CLINICAL STUDY PROTOCOL

Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE)
a prospective randomized clinical trial comparing a polypill versus standard of care treatment strategies in post MI elderly patients

Study Drug:	Cardiovascular Combination Polypill AAR
Funded By:	Horizon 2020 Programme
Study Principal Investigator:	Valentin Fuster, MD, PhD
Sponsor:	Centro Nacional de Investigaciones Cardiovasculares (CNIC)
EudraCT Number:	2015-002868-17
Protocol Number:	633765
ClinicalTrials.gov ID:	NCT02596126
Phase:	III

VERSION DATE: 25/09/2019

Funded by Horizon 2020 Programme

PROTOCOL APPROVAL SIGNATURES

Sponsor Signature

PROTOCOL TITLE: Secondary Prevention of Cardiovascular Disease in the Elderly Population (SECURE)

PROTOCOL NUMBER: 633765
EudraCT Number: 2015-002868-17

Sponsor Legal Representative: [redacted]

Principal Investigator Signature

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Study Principal Investigator: Valentin Fuster, MD, PhD

[redacted]

Site Principal Investigator Signature Page

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CONFIDENTIALITY AND cGCP COMPLIANCE STATEMENT

I have read the preceding clinical study protocol entitled: "Secondary Prevention of Cardiovascular Disease in the Elderly Population (SECURE)" and agree that it contains all necessary information for conducting the study.

I hereby confirm that I have carefully read and understood this clinical study protocol, and I agree to that my staff and I will conduct the study according to the study protocol and will comply with its requirements, including ethical and safety considerations.
I understand that, should the Sponsor decide to prematurely terminate or suspend the study for whatever reason such decision will be communicated to me in writing. Conversely, if I decide to withdraw from execution of the study I will immediately communicate such a decision to the Sponsor.
I agree not to publish any part of the results of the study carried out under this clinical study protocol without the prior written consent of the Sponsor.

Site Principal Investigator

_____
Signature

_____
Date

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DOCUMENT HISTORY

Document	Version	Version Date
Original protocol- VHP Approved	2.1	14 December 2015
Amendment 1	3.0	21 April 2016

- Added new exclusion criterion: "2. Inability to understand and comply with the protocol requirements and instructions."
- Section 4.3 and 4.4: Updated members of CEC and DSMB.
- Section 7.8, 7.9, 7.11, and 8.6: Updated per the request of German Lead Ethics Committee to clarify compulsory discontinuation criteria of the trial, study, and withdrawal of patients.
- Section 8.3.1: Added specification of drug supply for Germany
- Section 8.6: Added treatment compliance and missed dose procedure under 8.6.1.
- Section 8.10.1: Updated Resource Use and Costs in order to clarify the definition and variables to be collected.
- Section 9: Clarified patient follow-up for Germany and removed collection of Hb1Ac.
- Section 10.2.4.1: Added "Definitely Related" to Assessment of Causality.
- Annex 1: Name of Béla Merkely added for Hungary.
- Annex 3: Added clarification on definition of MI.
- Annex 8: Corrected MMAS-8's score assessment of question 5 and 8.
- Annex 13: Helsinki 1996 version was added.
- Annex 14: Added Withdrawal of Consent Checklist

Amendment 2	4.0	1 July 2017

- Section 1.1: Visiting Schema updated to reflect protocol changes on data collection and inclusion criteria (time of MI increased)
- Section 5, 6.1,7.2, 7.3, and 7.6: Inclusion Criteria on time of MI increased from 8 weeks to 6 months
- Section 7.7: Clarified information on safety assessment and patient follow-up
- Section 7.8: Reorganized, clarified, and condensed withdrawal of patient from treatment and trial discontinuation
- Section 7.11: New section added to address patient follow up after site closure
- Section 8.1: Updated storage conditions and added relabeling information
- Section 8.3: Updated drug supply section to clarify dispensation

- Section 9.1: Removed MMAS-8 from baseline, and transferred TSQM questionnaire from Baseline to six (6) month visit
- Section 13.3.2. and 11.4.2- Health Economic Endpoints were further specified and definition of the data/variables to be collected were included
- Section 10.3.4- Edited and updated the list of reportable Adverse Events
- Annex 13.2: Helsinki 2013 version was added per the request of Hungarian authorities

Amendment 3	5.0	11 June 2019

- Change in the target number of patients from 3206 to 2514 with updated statistical analysis (different sections through the protocol)+
- Section 1.1 Visiting Schema. Updated schema including 60 months follow-up by telephone call
- Section 1.2 Study Flow chart including 60 months follow-up by telephone call
- Section 4.3 Data Safety and Monitoring Board update
- Section 4.4 Clinical Events Committee update
- New Section 9.1.8 with telephone Follow-up 4
- Section 11.6.1 Determination of Sample Size. Updated calculations
- Annex 1: Participating Organization. Updated information of CNIC

CLINICAL TRIAL SUMMARY

PRINCIPAL INVESTIGATOR/TRIAL LOCATION	**Dr. Valentin Fuster, MD, PhD** **Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC)** Calle del Melchor Fernández Almagro 3 28029 Madrid, Spain
INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs):	Cardiovascular Combination Polypill AAR (acetylsalicylic acid 100 mg, atorvastatin 40 mg or 20 mg, and ramipril 10, 5 and 2.5 mg).
STUDY OBJECTIVES	**Primary Objective** To evaluate the efficacy of a polypill strategy containing aspirin (100 mg), ramipril (2.5, 5 or 10 mgs), and atorvastatin (40 or 20 mgs) compared with the standard of care (usual care according to the local clinical practices at each participating country) in secondary prevention of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, and urgent revascularization). The **secondary objectives** are to evaluate a polypill strategy as compared with standard of care for secondary cardiovascular prevention after MI in an elderly population in: - reducing other clinical endpoints. - improving baseline adherence. - improving quality of life. - controlling cardiovascular risk factors. (LDL cholesterol, systolic and diastolic blood pressure). - Cost-effectiveness - safety and tolerability - patient satisfaction - performance across the different socioeconomic and health settings.
STUDY DESIGN	Multicenter, open-label, randomized, open-label, repeated-dose, adaptive parallel two arms trial.
STUDY POPULATION	**A total of N=2514 patients will participate in this study (n=1257 polypill group, n=1257 control group).** **Subjects will be recruited in seven European countries (**Spain, Italy, Germany, France, Hungary, Poland, and Czech Republic) Approximately 115 active sites (i.e, sites with SIV performed)
Main Selection Criteria Inclusion and Exclusion Criteria	**Inclusion Criteria** 1. Giving consent after information. 2. Patients diagnosed with a type 1 myocardial infarction within the previous 6 months. 3. Subjects must be ≥65 years old, presenting with **at least one** of the following additional conditions: i. Documented diabetes mellitus or previous treatment with oral hypoglycemic drugs or

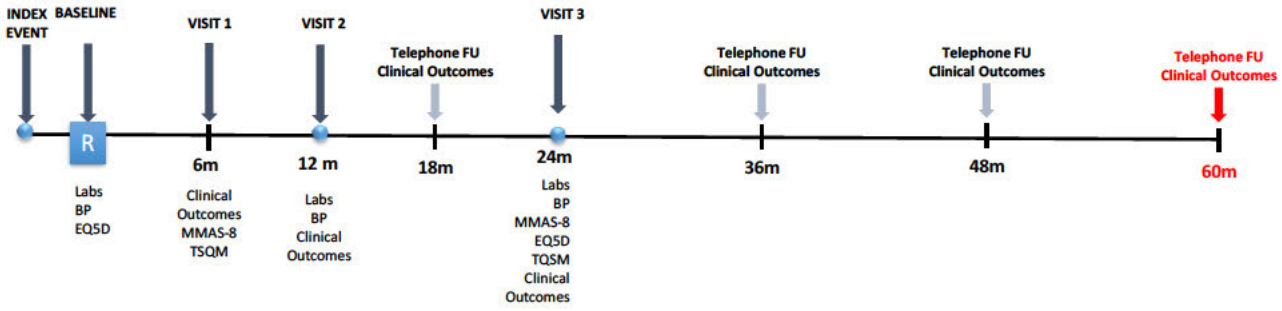
	insulin. ii. Mild to moderate renal dysfunction: creatinine clearance 60-30 mL/min/1.73 m^2. iii. Prior myocardial infarction: defined as an AMI occurring before the index event documented in a medical report. iv. Prior coronary revascularization: coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). v. Prior stroke: history of a documented stroke, defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue, not resulting in death. vi. Age ≥ 75 years.
	Exclusion Criteria 1. Unable to sign informed consent. 2. Inability to understand and comply with the protocol requirements and instructions. 3. Contraindications to any of the components of the polypill. 4. Living in a nursing home or committed to an institution by virtue of and order issued by the judicial or the administrative authorities. 5. Mental illness limiting the capacity of self-care. 6. Participating in another clinical trial. 7. Severe congestive heart failure (NYHA III-IV). 8. Severe renal disease (Creatinine Clearance (CrCl) <30ml/min/1.73 m^2). 9. Severe hepatic impairment. Liver cirrhosis transaminases exceeding 3 times the upper limit of the normal limit. 10. Allergies to lactose, peanut, or soy. 11. Need for oral anticoagulation at the time of randomization or planned in the future months. 12. Any condition limiting life expectancy <2 years, including but not limited to active malignancy. 13. Significant arrhythmias (including unresolved ventricular arrhythmias or atrial fibrillation). 14. Scheduled coronary revascularization (patients can be randomized after final revascularization is completed within the pre-specified timeframe). 15. Do not agree to the filing, forwarding and use of his/ her pseudonymised data. 16. Individuals dependent from the sponsor, investigator or investigational site/institution.
INVESTIGATIONAL PRODUCT Formulation(s):	**INTERVENTION ARM** Patients randomized to Cardiovascular Combination Pill AAR arm will receive one of the following treatments:

Route(s) of administration: Dose Regimen:	**<u>Cardiovascular Combination Polypill AAR 40</u>** ASA 100 mg, Atorvastatin 40 mg, Ramipril 2.5mg ASA 100 mg, Atorvastatin 40 mg, Ramipril 5 mg ASA 100 mg, Atorvastatin 40 mg, Ramipril 10 mg If considered necessary and per investigators' judgment, the Cardiovascular Combination Polypill AAR 40 may be switched to Cardiovascular Combination Polypill AAR 20 (Atorvastatin 20 mg, ASA 100mg and Ramipril 2.5, 5 or 10 mg) Oral **Intervention Arm:** once daily administration of one capsule (Cardiovascular Combination Polypill AAR). **Usual Care**: Standard of care for secondary prevention will be carried out according to current ESC clinical guidelines.
STUDY PROCEDURES AND TREATMENT:	Once the inclusion and exclusion criteria are confirmed, written consent will be obtained and patients will be included in the study. All patients will be assigned a unique study ID number. Randomization will occur within 6 months of the index event (AMI) in a 1:1 ratio to one of the two arms: • Cardiovascular Combination Polypill AAR 40 • Usual care Patients randomized to the Cardiovascular Combination Polypill AAR arm will begin treatment within 6 months of the index event at the discretion of the physician. There will be 3 follow-up visits at month 6, 12 and 24 and 3 telephone follow-up at month 18, 36 and 48.
STUDY DURATION PER PATIENT	Patients will be followed up for a minimum of 2 years and a maximum of 4 years.
SAMPLE SIZE ESTIMATION AND INTERIM ANALYSIS	The sample size of 2514 patients, with an accrual period of three years and a minimum follow-up of two years. Based on these assumptions and a primary event rate of 7.7% per year over a median 3.8 years follow-up and an estimated loss to follow-up of 1%, 2514 patients will provide 78% power to demonstrate a relative risk reduction of 21% with a two-sided alpha of 0.05 A total of 1257 will be assigned to each treatment arm. Non-inferiority will be tested first with the pre-specified non-inferiority margin of HR = 1.373. If the non-inferiority hypothesis is confirmed, superiority testing will be conducted

	Adaptive design: An unblinded interim analysis will be performed in order to check if the initial assumptions for sample size calculations (estimated event rate) are met with a possibility of the increase in the sample size and/or a long-term follow up to.
EVALUATION CRITERIA	**Primary Endpoint** The incidence of the first occurrence of any component of the following composite endpoint, as adjudicated by the Clinical Events Committee: • Cardiovascular death. • Any nonfatal type 1 myocardial infarction. • Any nonfatal ischemic stroke. • Any urgent coronary revascularization not resulting in death. **Secondary Endpoints** 1. Efficacy endpoints a. The first occurrence of any component of the following composite endpoint: CV death, MI type 1, stroke. b. The first occurrence of the individual components of the primary endpoint • CV death. • Nonfatal type 1 myocardial infarction. • Nonfatal ischemic stroke. • Urgent coronary revascularization. c. Improvement in treatment adherence at 2 years, as measured by Morisky Medication Adherence Scale (MMAS-8). d. Change of risk factor control at 2 years • LDL-cholesterol level. • SBP. • DBP. e. Cost effectiveness of the polypill strategy. f. Performance of the polypill strategy across different socioeconomic and health settings. g. Treatment Satisfaction. 2. Safety endpoints a. All-cause mortality. b. Adverse Events i. Bleeding ii. Renal dysfunction. iii. Drug allergic reaction. iv. Refractory cough leading to drug discontinuation. c. Drug Discontinuation.
EVENT REPORTING	Study endpoints should be reported after collecting all relevant clinical information (medical records, death certificate, imaging techniques, etc.) in order to adjudicate clinical events.

