION

1. Study Design

This is a multicenter, prospective observational study to evaluate the effectiveness of an amlodipine and perindopril arginine-based strategy over 90 days in hypertensive patients who were previously uncontrolled on monotherapy of amlodipine. Patients will be seen monthly (Day 30, Day 60 and Day 90) after initiation of the amlodipine and perindopril arginine-based strategy by the treating physician as per WHO recommendations (WHO, 2021). Please see the study design algorithm in Annex 1.

2. Procedure

Approximately 1 600 hypertensive patients on monotherapy of amlodipine who are uncontrolled and have perindopril arginine (5 mg) added to their treatment regimen (free combination of amlodipine and perindopril arginine) will be enrolled by their primary care physicians across Morocco. During the study, treating physicians will adjust the dosage of perindopril arginine and amlodipine or add a third drug of their choice in accordance with their routine clinical practice to achieve and maintain blood pressure control. Participants enrolled in the study will be followed up for 90 days according to routine practice and recommendations: Treating physicians will assess blood pressure after 30 and 60 days (+/- 7 days according to routine clinical practice) and adjust treatment based on the physician's judgement (change dosage of medication, add a third drug, substitute free combination with single-pill combination). All drugs that are added /removed or have the dosage adjusted would be recorded in the CRF indicating the reason for addition/removal or change in dosage as well as the current and previous dosage.

- A participant is considered to have completed the study if he or she has completed all study visits including the last visit (Day 90).

3. Rationale for Study Design

This prospective observational study will evaluate the effectiveness of an amlodipine and perindopril arginine-based strategy in uncontrolled hypertensive patients on amlodipine monotherapy. Combination therapy of multiple antihypertensive agents (for example perindopril arginine and amlodipine as in our study) has been shown to be effective in lowering blood pressure which is essential for managing hypertension (ESC/ESH, 2018). In Morocco, marketing approval for the single-pill combination treatment of hypertension using perindopril arginine and amlodipine is indicated as substitution therapy for the treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level. In addition, the single-pill combination regimen of perindopril arginine and amlodipine must be initiated at the same dosage of perindopril arginine and amlodipine as it is in the free combination treatment regimen. WHO suggests a monthly follow up after initiation or a change in antihypertensive medications until patients reach target and a follow up every 3–6 months for patients whose blood pressure is under control. (WHO, 2021).

III- SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to enrolment in the study.

1. Inclusion Criteria

- Men or women aged ≥ 18 years old who document their informed consent.
- Hypertensive patients previously treated with amlodipine in a monotherapy regimen who are uncontrolled and for whom the treating physician decides to add perindopril arginine.

2. Exclusion Criteria

- Age < 18 years
- Pregnancy, breastfeeding or possibility of becoming pregnant during the study
- Current participation in another randomised study or within the preceding 3 months
- Known symptomatic orthostatic hypotension
- Known hyperkaliemia, or hypokaliemia
- History of hypertension known to be resistant to the free or single-pill combination with perindopril and calcium channel inhibitors or contra-indications to treatment with perindopril or amlodipine
- Secondary hypertension or known complicated hypertension
- Known renal impairment: patients having a creatinine clearance value classifying them as moderate or severe renal failure using national or international classification of chronic kidney disease or bilateral renal artery stenosis or stenosis to a solitary kidney or a history of gout
- Known complicated liver disease
- Chronic pancreatitis
- History of heart disease: cardiogenic shock, myocardial infarction within the previous 6 months before selection, haemodynamically unstable heart failure after acute myocardial infarction, coronary revascularisation within the previous 6 months, congestive heart failure within the previous 6 months before selection or history of congestive heart failure with grade III or IV NYHA, severe aortic or mitral valve stenosis or hypertrophic obstructive myocardiopathy
- Recent ventricular rhythm disorders
- History of cerebrovascular disease
- Hypersensitivity to the active substances, to other sulphonamides, to dihydropyridine derivatives, and any other ACE-inhibitor
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioedema
- Hepatic encephalopathy
- Concomitant use of single-pill combination perindopril and amlodipine with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²)
- Any other contraindication according to the SPC (summary of product characteristics) of the medicinal product

3. Criteria for Discontinuation/Withdrawal of Subject

Every participant is free to withdraw from participation in the study at any time upon request. Their attending physician may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant non-compliance to treatment
- Lost to follow-up (participant fails to return for 2 scheduled visits)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study treatment
- If the participant meets an exclusion criterion (either newly developed or not previously recognised) that precludes further study participation.