1 VISITING SCHEMA

1.1 Visiting Schema



Patients enrolled during years 1 and 2 of the study will be followed up by telephone to ascertain events at years 3, 4 and year 5.

1.2 Study Flow chart

Assessments[1]	Study Visits							
	Screening and baseline	**Visit 1 (6m ± 2 w)**	**Visit 2 (12m ± 2 w)**	**Phone 1 (18m ± 2 w)**	**V3 (24m ± 2 w)**	**Phone 2 (36m ± 4 w)**	**Phone 3 (48m ± 4 w)**	**Phone 4 (60m ± 4 w)**
Informed Consent	x							
Inclusion/exclusion criteria	x							
Randomization (R)	x							
Demographic data	x							
Medical history	x							
Physical examination including body weight	x							
Vital signs and blood pressure[2]	x	x	x		x			
Previous/concomitant medications	x	x	x	x	x	x	x	x
Non-fasting blood analysis	x		x		x			
Adherence		x			x			
Quality of Life	x				x			
TSQM		x			x			
Resources Utilization		x	x		x			
Outcomes		x	x	x	x	x	x	x
Adverse Event Reporting		←						→

[1] Medication supply will be done every 3-6 months.

[2] Blood pressure and heart rate, a mean of two readings after 5 min sitting rest.

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2 LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ADR	Adverse Drug Reaction
AEs	Adverse Events
ACEI	Angiotensin Converting Enzyme Inhibitors
AMI	Acute Myocardial Infarction
ARBs	Angiotensin II Receptor Blockers
ASA	Acetylsalicylic acid
BP	Blood Pressure
CA	Consortium Agreement
CAD	Coronary Artery Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
CHD	Coronary Heart Disease
CNIC	Centro Nacional de Investigaciones Cardiovasculares
CTA	Clinical Trial Application
CTU	Clinical Trial Units
CAD	Coronary Artery Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EMA	European Medicines Agency
ESC	European Society of Cardiology
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EC	Ethics Committee
EU	European Union
EUROASPIRE III	European Action on Secondary Prevention through Intervention to Reduce Events
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FRS	Framingham Risk Score
GA	General Assembly
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
ICER	Incremental cost-effectiveness ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Intellectual Property
IPR	Intellectual Property Rights
LDL-C	Low-Density Lipoprotein Cholesterol
LMIC	Low and Middle Income Countries
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
MAQ	Morisky-Green Questionnaire
MMAS-8	Eight Item Morisky Medication Adherence Scale

NCA	National Competent Authorities
PGEU	Pharmaceutical Group of the European Union
PURE	Prospective Urban Rural Epidemiology
QALY	Quality-Adjusted Life Year
RCT	Randomized Clinical Trial
SAEs	Serious AEs
SBP	Systolic blood pressure
SADR	Serious Adverse Drug Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
USA	United States of America
WHO	World Health Organization

3 INTRODUCTION

3.1 Background Information

Cardiovascular disease (CVD) has become the number one cause of death among men and women aged over 65 in Europe[1], and the magnitude of the burden of CVD is expected to grow in parallel with the projected aging population.[2] Moreover, the overall ageing of the European population (projected to almost double by 2060 – rising from 85 million in 2008 to 151 million in 2060 in the EU)[2] and improving survival of patients with Coronary Heart Disease (CHD) has created a large population of older adults eligible for secondary prevention.

There is ample evidence on the massive treatment gap and room for improvement in secondary prevention. The European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE III) demonstrated that 54% of patients with a previous myocardial infarction (MI) had not achieved target blood pressure (BP) levels and 51% of patients had not achieved target low-density lipoprotein cholesterol (LDL-C) levels.[3]

On a global scale, the scenario is even more worrisome and wide variations in the use of cardio protective drug therapies exist among countries. Data from the Prospective Urban Rural Epidemiology (PURE) study showed that among participants with a history of CHD or stroke, only 25% were taking antiplatelet drugs, 17% were taking beta blockers, 20% were taking angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) and 15% were taking statins 5 years after their event.[4] In low and middle income countries (LMIC) within the same study, the use of these drugs was as low as 3%.

Despite ground-breaking advances in therapeutic interventions, rates of CVD mortality remain high mainly because patients are not following ideal medical management. The administration of guideline recommended CV medications (i.e.: statins, antihypertensive, and antithrombotic agents) remains the most common medical intervention for secondary prevention of CVD. It has been estimated that these medications alone might be responsible for half of the overall 50% reduction in mortality from coronary artery disease (CAD) observed over the past 20 years in some western countries.[1]

However, the efficacy of guideline recommended treatment is seriously hampered mainly due to non-adherence. Multiple registries have shown that CV treatments are nearly universally prescribed at discharge after a coronary event, shifting the focus from the prescribers adhering to clinical guidelines onto the multiple factors that impede adherence to medications by the patients. It is estimated that 20% to 30% of patients do not adhere to medication regimens that are curative or relieve symptoms, and 30% to 40% fail to follow regimens designed to prevent health problems. When long-term medication is prescribed, 50% of patients fail to adhere to the prescribed regimen. Unfortunately, and despite the established efficacy of CV medications, adherence in patients taking these medications for prevention of CVD has been estimated at only 57% in a recent meta-analysis of almost 400,000 patients.[5]

Suboptimal adherence reduces the effectiveness of these essential medications and is the primary reason for suboptimal clinical benefit, contributing significantly to worsening of diseases and deaths at the population level.[6] Absolute and relative risk assessments demonstrate that a considerable proportion of all CVD events (~9% in Europe) could be attributed to poor adherence to vascular medications alone.[7] Furthermore, medication non-adherence carries a huge medical and economic burden. According to the Pharmaceutical Group of the European Union (PGEU), it has been estimated that there are 194,500 deaths a year in the EU due to miss-dose and non-adherence to prescribed medication, resulting in an estimated cost of 125 billion € annually.[8] The issue is particularly relevant in wealthier nations, where access to and use of healthcare systems are high, and where further increasing the effectiveness of a medication could rely largely on improving adherence levels.

Non adherence is a complex phenomenon and barriers to adherence include factors related to the patient, the prescriber, and the health care system.[6] Certain characteristics inherent to the elderly population (such as treatment complexity, polypharmacy, poor accessibility to medical care and lack of treatment affordability) render this population especially vulnerable to CVD and preclude adequate CV prevention. Although medication non adherence in the elderly is not well described in the literature, increased frequency of dosing and treatment complexity have repeatedly been shown to decrease adherence.[6] Therefore, a better understanding of the burden of non-adherence to CV medication in the elderly, where evidence is incomplete, as well as developing and scaling up interventions to improve levels of adherence in this population, seem reasonable in order to have a societal, economic and health impact.

Ratified estimates of non-adherence in the older-aged with chronic conditions vary from 40% to 75%.[9] Non-adherence to medication regimens in the older-aged, regardless of disease state, is a common cause of residential care and hospital admissions. Eleven percent of hospital admissions in the ≥65-year age group are the result of non-adherence, and this increases to 26% in the ≥75-year age group. An even greater percentage (33%) of the older-aged undergoing hospitalization has a history of non-adherence.[9]

In addition to hospitalizations, re-hospitalizations and residential care admissions resulting from non-adherence in the older-aged are responsible for direct costs to society. In many cases, it seems likely that improvements in health outcomes and/or savings in healthcare utilization will repay the costs of improving adherence.

One of the barriers to adherence that has been consistently shown in registries, studies and trials is the number of pills and treatment complexity.[10, 11] In this aspect, the last decade has seen a surge of technical innovation in order to propose a polypill strategy to effectively improve adherence at the same time that it serves as a therapeutic vehicle to improve accessibility in LMIC.[12]

Recently a large body of data regarding the effects of the polypill on adherence has been published. Three important randomized clinical trials have recently tested the effect of such an approach of adherence, showing spectacular results. Kanyini GAP,[13] IMPACT[14] and UMPIRE[15] found relative risks of being adherent on the polypill compared to usual care of 1.49 (95% CI; 1.30-1.72; p<0.001); 1.75 (95% CI; 1.52-2.03; p<0.001); and 1.33 (95% CI; 1.26-1.41; p<0.001) respectively.

Beyond the results of these studies, the FOCUS (Fixed-dose Combination Drug for Secondary Cardiovascular Prevention) study, funded under the Seventh Framework Programme, has tried to answer the fundamental question of which factors impede adequate adherence to CV drugs in secondary prevention, as well as carrying out a RCT to study the impact of a polypill on adherence (measured through direct, pill count, as well as indirect self-reported methods) in a post MI population.[16] The study consisted of a cross-sectional study (Phase 1) aimed to elucidate factors that interfere with appropriate adherence to CV medications for secondary prevention after an AMI. Additionally, 695 patients from phase 1 were randomized into a controlled clinical trial (Phase 2) to test the effect of a polypill (containing aspirin 100 mg, simvastatin 40mg and ramipril 2.5, 5 or 10 mg) compared to the three drugs given separately on adherence, blood pressure (BP) and low density lipoprotein cholesterol (LDL-C), as well as safety and tolerability over a period of 9 months of follow-up. In phase 1, a 5-country cohort (Argentina, Brazil, Italy, Paraguay, and Spain) of 2118 patients was analyzed. Patients were randomized to either the polypill or the three drugs separately for phase 2. Primary end-point was adherence to the treatment measured at the final visit by the self-reported Morisky-Green questionnaire (MAQ) and pill count (patients had to meet both criteria for adherence at the in-person visit in order to be considered adherent).

In phase 1, overall CV medication adherence defined as a MAQ score of 20 was 45.5%. In a multivariable regression model, the risk of being non-adherent (MAQ<20) was associated with younger age, depression, being on a complex medication regimen, poorer health insurance coverage, and a lower level of social support, with consistent findings across countries.

In Phase 2, the polypill group showed improved adherence compared to the group receiving separate medications after 9 months follow up: 50.8% vs 41% (p=0.019; intention-to-treat population) and 65.7% vs 55.7% (p=0.012; per protocol population) when using the primary endpoint, attending the final visit with MAQ=20 and high pill count (80-110%) combined, to assess adherence. Adherence was also higher in the FDC group when measured by MAQ alone (68% vs. 59%, p=0.049). No treatment difference was found at follow-up in mean SBP (129.6 vs 128.6 mmHg), mean LDL-C levels (89.9 vs 91.7 mg/dL), serious adverse events (23 [6.6%] vs. 21 [6%]) or death (1, 0.2% in each group).
The collective data from these four Randomized Clinical Trials (RCTs) has consistently shown a significant benefit of the polypill on the adherence of CV medications.

3.2 Rationale

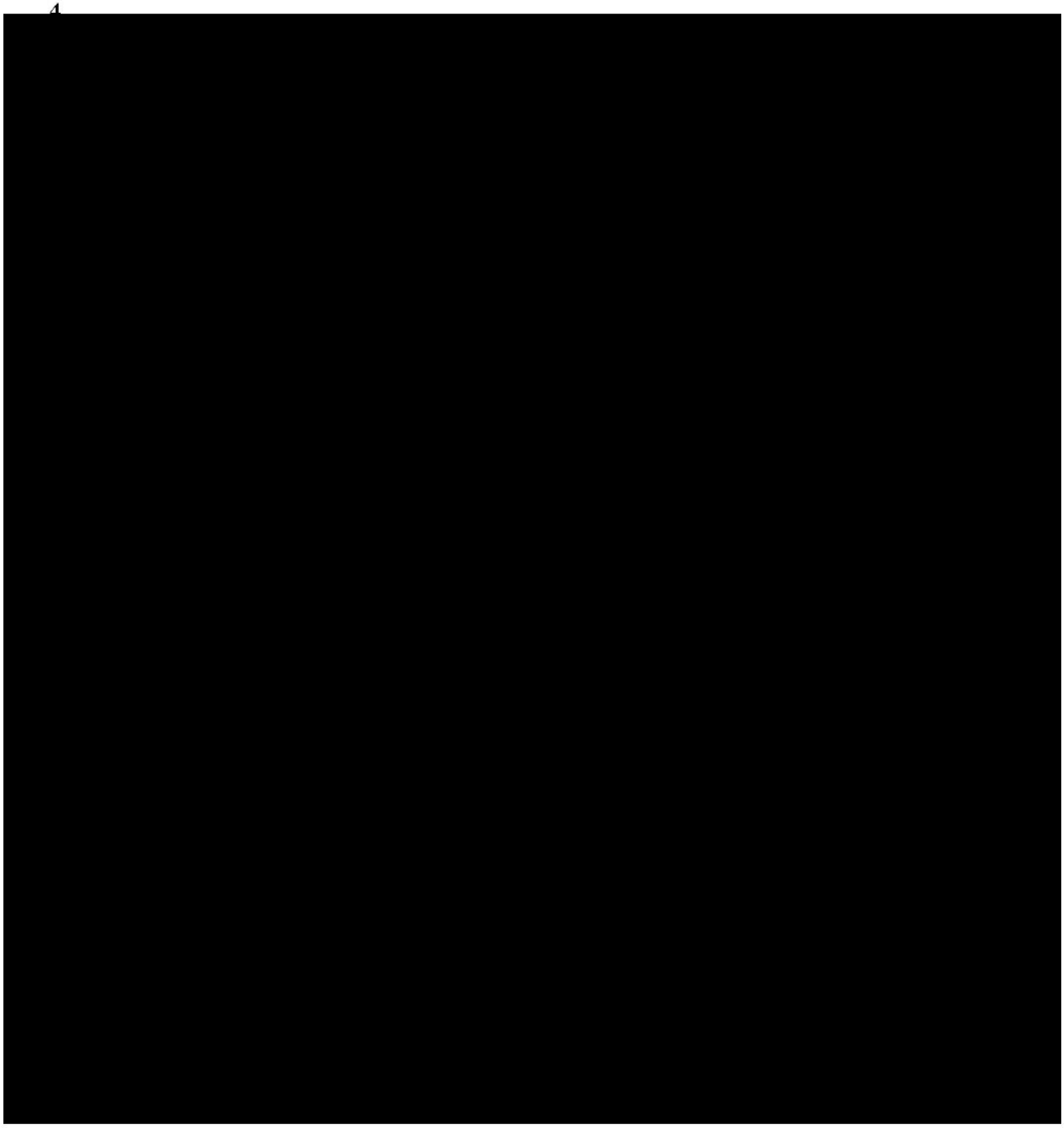
Together with the rising costs of treating CVD, this complex problem calls for the use of innovative, simple and cost-effective interventions that will diminish the burden of CVD. In this complex setting, the polypill concept appears as an attractive and novel idea that can significantly improve CV prevention by lowering costs and improving patient adherence to treatment.[17] Moreover, improved adherence has been consistently shown to decrease MACE and improve survival.[18]
Strategies addressing the issue of poor adherence and simplify treatment regimens but still provide the required interventions, such as the polypill, should improve elderly patients' management and adherence, and ultimately improve outcomes. To date, however, **no large RCT has been conducted to study the impact of a polypill strategy on outcomes for secondary CV prevention**. This is a crucial piece of information that is currently lacking, and is needed, in order to prove such a strategy to be effective.

3.3 Hypothesis

The use of a polypill strategy including three components with proven efficacy as well as demonstrated positive impact on adherence will reduce major cardiovascular events in patients with myocardial infarction (MI) by reducing treatment complexity, lack of adherence and achieving better risk factor control, reducing the risk of recurrent disease and death in elderly patients with CVD, and thereby reducing the burden of CVD in Europe.

In addition to the key question about clinical efficacy, a RCT comparing a polypill with standard of care in Europe should also allow to gather information on health and economic outcomes in different European countries and compare differences in the efficacy of a polypill strategy between Eastern and Western European countries.

4



5 STUDY OBJECTIVES

SECURE will test the efficacy of a polypill containing aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (40mg or 20mg), for secondary cardiovascular prevention in the elderly patients (≥65 years old) with a recent (within 6 months) myocardial infarction (MI).

5.1 Primary Objective

The primary objective of the SECURE study is to evaluate the efficacy of a polypill strategy containing aspirin (100 mg), ramipril (2.5, 5 or 10 mgs), and atorvastatin (40 or 20 mgs) compared with the standard of care (individual drugs with ad-hoc dosages) in secondary prevention of major cardiovascular events as defined by composite endpoint including:

- Cardiovascular death.
- Nonfatal myocardial infarction.
- Nonfatal ischemic stroke.
- Urgent coronary revascularization not leading to death.

5.2 Secondary Objectives

The **secondary objectives** of the study are:

- To evaluate all-cause mortality in both treatment arms.
- To evaluate whether a polypill strategy is effective in improving baseline adherence.
- To evaluate whether a polypill strategy is effective in improving baseline quality of life.
- To evaluate whether a polypill strategy is effective in controlling cardiovascular risk factors. (LDL cholesterol and systolic and diastolic blood pressure).
- To evaluate the costs and effectiveness of a polypill strategy vs standard therapy in the elderly population.
- To evaluate the performance of the polypill strategy in the elderly population across the different socioeconomic and health settings.
- To evaluate the safety and tolerability of the polypill strategy and the safety and tolerability of drugs prescribed in the usual care arm.
- To evaluate patient satisfaction on taking the polypill.

6 STUDY DESIGN

6.1 Description of Study Design

SECURE is a multicenter, prospective, randomized, open-label, repeated-dose, parallel two arms study comparing the efficacy of a polypill strategy with the standard of care (usual care according to the local clinical practices at each participating country) in secondary prevention of major cardiovascular events in elderly patients with a recent MI.

A total number of 2514 patients will be randomized (1:1) to treatment arms. Patients will be recruited across seven countries in Europe (Spain, Italy, Germany, France, Hungary, Poland, and Czech Republic).

Patients will be ≥65 years old and diagnosed with a type 1 myocardial infarction within 6 months prior to study enrolment.

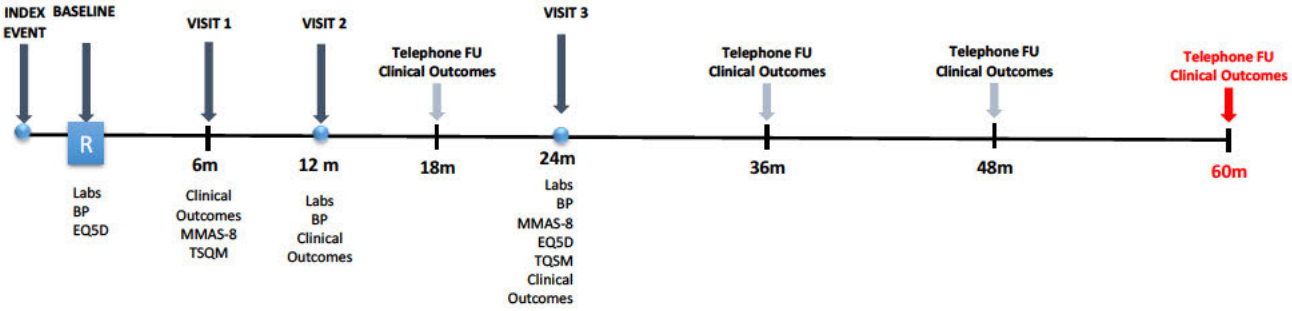
Once the inclusion and exclusion criteria are confirmed, patients will be included in the study after signing informed consent.

Randomization will take place within 6 months of the index event (AMI type I) in a 1:1 ratio to one of the two arms:

- Cardiovascular Combination Pill AAR
- Usual care

Patients randomized to the Cardiovascular Combination Pill AAR arm will begin the treatment within 6 months of the index event (AMI type I) at the discretion of the physician.
Patients will be followed up for a minimum of 2 years and a maximum of 4 years.
There will be 3 follow up visits at month 6, 12 and 24 and telephone follow up calls at month 18, 36, 48 and 60. (Figure 1)

Figure 1. Study Outline



R: Randomization

6.2 Study Design

SECURE is a multicenter, prospective, randomized, open-label, repeated-dose, adaptive parallel two arms study, which is considered adequate to compare both strategies.

6.3 Duration of Study Participation

The duration of the follow up of minimum of 2 years and a maximum of 5 years has been chosen to achieve the number of events needed. However, it will be decided after the interim analysis if the adaptive increase and/ or a prolongation of the follow up in the sample size are necessary in case the initial assumptions are not met.

6.4 Interim Analysis

An interim analysis will be performed when data of approximately 75% of patients are available (final visit) in order to check if the initial assumptions for sample size calculations (estimated event rate) are met with a possibility of the increase in the sample size and/or a long-term follow up to.

7 PATIENT SELECTION/ENROLLMENT

7.1 Number of Patients

A total of 2514 patients will be randomized (1257 patients per study arm).

7.2 Patient Screening

Patients can be screened at any time within the first 6 months after index event (type 1 myocardial infarction) whenever they are clinically stable and ready to receive secondary prevention therapy, including the hospital phase. Patients with ventricular arrhythmias needing further evaluation of therapy or patients with atrial fibrillation should not be randomized. Patients scheduled for coronary revascularization (either PCI or CABG) cannot be randomized until the procedure is being performed provided that this happens within the first 6 months of index event.

7.3 Inclusion Criteria

To be eligible to enter the study candidates must satisfy all of the following criteria:

1. Giving consent after information.
2. Patients diagnosed with **type 1 myocardial infarction within the previous 6 months**.
3. Subjects must be ≥65 years old, presenting with **at least one** of the following additional conditions:
   a. Documented diabetes mellitus or previous treatment with oral hypoglycemic drugs or insulin.
   b. Mild to moderate renal dysfunction: defined as creatinine clearance (CrCl) 60-30 mL/min/1.73 m^2.
   c. Prior myocardial infarction: defined as a myocardial infarction occurring before the index event reported in a medical record.
   d. Prior coronary revascularization: patients have previously undergone coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).
   Prior stroke: patients have previously suffered a stroke occurring before the index event reported in a medical record.
   e. Age ≥ 75 years.