IV- STUDY PLAN

1. Study Procedures

This section describes the study procedures and data to be collected. For each procedure, participants are to be assessed by the same physician. Informed consent, dated and signed must be obtained prior to the subject entering into the study, and before any protocol-directed activities are performed. During the study, participants would be assessed for side effects and adverse events. See Annex 2 for the collection of data during study visits.

2. Demographics, Medical History, and Medication History

Demographic information to be obtained will include the date of birth or age, and sex upon enrolment in the study. The smoking status of the participant will also be obtained at enrolment.

Medical history to be obtained will include determining whether the subject has or has had any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent.

3. Clinical Examination

A baseline clinical examination which is defined as the assessment prior to the first dose of Perindopril in a hypertensive patient that is uncontrolled on monotherapy using amlodipine will be performed. At each visit, each subsequent clinical examination should assess clinically significant changes from the baseline assessment. The clinical examination will consist of the following:

3.1. Review of Systems

The following body systems will be reviewed: (1) eyes; (2) ears, nose, and throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

3.2. Weight and Height

Participants will have their weight and height measured while wearing indoor clothing and with shoes off at their first study visit. Measurements should be taken on a flat surface. Height should be recorded in centimetres (cm) without decimal places and weight in kilograms (kg) with 1 decimal place.

3.3. Vital Signs

Vital signs will include respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (bpm). When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 30 mins before or after the scheduled blood draw. The blood pressure values will be defined by the office measurements, using an automatic device for at least 3 measurements, after at least 10 min rest in supine position, with a time interval between measurements of 5 mins. The following elements should be considered when measuring blood pressure (ESH, 2021):

- Don't eat or drink anything 30 minutes before you take your blood pressure.
- Empty your bladder before your reading.
- Sit in a comfortable chair with your back supported for at least 5 minutes before your reading.
- Put both feet flat on the ground and keep your legs uncrossed.
- Rest your arm with the cuff on a table at chest height.
- Make sure the blood pressure cuff is snug but not too tight. The cuff should be against your bare skin, not over clothing.
- Do not talk while your blood pressure is being measured.

Ambulatory blood pressure monitoring will be considered if available.

3.4. Compliance Measures

Given the real-world nature of the study, compliance would be assessed using patient interviews. Questions to assess drug non-adherence would be adapted from a drug adherence assessment tool previously validated in the French population (Stéphanie Sidorkiewicz, 2016).

4. Clinical Laboratory Measurements

If available based on routine clinical practice, the following clinical laboratory measures will be recorded at baseline, before initiation of single pill combination of amlodipine and perindopril arginine and at the final study visit: serum creatinine, serum potassium, serum sodium, serum calcium, fasting blood sugar, total cholesterol and HDL cholesterol.

V- ADVERSE EVENTS

1. Definitions

An adverse event (AE): is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

A severe adverse event (SAE): is defined as any untoward medical occurrence that at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious when, based upon appropriate medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

2. Severity of Adverse Events

The different categories of intensity (severity) are characterised as follows:

- Mild: The event is transient and easily tolerated by the subject.
- Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.
- Severe: The event causes considerable interference with the subject's usual activities.

3. Causality of Adverse Events

The relationship of each AE to study medication(s) will be assessed using the following categories:

- **Related:** An AE that follows a reasonable temporal sequence from taking a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
- **Not Related:** An AE that does not follow a reasonable temporal sequence from taking a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

OR

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug

treatment and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug treatment (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after study drug treatment, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- **Potentially Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after taking the study drug treatment). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to study drug treatment makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after taking the study drug) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related:** The AE is completely independent of study drug treatment, and/or evidence exists that the event is definitely related to another aetiology. There must be an alternative, definitive aetiology documented by the clinician.