7.4 Exclusion Criteria

1. Unable to sign informed consent.
2. Inability to understand and comply with the protocol requirements and instructions.
3. Contraindications to any of the components of the polypill.
4. Living in a nursing home or committed to an institution by virtue of and order issued by the judicial or the administrative authorities.
5. Mental illness limiting the capacity of self-care.
6. Participating in another clinical trial.
7. Severe congestive heart failure (NYHA III-IV).
8. Severe renal disease (creatinine clearance (CrCl) < 30ml/min/1.73 m^2).
9. Severe hepatic impairment, liver cirrhosis transaminases exceeding 3 times the upper limit of the normal limit.
10. Allergies to lactose, peanut or soy.
11. Need for oral anticoagulation at the time of randomization or planned in the future months.
12. Any condition limiting life expectancy < 2 years, including but not limited to active malignancy.
13. Significant arrhythmias (including unresolved ventricular arrhythmias or atrial fibrillation) leading to hemodynamic instability.

14. Scheduled coronary revascularization (patients can be randomized after final revascularization is completed within the pre-specified timeframe).
15. Do not agree to the filing, forwarding and use of his/ her pseudonymised data
16. Individuals dependent from the sponsor, investigator or investigational site/institution.

Patients fulfilling inclusion criteria and not presenting with any of the exclusion criteria at time of trial screening will be invited to participate in the SECURE clinical trial.

Please refer to section 8.1.2 for further details on contraindications to the components of the cardiovascular combination polypill.

7.5 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from the patient. A Patient Information Sheet (PIS) will be provided to facilitate this process. Investigators must adequately explain the aim, trial treatment, anticipated benefits and potential risks of taking part in the trial to the participant. The investigator should also emphasize that the patient is completely free to refuse to take part or withdraw from the trial at any time. Time should be given for patient to read the Information Sheet and ask questions, which should be answered to patient satisfaction. Once patient express continued interest in participating in the trial, patient will be asked to sign and date the latest version of the Informed Consent Form (ICF). The Investigator will also sign and date the ICF. A copy of the ICF will be provided to the patient, another copy of the ICF will be filed in the hospital notes (if applicable), and the original placed in the Investigator Site File (ISF).

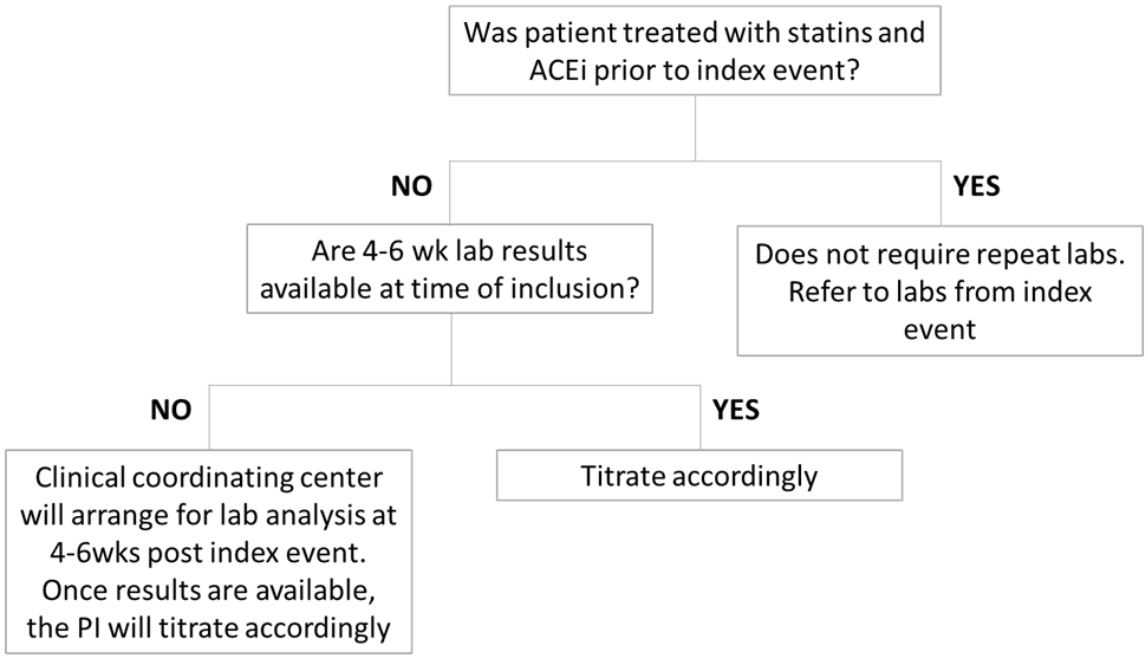
7.6 Randomization

After signing the informed consent form (ICF), patients will be randomized (1:1) stratified by center to Cardiovascular combination pill AAR or standard therapy for cardiovascular prevention within 6 months of the index event (AMI type I). A centralized online system will be used to generate randomization.

7.7 Post Randomization Safety Assessment

In order to maximize monitoring adverse effects of therapy and to comply with current guidelines, a 4-6 week laboratory analysis (for safety and efficacy of statins and ACEI) will be performed. It is expected that a large proportion of patients will already be on chronic statin and ACEI treatment prior to the index event and may therefore not need further analysis at 4-6 weeks to check for efficacy or safety. Alternatively, for those patients requiring close monitoring due to initiation of statins and/or ACE (i.e. naïve patients), patients may be enrolled either before the 4-6 weeks lab analysis or after. For patients being enrolled after the 4-6 week analysis, the PIs will titrate statins and ACEI according to CPK, LFTs, creatinine clearance, ionogram and cholesterol levels. For patients enrolled before the analysis, each clinical coordinating center will coordinate lab analysis 4-6 week post event period (to be carried out either by GP or in hospital following standard follow up procedure for each center) to ensure patients undergo analysis. Once lab results are available, titrate accordingly.

The following algorithm describes the monitoring of patients in the subacute phase:



If the 4-6 week lab results indicate patient will not tolerate treatment, IMP will be discontinued, but patient follow-up will be continued as planned. For patients in the SOC, allowed medication and follow-up will be continued.

This lab assessment is mandatory. If lab assessment is not carried out, further assessment of the Sponsor will be required, which may result in patient withdrawal from the study.

7.8 Withdrawal of Patients

7.8.1 Withdrawal of Consent

Patients are free to withdraw from the study at any time without providing reason for withdrawal and with the assurance that their decision will not influence ensuing medical care. Patient withdrawal should be documented in writing in the electronic case report form (eCRF) and if available, reason for withdrawal should be documented in the electronic case report form (eCRF).

Patients withdrawing from the study will be encouraged to continue follow-up and appropriately complete the evaluations as patients completing the study according to the protocol, particularly efficacy and safety endpoints (see Annex 14: Withdrawal of Consent Checklist). Reasonable efforts will be made to contact patients who are lost to follow-up.

Although patients may withdraw from the study drug or study at any time and for any reason, patient withdrawal should be avoided as much as possible.

7.8.2 Trial Discontinuation

Please refer to Section “7.12 Criteria for Discontinuation of the Trial”

7.8.3 Investigator’s request

Patients who withdraw or are withdrawn from the study or study treatment will not be replaced.

7.9 Lost to Follow-up

In case a subject fails to come to scheduled follow-up visits, every reasonable effort will be made to contact the subject to determine (A) the endpoint status; (B) reason for discontinuation; and (C) vital status, as local law permits. A subject will be considered lost to follow-up only after patient has not been confirmed alive or dead in more than 18 means AND all means of all subsequent contact have been exhausted.

7.10 Discontinuation of Study Treatment

The study medication AAR 20 and AAR40 contain standard medical compounds that are part of the regular state of the art treatment regimen of the respective patients. Therefore, any discontinuation of the study medication may occur only if one of its components should be discontinued according to the clinical condition of the patients and in accordance with state of the art medical therapy standards. This decision for discontinuation has to be made by the study physician in accordance with state of the art clinical treatment recommendations.

All drug discontinuations have to be reported in the electronic Case Report Form (eCRF), together with time and reasons for discontinuation. Drug discontinuation will be classified as either (A) Temporary or (B) Permanent, refer to section 7.10.1 and 7.10.2 respectively.

If a subject's treatment has been interrupted for more than 14 days due to toxicity or to reasons other than toxicity (unplanned travel or vacation, or lack of transportation to the site), the Investigator must review the subject's condition in order to restart the treatment.

All randomized patients must be followed up according to the study flowchart until study end date or death, regardless of whether they discontinued study drug prematurely or not. Unless patient decides to withdraw consent and not take further participation in the study.

7.10.1 Temporary Discontinuation of Cardiovascular Combination Polypill AAR

7.10.1.1 Temporary Discontinuation Definition

- Brief Temporary Discontinuation of polypill is defined as a period of 1 to 5 days.
- Temporary Discontinuation of polypill is defined as a period of 6 to 30 days.

For patients allocated to the intervention group (AAR), during the Temporary Discontinuation of the study drug, if applicable and safe, patients will be given the separate components (ASA, statin, and Ace-I) until intervention drug can be resumed.

After brief temporary and temporary discontinuation, patients can continue treatment with Cardiovascular Combination Polypill AAR, if investigator considers to be safe to do so.

7.10.1.2 Temporary Discontinuation Criteria

Study drug should be temporarily discontinued if subject:

1. Undergoes PCI, CABG, or any other surgical procedure or medical condition that may require temporary interruption of study drug, or use of prohibited therapy due to bleeding risk.
2. Experiences a significant bleeding event.
3. Presents any serious adverse event possibly related or exacerbated by study drug administration

4. Requires a therapy on a temporary basis that may react or is contraindicated with study drug

7.10.2 Permanent Discontinuation

7.10.2.1 Permanent Discontinuation Definition

Permanent Discontinuation of polypill is defined as any period longer than 30 days will be considered permanent discontinuation. Patients will be followed up according to regular protocol until the end of the follow up period.

7.10.2.2 Permanent Discontinuation Criteria

Study drug should be permanently discontinued for the following reasons:

1. Patient Safety:
    a. If labs indicate treatment is not safe for patient
        - Creatinine Clearance < 30 ml/ min/ 1.73m²;
        - ALT/AST >3x the laboratory upper normal limit
        - Creatine Kinase (CK) ≥ 10x the laboratory upper normal limit

    b. Occurrence of SUSARs or SAEs not compatible with the continuation of patient participation in the study treatment, in the investigator's opinion, which may include but are not limited to:
        - Results in death.
        - Is life-threatening.
        - Requires inpatient hospitalization or prolongs existing hospitalization.
        - Results in persistent or significant disability or incapacity.
        - Is a congenital anomaly or birth defect.
        - Is any other medically important event that may jeopardize the patient's well-being or may require intervention to prevent one of the other above outcomes.

    c. Adverse Drug Reaction: if patient presents an adverse reaction that given its seriousness or nature, justifies study discontinuation. To minimize the risk of adverse reaction, the study protocol includes a substantial list of medical conditions that contraindicate treatment with the IMP (section 8.1.2). Furthermore, the clinical protocol includes adverse effects that have been described by the manufacturer of the individual components of the IMP.

    d. Drug allergic reaction

    e. Bleeding greater or equal to type 2 according to Bleeding Academic Research Consortium Definition for Bleeding (Annex 5)

2. Subject requests to discontinue study drug permanently.

The study investigator will document reason for study discontinuation in the eCRF. Patients permanently discontinued from study drug treatment should be treated with guideline-directed medical therapy in accordance with ESC guidelines.

7.11 Patient Follow up After Site Closure.

In the event of site closure due to low recruitment, if applicable and allowed by regulatory authorities, the follow-up of randomized patients from that site might be transferred to nearby participating sites in order to avoid patient lost to follow-up.

7.12 End of Trial Definition

End of trial is defined as the last visit of the last patient, which will take place on October 30th 2019.

7.13 Criteria for Discontinuation of the Trial

The Data and Safety Monitoring Board (DSMB) may recommend stopping for reasons of safety, if there is excess mortality in the polypill arm with $p<0.01$. At the main interim analysis, the DSMB may recommend stopping for efficacy if the primary event rate is lower in the polypill arm with $p<0.001$.