Causality to study procedures should be determined for all AEs.

4. Reporting of AEs

At each study visit, the study clinician will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. All participants experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented on the AE page of the CRF, whether or not the study clinician concludes that the event is related to the drug treatment. The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered related to the drug treatment, including those listed in the protocol or brochure. All SAEs will be followed until satisfactory resolution or until the study clinician deems the event to be chronic or the participant is stable. The following information will be documented for each event:

- Event term.
- Start and stop date.

- Severity.
- Study clinician's opinion of the causal relationship between the event and administration of study medication(s) (related or not related).
- Study clinician's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study medications.
- Outcome of event.
- Seriousness

Independently of the regulatory obligations of the treating physician, the Sponsor/Marketing Authorisation Holder must report the pharmacovigilance data to the appropriate Authorities (including Ethics Committees if applicable) according to Good Vigilance Practice Module VI and local regulations.

Cases are closed when an event has recovered or condition stabilised and the report is deemed sufficiently detailed for adequate medical assessment.

5. Additional Considerations

Unscheduled visits (visits to study clinician at a time point not required by the protocol) due to disease exacerbation will undergo the following:

- Vital Signs assessment.
- Review of Systems
- Physical examination.
- Collection of concomitant medications and procedures.
- Collection of AEs and SAEs.
- Clinical chemistry and haematology, as indicated

If a participant experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Study clinicians should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

VI- DATA HANDLING AND RECORD KEEPING

All data collected during the study (clinical and laboratory) will be recorded in individual case report forms (CRFs). Adverse events will be reported to Servier Maroc and recorded in the adverse event section of the CRF as well. Participant confidentiality and privacy is strictly held in trust by the participating clinicians, their staff, and the sponsor(s) of the study. This confidentiality is extended to cover information from the testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party without prior written approval of the sponsor.

1. Case Report Forms (CRFs)

Completed CRFs are required for each subject who signs an informed consent. The marketing authorisation holder will supply study sites with access to CRFs. CRFs must be completed in French. Data are transcribed directly onto CRFs. After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the sponsor or designees and will be answered by the site. The study clinician must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the study clinician must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs. CRFs will be reviewed for completeness and acceptability at the study site during periodic visits. The completed CRFs are the sole property of the marketing authorisation holder and should not be made available in any form to third parties, except for authorised representatives of appropriate governmental health or regulatory authorities, without written permission of the marketing authorisation holder.

2. Record Retention

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IEC, institutional policies, or sponsor requirements.

VII- STATISTICAL CONSIDERATIONS

1. Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalised prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

1.1. Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarised using means and standard deviations for normally distributed continuous variables (or medians and interquartile ranges for non-normally distributed data) and counts and percentages for categorical variables.

Medical history and concurrent medical conditions will be summarised by system organ class and preferred term. Medication history and concomitant medications will be summarised by preferred term.

1.2. Effectiveness Analysis

All proportion-based effectiveness endpoints will be summarised by presenting the point estimate and 95% confidence intervals for the proportion. Based on the type of missingness of data, complete case analysis or multiple imputation will be used to account for missing data. All changes from baseline efficacy endpoints will be summarised descriptively by time point.

The evolution of supine SBP and DBP, as well as biological data will summarised by time point.

1.3. Safety Analysis

Safety endpoints will be analysed as summary statistics during treatment and counted once only for a given participant. Start/stop dates, severity, as determined by the study clinician, relationship, expectedness, outcome and duration, will be reported. Adverse events leading to premature discontinuation from the study and SAEs will be presented separately in a listing.

1.4. Sample Size Determination

For a 95% power to determine a mean difference in SBP of 15.1 mmHg between baseline and end of the study, considering a SD of 10.3 mmHg, alpha level of 5% and a 20% dropout rate we will require a minimum sample size of 1440 participants. This study will aim to enrol 1600 participants which is above the minimum calculated sample size.

VIII- QUALITY CONTROL AND QUALITY ASSURANCE

1. Investigator Monitoring Visits

Monitoring visits will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee. All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the study medication, subject medical records, informed consent documentation, documentation of subject authorisation to use personal health information (if separate from the informed consent forms), and review of CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

2. Protocol Deviations

There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria. The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. Significant protocol deviations will be entered into the CRF, which is reviewed by the study sponsor or designee.

IX- PHARMACOVIGILANCE

1. Definitions

1.1. Pharmacovigilance information

Pharmacovigilance data include any unintended or adverse event associated with the use of a medicinal product in humans, whether or not considered drug related, including the following special situations (situations where no adverse event occurred but information needs to be collected):

- exposure during pregnancy (maternal and/or transmission of a medicinal product via semen following paternal exposure) or breastfeeding,
- overdose, abuse, misuse, off label uses, medication error, occupational exposure, drug-drug or drug-food interactions,
- lack of efficacy

1.2. Adverse Event (AE)

Adverse event (synonym adverse experience): any untoward medical occurrence in a patient or a clinical-trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

1.3. Adverse (drug) reaction (ADR)

Adverse reaction (synonyms: Adverse drug reaction, Suspected adverse (drug) reaction, Adverse effect, Undesirable effect: a response to a medicinal product which is noxious and unintended.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

1.4. Serious adverse (drug) reaction (SADR)

Serious adverse reaction: an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

2. Responsabilities

2.1. Events to be reported

All available information about the following reported events occurring during the study will be recorded:

- All serious adverse drug reactions to Coversyl® or Coveram®
- All non-serious adverse drug reactions to Coversyl® or Coveram®
- Reports about special situations (see paragraph Pharmacovigilance information)
- All adverse events

In general, investigators are reminded to report any adverse reaction or any special situation associated with the use of a drug to the Moroccan Center for Pharmacovigilance and/or to the holder of the marketing authorization for the product concerned (Coversyl® and Coveram® for Servier Maroc), in accordance with local pharmacovigilance practices.

As part of the study, all adverse events, suspected adverse effects and special pharmacovigilance situations occurring in patients participating in the study must be reported using the pharmacovigilance form presented in the annex 3 to this protocol. This pharmacovigilance form should be sent immediately to the pharmacovigilance manager of Servier Maroc at the following address: fatima.lahmouddi@servier.com or by fax to the number: 05 22 79 52 53

2.2. Responsibilities of the treating physician

In prospective studies, at medical visits, the treating physician will ask the participating patient to indicate whether or not an adverse event (serious or not) has occurred.

The treating physician has to assess the causal relationship between an adverse event and the investigated drug intake, as well as the seriousness criteria and later on the outcome of the event.

In case of Adverse Events, Adverse Drug Reactions or special situations that occurs during the study (both serious and non-serious), the participating physician must complete the PHARMA-FORM-032, without waiting for the clinical outcome or the results of additional investigations.

If the event is serious, it will be notified immediately (same or next working day at the latest) to Mrs. Fatima LAHMOUDDI, pharmacovigilance manager of Servier Maroc, by email or by fax via e-mail or fax. Any available and relevant laboratory findings, hospitalisation reports or other investigation results performed in connection with the adverse event should be attached to the PHARMA-FORM-32. All other events should be transmitted by the treating physician within 2 working days.

The same obligations will apply for follow-up reports. The treating physician must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution. She/he will continue to notify follow up data according to timeframes defined above.

If the follow-up of the participant is not done by the treating physician him/herself (hospitalisation, followed by a specialist or the participant's general practitioner,…), the treating physician will do every effort to establish/maintain contact with the person/department in charge of follow-up of the participant, so as to have additional information and report it.

2.3. Responsibilities of the Marketing Authorisation Holder

Independently of the regulatory obligations of the treating physician, the MAH must report the pharmacovigilance data to the appropriate Authorities (including Ethics Committees if applicable) according to Good Vigilance Practice Module VI and local regulations.