In making any recommendation, the DSMB will weigh up the totality of the evidence for both efficacy and harm.

If persistently low recruitment, poor protocol adherence, low event rates or other problems with the conduct of the trial are likely to limit its ability to provide a clear answer to the primary research question, then consideration will be given to terminate the trial early. Such a decision will only be made once all measures to improve the limiting problems have been exhausted.

Early termination of the trial will take place in the following instances:

- The primary endpoint is reached during interim analysis
- Due to safety issues.
- If persistent low recruitment, poor protocol adherence, low event rates or other problems with the conduct of the trial that are likely to limit its ability to provide a clear answer to the primary research question. Decision based on these criteria will only be made after all measures to improve the limiting problems are exhausted.

8 TREATMENTS

8.1 Identity of Investigational Medicinal Products (IMPs)

8.1.1 Formulation

The Cardiovascular Combination Polypill AAR 40 contains 100 mg acetylsalicylic acid, 40 mg atorvastatin, and 2.5, 5 or 10 mg ramipril.

Cardiovascular Combination Polypill AAR 20 contains 100 mg acetylsalicylic acid, 20 mg atorvastatin, and 2.5, 5 or 10 mg ramipril.

8.1.2 Contraindications to IMP

- Hypersensitivity to the active substances, to any of the excipients, to other salicylates, to nonsteroidal anti-inflammatory drugs (NSAIDs), to any other ACE (Angiotensin Converting Enzyme) inhibitors or to tartrazine.
- Hypersensitity to soya or peanut.
- In case of history of previous asthma attacks or other allergic reactions to salicylic acid or other non-steroidal analgesics / anti-imflamatories.
- Acute gastric and enteric ulcers.

- Haemophilia and other bleeding disorders.
- Severe kidney and liver impairment.
- Patients in hemodialysis.
- Severe heart failure.
- Concomitant treatment with methotrexate at a dosage of 15 mg or more per week.
- Patients with nasal polyps associated to asthma induced or exacerbated by acetylsalicylic acid.
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- Due to the risk of rhabdomyolysis concomitant treatment with tipranavir or ritonavir.
- Due to the risk of rhabdomyolysis concomitant treatment with ciclosporin.
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or Angiotensin II receptor antagonists (AIIRAs).
- Extracorporeal treatments leading to contact of blood with negatively charged.
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.
- Ramipril must not be used in patients with hypotensive or haemodinamically unstable states.
- Existing contraindication to Aliskiren containing products.

Acetylsalicylic Acid is a salicylate drug with the chemical name 2-ethanoylhydroxybenzoic acid.

The adverse effects of aspirin have been well studied and characterized. Gastrointestinal tract perforation, ulceration, and bleeding are adverse effects associated with long-term aspirin therapy. Because inhibition of prostaglandin synthesis is the common mechanism for both the beneficial thrombo-prophylactic effects and the adverse effects on the gastrointestinal tract, it is unlikely that the benefits can be achieved without some degree of risk.

The major risk of aspirin, as with other nonsteroidal anti-inflammatory drugs (NSAIDs), is bleeding. Although the antiplatelet effects of aspirin likely contribute to an increase in the risk of bleeding, as highlighted by an increased risk of hemorrhagic stroke of 0.2 events per 1000 patients-year[19], the majority of the increased risk of bleeding has a gastrointestinal tract etiology. A relationship between aspirin dosage and bleeding as well as chronic gastric ulcer has been demonstrated in clinical trials. Unfortunately, enteric-coated or buffered aspirin preparations do not appear to influence the risk of major bleeding in the upper gastrointestinal tract. In fact, no differences have been found in the frequency of gastrointestinal complications with the use of low doses of aspirin either as entericcoated or plain tablets.[20]

While gastrointestinal bleeding is increased with the use of aspirin, in the secondary prevention studies this outcome is rare, manageable, and does not use to cause deaths. Furthermore, the potential for this adverse outcome must be compared with the highly significant and clinically meaningful finding of a reduction in all-causes of mortality (the gold standard for drug effectiveness). This benefit, together with substantial and comparable reductions in nonfatal vascular events, leads to the conclusion that the benefit-to-risk ratio for aspirin in the secondary prevention of cardiovascular and cerebrovascular events is highly favourable.[21]

Acetylsalicylic Acid Contraindications
Hypersensitivity to salicylates or NSAIDs; hemophilia, bleeding ulcers, or hemorrhagic states.

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor with the chemical name (2S,3aS,6aS)-1[(S)-N-[(S)-1-Carboxy-3-phenylpropyl] alanyl] octahydrocyclopenta [b]pyrrole-2-carboxylic acid, 1-ethyl ester

The safety profile of ramipril appears to be consistent with that of other ACE-I. Adverse effects associated with these agents in clinical trial settings were generally mild and rarely required discontinuation of therapy. Known adverse effects include cough, hyperkalemia, renal dysfunction, and angioedema. Overall, ramipril has a good safety profile and is generally well tolerated.

Renal: Treatment with Ramipril may impair renal function and in isolated cases progression to acute renal failure may occur.

Allergic: Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of Ramipril. In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema, erythema multiforme), sometimes pronounced hair loss, exacerbation of perfusion disturbances due to vascular stenoses and precipitation or intensification of Raynaud's phenomenon. In isolated cases, pemphigus, exacerbation of psoriasis, psoriasiform and pemphigoid exanthema and enanthema, Stevens- Johnson syndrome, toxic epidermal necrolysis, hypersensitivity of the skin to light, and onycholysis have been observed.

Haematological reactions: Rarely, a mild - in isolated cases severe – reduction in the red blood cell count and haemoglobin content, white blood cell or blood platelet count may develop. In isolated cases, agranulocytosis, pancytopenia and bone marrow depression may occur. In isolated cases haemolytic anaemia may develop. Vasculitis, muscle and joint pains, fever, or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors. Respiratory tract: A dry tickling cough may occur. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm. Other adverse reactions: Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, uncommonly, disturbances of smell and taste or partial, sometimes complete loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

Laboratory test findings: Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pre-treated with a diuretic. Pre-existing proteinuria may deteriorate (though ACE inhibitors usually reduce proteinuria), or there may be an increase in urinary output.

Ramipril Contraindications

Ramipril capsules are contraindicated in patients who are hypersensitive to this product or any other ACE inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

Atorvastatin is a completely synthetic hypolipidemic drug belonging to the class of pharmaceuticals named statins. Atorvastatin has the chemical name [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1Hpyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate.

Atorvastatin Side Effects

Most common adverse reactions in patients treated with Atorvastatin that led to treatment discontinuation and occurred at a greater rate than placebo were in data from RCT were:

- Myalgia (0.7%)
- Diarrhea (0.5%)
- Nausea (0.4%)
- Alanine aminotransferase increase (0.4%)
- Hepatic enzyme increase (0.4%).

Extensive data are available on the safety of atorvastatin from randomized clinical trials, postmarketing analyses and reports to regulatory agencies. Atorvastatin is generally well tolerated across the range of therapeutic dosages, with the exception of a slightly higher rate of liver enzyme elevations with atorvastatin 80 mg/day which does not appear to confer an increased risk of clinically important adverse events. Atorvastatin is associated with a low incidence of muscular toxicity. It is not associated with neurological, cognitive or renal adverse effects and does not require dosage adjustment in patients with renal dysfunction, due to its favourable pharmacokinetic profile.

In **patients aged ≥65 years**, atorvastatin is well tolerated with no dose-dependent increase in adverse events up to the maximum daily dosage of 80 mg/day. Thus, atorvastatin is a safe and well tolerated statin for use in a wide range of patients. The following adverse events are described (extracted from the respective SmPC).

Skeletal Muscle: Myopathy is the most concerning adverse effect of statins. The most common symptom of statin myotoxicity is myalgia (muscle pain, weakness or cramps) with normal creatine phosphokinase (CK) levels. Fortunately, myopathy and rhabdomyolysis are very rare with monotherapy. The risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis. There have been rare reports of immunemediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use.

IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Liver Dysfunction: Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received LIPITOR in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

Endocrine Function: Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin. Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Other adverse reactions reported in placebo-controlled studies include:

Body as a whole: malaise, pyrexia;

Digestive system: abdominal discomfort, eructation, flatulence, hepatitis, cholestasis;

Musculoskeletal system: musculoskeletal pain, muscle fatigue, neck pain, joint swelling;

Metabolic and nutritional system: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia;

Nervous system: nightmare;

Respiratory system: epistaxis;

Skin and appendages: urticaria;

Special senses: vision blurred, tinnitus; Urogenital system: white blood cells urine positive.The adverse events of atorvastatin are summarized below (extracted from the correspondingSmPC):

Common side effects (affects 1 to 10 users in 100) include:inflammation of the nasal passages, pain in the throat, nose bleed allergic reactions increases in blood sugar levels (if you have diabetes continue careful monitoring of your bloodsugar levels), increase in blood creatine kinase headache nausea, constipation, wind, indigestion, diarrhea joint pain, muscle pain and back pain blood test results that show your liver function can become abnormal

Uncommon side effects (affects 1 to 10 users in 1000) include: anorexia (loss of appetite), weight gain, decreases in blood sugar levels (if you have diabetes you should continue careful monitoring of your blood sugar levels) having nightmares, insomnia dizziness, numbness or tingling in the fingers and toes, reductions of sensation to pain or touch, change in sense of taste, loss of memory blurred vision ringing in the ears and/or head vomiting, belching, abdominal pain upper and lower, pancreatitis (inflammation of the pancreas leading to stomach pain) hepatitis (liver inflammation) rash, skin rash and itching, hives, hair loss neck pain, muscle fatigue fatigue, feeling unwell, weakness, chest pain, swelling especially in the ankles (oedema), raised temperature urine tests that are positive for white blood cells

Rare side effects (affects 1 to 10 users in 10,000) include: visual disturbance unexpected bleeding or bruising cholestasis (yellowing of the skin and whites of the eyes) tendon injury

Very rare side effects (affects less than 1 user in 10,000) include: an allergic reaction - symptoms may include sudden wheezing and chest pain or tightness, swelling of the eyelids, face, lips, mouth,

tongue or throat, difficulty breathing, collapse hearing loss gynecomastia (breast enlargement in men and women).

Possible side effects reported with some statins (medicines of the same type): Sexual difficulties, depression, breathing problems including persistent cough and/or shortness of breath or fever, cholestasis (yellowing of the skin and whites of the eyes), tendon injury

Very rare side effects (affects less than 1 user in 10,000) include: an allergic reaction - symptoms may include sudden wheezing and chest pain or tightness, swelling of the eyelids, face, lips, mouth, tongue or throat, difficulty breathing, collapse hearing loss gynecomastia (breast enlargement in men and women).

Atorvastatin Contraindications

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.
- Hypersensitivity to any component of this medication

8.1.3 Presentation

The Cardiovascular Combination Polypill AAR 40 and 20 are supplied as hard gelatin capsules.

8.1.4 Manufacture

The Cardiovascular Combination Polypill AAR will be manufactured by Ferrer S.A. (Sant Cugat, Barcelona, Spain) according to the current regulatory requirements (Directive EU 2001/20/EC and subsequent versions combined with communication from the Commission – detailed guidance "CT-3"). Medications in the usual care arm are commercially available in all participating countries.

8.1.5 Storage conditions

All investigational drug supplies in the study will be stored in a secure, safe place, under the responsibility of the Investigator or other authorized individual.

8.1.6 Packaging and Labelling

Medication packaging and labeling will be performed by a specialized company for the Cardiovascular Combination Polypill AAR, in accordance with Good Manufacturing Practice for Medicinal Products.

Relabeling of IMP will be performed according to extension of expiration date production and supply needs of recruiting centers.

8.1.7 IMPs administered

Patients allocated to polypill will start treatment with Cardiovascular Combination Polypill AAR 40 by default, so they will receive one of the following polypills:

- ASA 100 mg, atorvastatin 40 mg, ramipril 2.5mg
- ASA 100 mg, atorvastatin 40 mg, ramipril 5 mg
- ASA 100 mg, atorvastatin 40 mg, ramipril 10 mg

If considered necessary and per investigators judgment polypill Cardiovascular Combination Polypill AAR 40 may be switched to Cardiovascular Combination Polypill AAR 20 (ASA 100mg, atorvastatin 20 mg, and ramipril 2.5, 5 or 10 mg).

Patients randomized to receive usual care will follow standard therapy (which will be initiated at admission), according to clinical guidelines and local clinical practice.

8.2 Blinding

Study treatments are not blinded.
The main objective of SECURE is to test the efficacy of simple treatment strategy of bioequivalent active principals in an easy to use, once daily capsule versus the multi-pill treatment regimen. In order to test this hypothesis, the design does not allow for blinding the treatments.

8.3 Drug Supply

8.3.1 Drug Supply in the Intervention Arm

- Drug will be shipped to each participating site by a specialized company
- Medication supply will be provided to all patients in the polypill arm in all countries.
- Participants will be provided with IMP to cover the treatment period and will take the assigned dose at home (a total of 105 doses to cover 3 months + two weeks of polypill supply or a total of 210 doses to cover 6 months + two weeks of polypill supply).
- Patients will be provided with a prescription refill date at 90 days. If patients do not comply after 104 days they will be contacted by telephone.
- If needed and allowed by regulatory authorities of the corresponding country, drug supply/ies will be shipped to patients.

8.3.2 Drug Supply in the Usual Care Arm

- Prescriptions to elderly patients following AMI (hence chronic medication) are usually renewed every 1 to 3 months in the participating countries.

According to the national regulations, dispensing of standard therapy is carried out as the following:

Spain, Italy, Germany, France, and Czech Republic:

- Patients randomized to usual care arm in the countries listed above will be treated at the discretion of their physician following clinical guidelines.
- Patients will receive free or heavily subsidized medication (Co-payment of less than 2EUR per month).
- These patients will follow the standard care at their country, both medication prescription and dispensing. Patients will collect their prescriptions at their **local pharmacy or study site**.

Germany

- After discharge from hospital /rehabilitation clinic it may be more suitable for logistical reasons (patient travel) that study visits are performed at the central study site Charité – Universitätsmedizin Berlin, Virchow Klinikum in Berlin. This transfer will be done only after patient's consent.

- If the pick-up of the Polypill every three months is unfeasible for the study participant, e.g. due to long distances, it may be considered to send the study medication via mail to patient after patient submits the request by phone.

Hungary and Poland

- Pharmacological therapy is only partially subsidized for patients after an MI. Buying medicine in standard pharmacy by patients randomized to usual care may have a significant

impact on adherence compared to patients randomized to Polypill Cardiovascular Combination Polypill AAR.

- Patients will receive a 3 or a 6-month prescription for **usual care treatment** (to be chosen by the physician) and will be asked to return to the **research pharmacy or site** before the end of medication supply. Therefore, **patients will collect study medication at their research pharmacy or site every 12-24 weeks.**

8.3.3 Receipt of Drug Supplies

Upon receipt of the Cardiovascular Combination Polypill AAR 40 and 20, an inventory must be performed and signed by the person receiving the shipment. The following will be checked:

- Medication quantity corresponds with the shipment inventory
- Damage or unusable study drug

A copy of the appropriate form should be retained in the site file and another copy sent to the Sponsor.

8.3.4 Return or Destruction of Drug Supply

At the completion of the study, final reconciliation of study drug (shipped, consumed, and remaining) must be performed. The final drug reconciliation will be recorded on the correspondent form, signed, and dated. Any discrepancies will be investigated, resolved, and documented prior to return or drug destruction. For drugs destroyed on site, a dug destruction certificate will be issued and provided to the Sponsor and a copy retained in the study files.

8.4 Dose Regimen

A total of 1257 patients will receive a once daily oral dose of the Cardiovascular Combination Polypill AAR for the whole duration of the study.

A total of 1257 patients randomized to the usual care arm will follow standard therapy for secondary CV prevention, according to the ESC clinical practice guidelines.

8.5 Dose Adjustment

Dose adjustment must be done with caution in both groups.

General guidelines are provided for patients already receiving statins and ACEI prior to inclusion and for naive patients:

1. Patients already taking statins or ramipril before enrollment: Replacement of previous medication by the study drugs should be undertaken taking into account differences in potency, pharmacodynamic and pharmacokinetic properties of different drugs.

a. Statin treatment:

Patients randomized to the polypill arm: start in with Cardiovascular Combination Polypill AAR 40 (40mg of atorvastatin) dose unless contraindicated.

Patients randomized to control arm: physicians must individualize statin dosage according to individual patient risk factor profile, cholesterol level, and history of side effects

b. ACEI treatment:

Patients randomized to the polypill arm: **Patients with prior ACEI treatment should be treated with bioequivalent doses of ramipril**

Patients randomized to control arm: continue treatment as previously prescribed unless contraindicated by patient's current hemodynamic conditions.

2. Naive patients: ESC guidelines clearly state the following recommendations:

a. Statin treatment:

ESC guidelines recommend high-intensity statin therapy regardless of the baseline LDL-C level and to continue it indefinitely. "This treatment should be started early during admission, as this increases patient adherence after discharge, and given at high doses, as this is associated with early and sustained clinical benefits.. The treatment goal is an LDL-cholesterol concentration of 1.8 mmol/L (70 mg/dL). The use of **lower-intensity statin therapy should be considered in patients at increased risk of side-effects from statins (e.g. the elderly, patients with hepatic or renal impairment, with previous side-effects of statins or the potential for interaction with essential concomitant therapy**)."[1]

Therefore, patients receiving the polypill should start in with Cardiovascular Combination Polypill AAR 40 (40mg of atorvastatin) dose unless contraindicated.

Important: ESC Guidelines clearly state that "Lipids should be re-evaluated 4–6 weeks after the ACS, to determine whether the target levels have been reached and regarding safety issues; the statin dose can then be adjusted accordingly."[1] Taking into account the high risk elderly population of the trial, participating centers must comply with this recommendation in order to achieve an efficacious and safe titration.

If dose adjustment for atorvastatin is necessary, it can be switched to Cardiovascular Combination Polypill AAR 20, containing 20mg of Atorvastatin.

b. ACEI treatment

ACEI reduce total mortality, MI, stroke and heart failure among specific subgroups of patients, including those with heart failure, previous vascular disease alone, or high-risk diabetes. Hence, it is appropriate to consider ACE inhibitors for the treatment of patients with SCAD, especially with co-existing hypertension, LVEF ≤40%, diabetes, CKD, unless contra-indicated. [1]

For naive patients, the **recommended starting dose of Ramipril capsules is 2.5 mg daily**. Clinical benefit of use of Ramipril has been shown to increase with increased dose (if tolerated) toward a target dose of 10 mg daily, with dosage increases being about 3 weeks apart.

If down titration is necessary for ramipril, two dose reductions are permitted in a stepwise fashion (initially to 5 mg and subsequently to 2.5 mg, if necessary). The dose can then be increased step-wise back to 5 mg and 10 mg in the next scheduled or unscheduled visits after monitoring for 3 weeks at each step if side effects do not recur or worsen.

The ramipril dose in the polypill arm will be adjusted by the investigator and adapted to patients' needs throughout the study period.

Supplementary medication to achieve adequate secondary prevention targets is allowed and left to the investigators' discretion. This includes blood pressure and lipid lowering drugs.

For drug equivalences: see annex 7

8.6 Treatment Compliance

Study drug accountability will be performed at each visit. Intentional or unintentional stopping of study drug by either the patient or investigator or other physician must be documented. The following criteria will be used:

- Brief Temporary Discontinuation of polypill is defined as a period of 1 to 5 days.
- Temporary Discontinuation of polypill is defined as a period of 6 to 30 days.
- Permanent Discontinuation of polypill is defined as any period longer than 30 days will be considered permanent discontinuation. Patients will be followed up according to regular protocol until the end of the follow up period.

After brief temporary and temporary discontinuation, patients can continue treatment with Cardiovascular Combination Polypill AAR, if advised by investigator.

8.6.1 Missed dose

A missed dose from a previous calendar day should not be taken with the current dose.

8.7 Prior and Concomitant Therapy

Details of all prior and concomitant medications and therapies administered before randomization will be recorded in the eCRF.

8.8 Treatment Adherence

Adherence to all treatments will be assessed by the self-reported eight-item Morisky-Medication Adherence Scale (MMAS-8), which has been validated in various CV treatment scenarios as an indirect, self-reported measure of adherence. (87)

8.9 Quality of Life

Quality of Life will be assessed with the validated EQ-5D scale. (Annex 10)

8.10 Health Economic Evaluation

A within-trial health economic evaluation will be conducted comparing Cardiovascular Combination Polypill AAR with usual care using a third party payer perspective.

8.10.1 Resource Use and Costs

Within-trial data collection will inform of significant health service resource inputs following the index event. The individual costs associated with the following secondary clinical events and procedures will be considered including: death from CV causes, nonfatal MI, nonfatal ischemic stroke, and urgent revascularization. The latter includes the identification and quantification of the number of hospitalizations due to CV causes, the number of revascularization procedures, and the follow-up emergency room, outpatient and rehabilitation visits due to CV causes beyond the study visits. The number of days per hospitalization due to CV causes will also be collected.

Information on health service resource usage will be obtained through the eCRF.

Costs for secondary clinical events and procedures associated with hospitalization including death from CV causes, nonfatal MI, nonfatal ischemic stroke, and urgent revascularization will be calculated. Costs for emergency room, outpatient and rehabilitation visits for CV causes in the follow up period not requiring hospitalization will also be calculated.
The costs for the use of resources for secondary clinical events and procedures in the follow up period associated with hospitalization and visits for CV causes not requiring hospitalization will be valued according to national or regional health tariffs, and on the collection of costs from the participating study centers.
The costs for the use of resources for secondary clinical events and procedures in the follow up period associated with hospitalisation and visits for CV causes not requiring hospitalisation will be valued according to national or regional health tariffs, and when available on the collection of costs from the participating study centers. Costs for emergency room visits, rehabilitation visits and outpatient visits beyond study visits for CV causes in the follow up period not requiring hospitalisation will also be calculated.

9 STUDY PROCEDURES

9.1 Visit Schedule

See Section 3. Study Flowchart at the beginning of the protocol.

See Section 10.1. Assessment schema and descriptions.

For Germany, after discharge from hospital /rehabilitation clinic it may be more suitable for logistical reasons (patient travel) that study visits are performed at the central study site Charité – Universitätsmedizin Berlin, Virchow Klinikum in Berlin. This transfer will be done only after patient's consent.

9.1.1 Screening and Baseline

At the screening and baseline visit, written informed consent will be obtained before any assessments are made. All patients will be assessed for eligibility against the inclusion and exclusion criteria.
The patient's full medical history, baseline ECG, and previous labs*: full blood count, full lipid profile, haemoglobin, serum creatinine, creatinine clearance, creatine kinase (CK), liver function tests (ALT, AST, and alkaline phosphatase), and ionogram; concomitant illnesses and medication use will be documented. Demographic data, such as race, age and sex, and historical disease data and diagnostic information will be recorded in the eCRF.).

**Most recent lab values from date of qualifying MI up-to randomization date.*

Following ESC guidelines, patients will undergo laboratory analysis (full blood count, full lipid profile, haemoglobin., serum creatinine and creatinine clearance, CK, liver function tests, and ionogram) 4-6 weeks post ACS to monitor drug response and potential toxicity to drug therapy. Patients included before that first analysis will be followed by the PI of each participating site to ensure access to lab results and determine dose regimen accordingly. For patients enrolled after the 4-6 week analysis, results will be made available to the PI to monitor that dose modification has been undertaken appropriately.