Cases are closed when an event has recovered or condition stabilised and the report is deemed sufficiently detailed for adequate medical assessment.

X- ETHICAL CONSIDERATIONS

This study will be conducted with the highest respect for the individual participant according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local regulatory requirements.

1. IEC Approval

This protocol, a copy of the informed consent form, and, if applicable, subject recruitment materials and other documents required by all applicable laws and regulations, must be submitted to the local IEC for approval. The IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g. informed consent form) reviewed; and state the approval date. Sites must adhere to all requirements stipulated by their respective IEC. This may include notification to the IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IEC, and submission of the investigator's final status report to IEC. All IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

2. Subject Information, Informed Consent, and Subject Authorisation

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorisation form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The informed consent form, subject authorisation form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorisation form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to

participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorisation form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorisation (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorisation form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorisation form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

3. Subject Confidentiality

Servier Maroc affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number. To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory and the appropriate IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorisation of the subject as part of the informed consent process. Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's CRF).

4. Publication and Disclosure

The investigator is obliged to provide Servier Maroc with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the

protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor. The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

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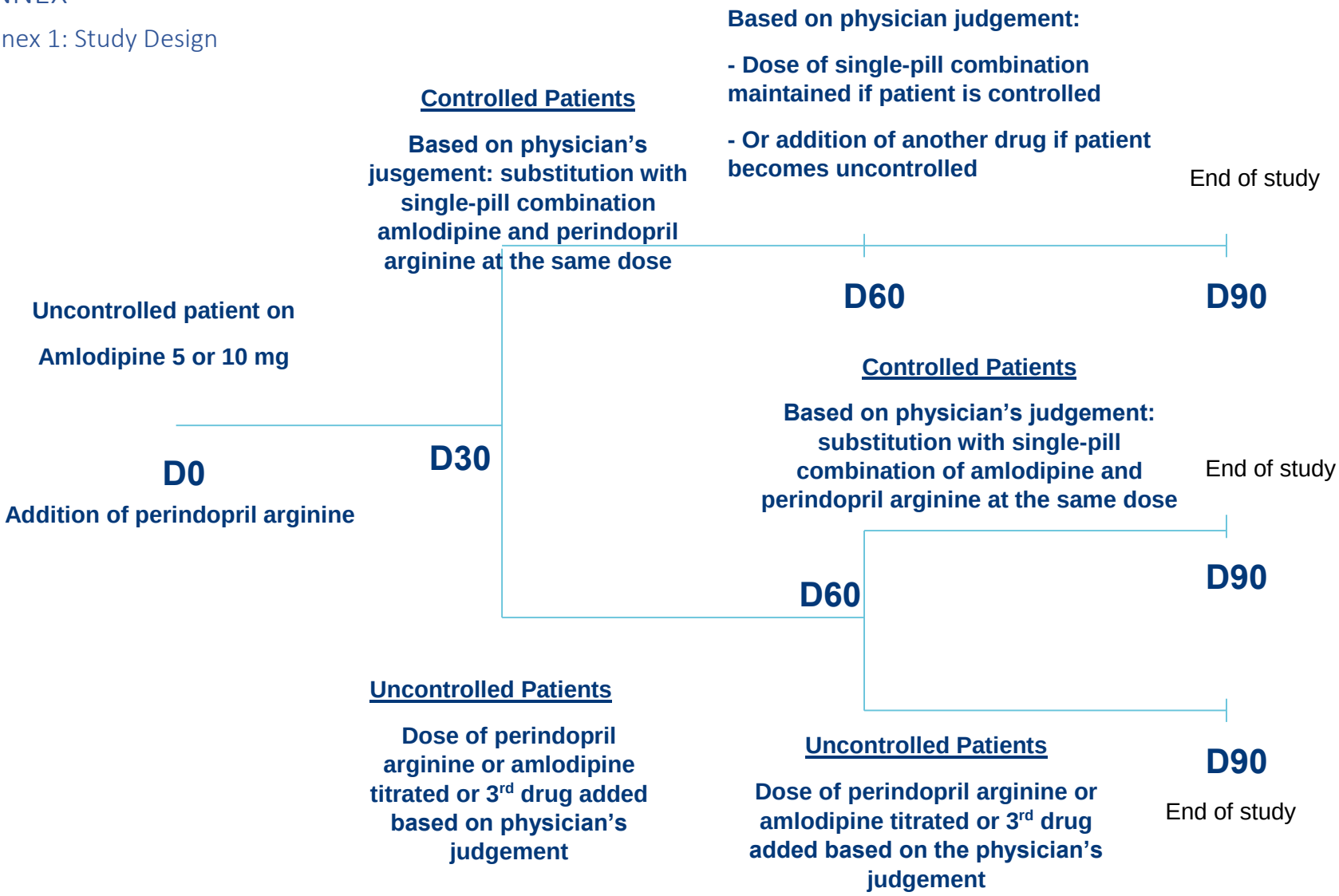
ANNEX