Once the eligibility criteria are confirmed patients will be randomized to one of the treatment arms. Medication supply will be provided to the patients randomized to the Cardiovascular Combination

Polypill AAR arm and prescription to collect the medication at the local pharmacy will be given to usual care arm.

Questionnaires regarding quality of life (EQ-5D) will be run at inclusion to have a baseline measure.

9.1.2 Visit 1 (At 6 months Post Randomization ± 2 weeks)

- Information on outcomes (MACE).
- Changes in concomitant diseases/illnesses and medication since Baseline visit.
- Adverse Events.
- Vital signs (blood pressure and heart rate after 5 min sitting rest).
- Medication Self-Adherence Questionnaire, MMAS-8.
- Treatment satisfaction questionnaire, TSQM.

9.1.3 Visit 2 (At 12 months Post Randomization ± 2 weeks)

- Information on outcomes (MACE).
- Changes in concomitant diseases/illnesses and medication since Visit 1.
- Adverse Events.
- Vital signs (blood pressure and heart rate after 5 min sitting rest).
- Blood Sample will be collected and analyzed by the local laboratory linked with each trial center:
    - Full Blood Count.
    - Full Lipid Profile (total cholesterol, LDL-cholesterol, and HDL-cholesterol).
    - Haemoglobin.
    - Serum Creatinine and Creatinine Clearance.
    - Creatine Kinase
    - Liver Function Tests
        - Alanine aminotransferase (ALT)
        - Aspartate aminotransferase (AST)
        - Alkaline phosphatase
    - Ionogram

9.1.4 Telephone Follow-up 1 (At 18 months Post Randomization ± 2 weeks)

- Information on outcomes (MACE).
- Changes in concomitant diseases/illnesses and medication since Visit 2.
- Adverse Events.

9.1.5 Visit 3 (At 24 months Post Randomization ± 2 weeks)

- Information on outcomes (MACE).
- Changes in concomitant diseases/illnesses and medication since Telephone Follow-up 1.
- Adverse Events.
- Vital signs (blood pressure and heart rate after 5 min sitting rest).
- Blood Sample will be collected and analyzed by the local laboratory linked with each trial center (Section 9.1.3).
- Medication Self-Adherence Questionnaire, MMAS-8.
- Quality of Life Questionnaire, EQ-5D.
- Patient Preference, Treatment Satisfaction Questionnaire for Medication (TSQM).

9.1.6 Telephone Follow-up 2 (At 36 months Post Randomization ± 4 weeks)

- Information on outcomes (MACE).
- Changes in concomitant diseases/illnesses and medication since Visit 3.
- Adverse Events.

9.1.7 Telephone Follow-up 3 (48 months Post Randomization ± 4 weeks)

- Information on outcomes (MACE).
- Changes in concomitant diseases/illnesses and medication since Telephone Follow-up 3.
- Adverse Events.

9.1.8 Telephone Follow-up 4 (60 months Post Randomization ± 4 weeks)

- Information on outcomes (MACE).
- Changes in concomitant diseases/illnesses and medication since Telephone Follow-up 3.
- Adverse Events.

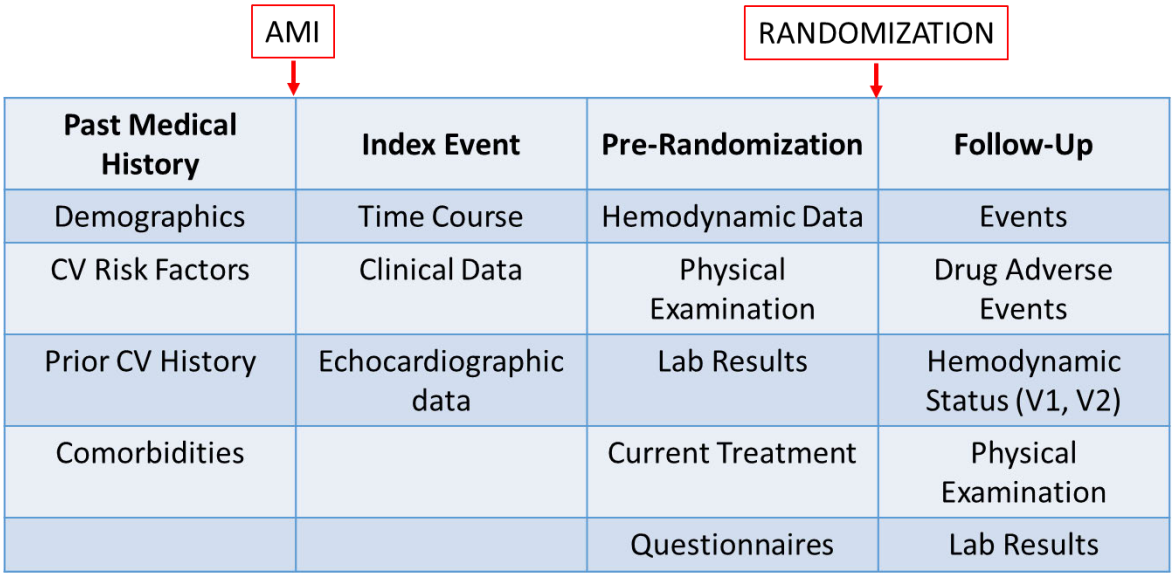
9.1.9 Treatment Duration

The duration of the treatment will be a minimum of 2 years and a maximum of 5 years.
Treatment with the components of the polypill is considered long term, and thus clinical guidelines recommend chronic treatment with statins, ASA and ACEI unless adverse effects present.

10 STUDY ASSESSMENTS

10.1 Assessment Schema

Assessments planned to be conducted throughout the course of the study:



Past Medical History	Index Event	Pre-Randomization	Follow-Up
Demographics	Time Course	Hemodynamic Data	Events
CV Risk Factors	Clinical Data	Physical Examination	Drug Adverse Events
Prior CV History	Echocardiographic data	Lab Results	Hemodynamic Status (V1, V2)
Comorbidities		Current Treatment	Physical Examination
		Questionnaires	Lab Results

10.2 Primary Endpoints

Major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal ischemic stroke, and urgent revascularization) will be monitored as the primary outcome and include the following:

- **Cardiovascular death:** includes any death resulting from acute myocardial infarction, sudden cardiac death, heart failure, stroke, or any other cardiovascular causes.

- **Nonfatal myocardial infarction:** Evidence of spontaneous myocardial necrosis related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis in a clinical setting consistent with acute myocardial ischaemia with a rise and/or fall of cardiac biomarker values [preferably cardiac troponin with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment or T wave changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- **Nonfatal ischemic stroke:** Acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of infarction documented by imaging technique (CT or MRI).

- **Urgent coronary revascularization:** Coronary revascularization (either PCI or CABG) of a lesion or lesions with diameter stenosis >50% by QCA triggered by the presence of clinical

or functional ischemia with severe ischemic signs and symptoms leading to urgent hospitalization and intervention.

10.3 Secondary Endpoints

10.3.1 Efficacy Endpoints

1. Incidence of the first occurrence of any component of the following composite endpoint: CV death, MI, stroke.

2. The first occurrence of the individual components of the primary endpoint
   - CV death.
   - Nonfatal type 1 myocardial infarction.
   - Nonfatal ischemic stroke.
   - Urgent coronary revascularization.

3. **Treatment Adherence:** Changes in Treatment Adherence at two years will be measured by the Eight-Item Morisky-Medication Adherence Scale (MMAS-8), which has been validated in various CV treatment scenarios as an indirect, self-reported measure of adherence (8).

4. **Patient Satisfaction:** Assessed with the validated Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4 (Annex 9)

5. **Change in Risk Factors at Two Years**
   a. **Systolic and Diastolic Blood Pressure (SBP and DBP):** BP will be measured using a sphygmomanometer. A mean of two readings will be taken after 5 min sitting rest. Patients are required to avoid drinking coffee or beverages containing caffeine for at least one hour before study visits. Patients are also required to refrain from smoking for at least one hour before study visits.
   b. **LDL cholesterol level** will be collected and analyzed by the local laboratory linked with each trial center.

6. **Regional differences in performance of the polypill in the previous endpoints.**

10.3.2 Health Economic Endpoints

1. **Quality of Life** will be assessed with the validated EuroQol EQ-5D (3L) scale. EQ-5D scores will be transformed into quality adjusted life years (QALYs). Annex 10.

2. **Cost differences and Incremental Cost-Effectiveness Ratio (ICER)**, expressed as the costs per QALY gained, of the Cardiovascular Combination Polypill AAR versus usual care.

3. Occurrence of the following events (section 11.4.2):
   - Scheduled Revascularization (non-urgent)
   - Angina
   - Atherosclerosis
   - Other Cardiovascular Hospitalizations or Interventions
   - Emergency Room Visits

10.3.3 Safety Endpoints

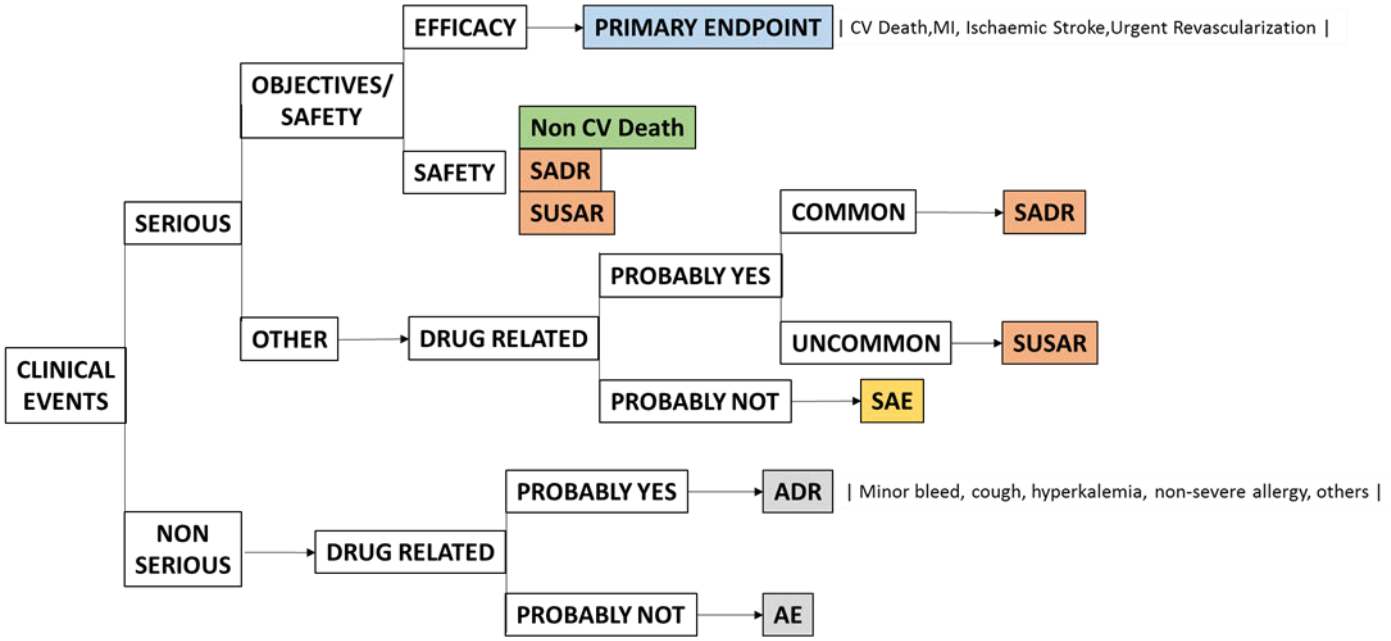
1. **All-cause mortality:** Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.
2. **Adverse Events**
    a. Bleeding: according to Bleeding Academic Research Consortium Definition[22] (Annex 5).
    b. Renal dysfunction (increase in creatinine by 0.5 mg/dl or more) or hyperkalemia (K 5.5 mEq/L) reported by physician in charge and leading to a change in doses or drug interruption.
    c. Drug allergies.
    d. Refractory cough leading to drug discontinuation.