Annex 1: Study Design



Annex 2: Study measurement check list

	D0	D30(+/- 7 days)	D60 (+/- 7 days)	D90
Informed consent	X			
Identification and past medical history	X			
Demography and socio-economic status	X			
Previous and concomitant treatment	X	X	X	X
Anthropometric measurements	X	X	X	X
Vital Signs	X	X	X	X
Office BP	X	X	X	X
Ambulatory blood pressure measurement*	X	X	X	X
Biochemistry*	X	X	X	X
Adverse event	X	X	X	X

***If available**

Annex 3: Adverse event - Adverse drug reaction - Special situation form

PHARMA-FORM-32-6.0-EN- attached to PHARMA-SOP-17

Adverse event / Adverse drug reaction / Special situation* form

NON-INTERVENTIONAL STUDY
PROTOCOLE N° : IC4-05985-014-MAR

To be sent immediately by fax/e-mail to Mrs F. LAHMOUDDI, at the fax number: 00212 5 22 79 52 53 or by e-mail at the address fatima.lahmouddi@servier.com

Year of birth or Age	Gender	Height	Weight	Patient number
⌊_⌊_⌊_⌊_⌋ or ⌊_⌊_⌋	M / F	⌊_⌊_⌋	⌊_⌊_⌋	⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Observed adverse event:	Date of onset	Until (if recovered)
	⌊_⌋ ⌊_⌋ ⌊_⌊_⌊_⌋	⌊_⌋ ⌊_⌋ ⌊_⌊_⌊_⌋

Serious: r No
r Yes, because: (please choose below)
r Fatal
r Life-threatening
r Hospitalisation or prolongation of hospitalisation
r Persistent or significant disability or incapacity
r Congenital anomaly/birth defect
r Medically significant

Outcome:
r Recovered
r Recovered with sequelae
r Recovering
r Not recovered
r Fatal
r Unknown

General disease(s) / Concomitant disease(s) (please indicate year of first diagnoses):

Course (please enclose relevant findings e.g. laboratory, hospital reports, histology, etc...):

Causal relationship with the studied drug:
r No r Yes r Not applicable

If yes, please specify dates of treatment with the studied drug in the table below on the first line:

If no or not applicable, please indicate whether the adverse event /special situation is related to a Servier medicinal product (as mentioned in the following table):
r No r Yes *please specify which Servier medicinal product:* .....

Medication list	Daily dosage / application	Administered from to	Indication
		-	
		-	
		-	

Name of physician: Speciality: Address: Phone: (stamp, if available)	Date: Signature:

Special situations: situations where no adverse events occurred but information needs to be collected: exposure during pregnancy (maternal and/or transmission of a medicinal product via semen following paternal exposure) or breastfeeding, abuse, misuse, medication error, overdose, off label use, drug-drug or drug-food interactions, occupational exposure, lack of efficacy, any suspected transmission via a medicinal product of an infectious agent, unintended therapeutic benefit ...*