10.3.4 Adverse Events (AE) Assessment Guidelines

Aspirin, Atorvastatin, and Ramipril have been extensively studied in Phase 1 through Phase 4 clinical studies and their overall safety profile has been well characterized. Thus, appropriate information concerning adverse events were systematically collected and submitted to regulatory authorities in the past. For the purposes of this study (and after discussion with appropriate pharmacovigilance experts) certain not serious adverse events will not be collected, while certain events will be collected as endpoints and therefore not reported as serious adverse events.

The investigator will closely monitor the AE and will adopt the necessary clinical measures to ensure the safety of the patients, following the proposed Event Flow Chart on figure 2.

Figure 2. Clinical Events Flow Chart



10.3.4.1.1 Definitions and Classifications

Adverse Event
An AE is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended medical occurrence in a study patient, including an abnormal value in a laboratory assessment, an ECG abnormality or an abnormal finding in the physical examination.

Criteria to assess an abnormal result in a complementary test as an AE are the following (one is enough): is associated to signs or symptoms, requires diagnostic tests, medical or surgical intervention, requires modification of the IMP dosage or its discontinuation, requires the administration of medication or other type of treatment or when the investigator or the sponsor consider it as clinically significant.

Planned surgical interventions or planned hospitalizations scheduled prior to signing the informed consent but performed during the study should not be considered as AEs.

Adverse Drug Reaction (ADR)
An ADR is an untoward and unintended response to an IMP related to any dose administered. Therefore, it is an AE assessed as being related to the IMP administered.

Serious Adverse Event and Serious ADR
An SAE is any AE or ADR that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongs existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is any other medically important event that may jeopardize the patient's well-being or may require intervention to prevent one of the other above outcomes.

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

Hospitalization is defined as an overnight stay at the hospital or emergency room.

Prolongation of hospitalization is defined as any extension of an in-patient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician.

Assessment of Expectedness
An AE is defined as expected or unexpected according to the list of AEs in the valid Investigator's Brochure (or the Reference Product Information) and not on the basis of what might be anticipated from its pharmacological properties.

An unexpected AE relates to an event the nature or severity of which is not consistent with the reference product information for the IMP (Investigator's Brochure/Reference Product information).

Assessment of Intensity
For grading the intensity of an AE the following 3 categories will be considered:

- Mild: means awareness of symptoms or signs, but easily tolerated (acceptable).
- Moderate: means enough discomfort to interfere with usual activity (disturbing).
- Severe: means incapacity to work or to perform usual activities (unacceptable).

Assessment of Causality
Causality of an AE to the IMP or study procedures will be assessed in 5 categories according to the information provided below:

- Probable: To be applied when there is a plausible temporal relationship, a biological plausibility and additional explanations such as concomitant medications, drug interactions, or intercurrent diseases are lacking. In addition, the event should follow a clinically reasonable response on product withdrawal.

- Possible: To be applied when there is a plausible temporal relationship and a biological plausibility but the event could have been due to another equally likely cause such as concomitant medications, drug interactions, or intercurrent diseases.

- Unlikely: To be applied when the temporal relationship is plausible but the event is likely to be explained by another cause which can, by itself, explain the occurrence of the event.

- Not related: To be applied when the temporal relationship is not plausible or another cause can by itself explain the occurrence of the event.

- Definitely related: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

10.3.4.1.2 Reporting Adverse Events

Study endpoints or suggestive study endpoints will not be reported as adverse events. These events will be captured on an event page in the eCRF and final event assessment will be performed by the CEC. All other events that are serious such as SAE, SUSARs, ADR, or events that lead to permanent discontinuation will be collected in the AE/SAE eCRF page. As stated in section 10.2 and 10.3, the study endpoints/events include, but are not limited to:

- Cardiovascular Death
- All-cause Mortality
- Non-fatal Myocardial Infarction
- Non-fatal Ischemic Stroke
- Urgent Coronary Revascularization

- Scheduled Revascularization (non-urgent)
- Angina
- Atherosclerosis (definition Section 11.4.2)
- Other Cardiovascular Hospitalizations or Interventions (definition Section 11.4.2)
- Emergency Room Visits (definition Section 11.4.2)

The following adverse events or serious adverse events will be collected and entered into the eCRF:

- Adverse events leading to change of dose or permanent study drug discontinuation
- All drug related adverse event: ADR, SADR and SUSAR
- Bleeding: according to Bleeding Academic Research Consortium Definition (Annex 5)
- Renal dysfunction
- Angioedema

Although not required, any nonserious adverse events, of particular concern to the investigator may be recorded in the eCRF to bring them to the attention of the sponsor. All other non-serious adverse events not fulfilling the above mentioned criteria will not be reported as adverse events in the eCRF.

Reported AEs will be coded using MedDRA, classified by system organ class and preferred term and tabulated by intensity and causal relationship for each treatment.

The AEs listed in the investigator's brochure would, by definition not be considered unexpected and thus would not be unanticipated problems. Possible exceptions would include situations in which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.

The above mentioned adverse events should be reported from the time a signed and dated ICF is obtained, to the completion of the clinical study (including the Follow-up Visit); or premature patient withdrawal from the study; and until 30 days after the last dose of study drug was taken by the subject. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the timeframe specified in the protocol.

AE information will be collected through in-person visits, telephone follow-up, physical examination, laboratory assessments, medical records, and/or other complementary tests results. Assessment will be based on the seriousness, intensity, causal relationship to the IMP, and according to the definitions provided above.

10.3.4.1.3 Follow Up of Adverse Events

As a general rule all patients with reported AEs will be followed up until the complete resolution of the AE or until the stabilization of its progression is confirmed.

Reported AEs that are still present after the last patient's scheduled visit will be followed up within 30 days of receiving the last IMP by phone call or in-person visit, as considered appropriate. After that time point, the need for additional follow-up of ongoing AEs/SAEs will be discussed between the investigator and the sponsor, although in the event of discrepancies, the investigator's criteria will prevail.

All reported and unresolved non-serious AEs beyond this date will be considered as ongoing and recorded on the AE eCRF page with an outcome of "recovering" (if the event improved compared with the previous observation), "not recovered" (if the event did not vary or worsened compared with the previous observation) or "unknown" (if the patient is lost to follow-up and no previous information is available).

10.3.4.2 Serious Adverse Events (SAEs)

10.3.4.2.1 Reporting Requirements of Serious Adverse Events

Reporting During the Study
In the event of a reportable SAE the investigator or a delegate will:

1. FILL IN immediately the SAE form in English.
2. The MINIMUM INFORMATION that must be included in the initial report is:
   - An event meeting the criteria of SAE.
   - A qualified reporter, defined as an investigator of this study or his/her delegate.
   - A qualified patient, defined as a patient who has consented to this study.
   - Suspected medicinal product (test or reference), if initiated.
   - The investigator's or delegate's causality assessment.
3. SUBMIT information immediately in the eCRF (within 24 hours of the moment the investigator or delegate first learnt of it) and notify CNIC and the CRO responsible for pharmacovigilance.
4. CONTACT immediately by phone all pharmacovigilance contacts in case of SUSAR

CNIC Safety Contact Details
Phone numbers and email addresses will be provided directly to the investigator and research staff prior or during site initiation

5. ARCHIVE the original documents in the investigator's file.
6. FOLLOW-UP information. Unless the SAE has been sufficiently documented in the initial report, the investigator has to provide all available additional information in follow up reports by using a new form and adhering to the same routing and timeframes as defined by the initial report. This will be continued until the event has been fully documented and reported
7. NULLIFICATION. An event reported to the sponsor that does not meet the SAE criteria shall be nullified by the investigator by forwarding a follow-up report.

Reporting after Completion or Premature Discontinuation of the Study

Any reportable SAE coming to the knowledge of the investigator that has occurred to a patient after his/her participation in the study will be collected and reported up to 30 days after the last IMP administration, but only if the investigator judges that is related to the IMP or the study procedures. The same reporting procedure and timeframes apply as during the study.

Expedited Submission to the Competent Authorities, ECs and Investigators

CNIC will submit the regulatory report to the Competent Authorities and the Ethics Committees as soon as possible but no later than 7 calendar days (fatal or life-threatening SUSARs) or 15 calendar days (other SUSARs), after becoming aware of the information. All investigators will also be informed.

Other Safety Findings

In addition, the CNIC will promptly notify the Competent Authorities and the Ethics Committees of findings that could adversely affect the safety of patients, impact on the conduct of the study or alter the EC approval/favorable opinion of the study, as well as the investigators.

10.3.4.3 Suspected Unexpected Serious Adverse Reaction (SUSARs)

A SUSAR is an adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Reaction and must meet the following criteria:

1. The event must be serious, that is to say irrespective of the dose the event:

- is fatal, and/or
- is life-threatening for the patient, and/or;
- makes hospital admission or an extension of the admission necessary, and/or
- causes persistent or significant invalidity or work disability.

2. There must be a certain degree of probability that the event is harmful, and an undesirable, reaction to the medicinal product being research, regardless of the administered dosage. In other words, there is an adverse reaction.

3. The adverse reaction must be unexpected. That is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:

- for an authorized medicinal product: the IMPD text.
- for an unauthorized medicinal product: the Investigator's Brochure.

10.3.4.3.1 Definition of SUSAR

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For the CV polypill, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For comparator agent and background/combination therapy agents with a marketing authorization, ie, ASA, ramipril, atorvastatin, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert.

10.3.4.3.2 Reporting SUSAR

In the event of an SUSAR the investigator or a delegate will inform the sponsor or delegated party immediately of every event in the study that 'takes a course that is significantly more unfavorable to study participants than foreseen in the research protocol'. The same applies to all undesirable effects that are both serious and unexpected and/or form a risk to the research subject. The investigator or a delegate are required to report all relevant information on SUSARs, including SUSARs relating to the comparative product which have occurred in a control group.

SUSARs within the study that are life-threatening or have had fatal consequences must be reported, at the latest, within 7 days after the sponsor has become aware of them. All relevant information on the aftermath of this must be reported within a time period of a further 8 days. Other reports of SUSARs must be made within 15 days after the sponsor has become aware of them. SUSARs from another study with the same product will be submitted within the 6 monthly line-listings, unless there are direct consequences for the subject within the study. In that case expedited reporting within the same terms as noted above is required.

11 DATA MANAGEMENT AND STATISTICAL ANALYSIS

11.1 Data Management and Coding

Data will be captured in an eCRF and the Investigator is responsible for ensuring the prompt and accurate reporting of study data into the eCRF. Data management documentation will be prepared by CNIC.

Previous and concomitant medications (including rescue medication) will be coded using the latest available WHO Drug Reference Dictionary. Coexistent diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between Ferrer, S.A. and the CNIC project team.

11.2 Statistical Methods

Statistical Analysis will be performed by London School of Hygiene and Tropical Medicine, under the supervision of [redacted]

In general terms, categorical data will be presented as absolute and relative frequencies and continuous variables will be presented as mean, median, standard deviation (SD), minimum, maximum, and number of patients with an observation (n). In general, minima and maxima will be recorded to the number of decimal places as recorded in the CRF; means, medians, and SDs will be recorded to one further decimal place. Percentages will be rounded to one decimal place.

The inferential analysis will be limited to the primary endpoint incidence of combined endpoint (occurrence of MACE). Other analysis will include change in blood pressure (SBP and DBP), lipid profile variables (LDL-cholesterol, HDL-cholesterol, total cholesterol and triglycerides) and adherence (MMAS-8). Other variables will be analyzed descriptively. All statistical tests will be 2-sided and will be performed using a 5% significance level if not stated otherwise.

All individual patient data will be listed.

11.2.1 Statistical and Analytical Plans

Datasets Analyzed

The following datasets will be defined:

Safety dataset: All patients who have given informed consent.

Intent-to-treat (ITT) dataset: All randomized patients who received at least one dose of IMP. This will be the population for the primary analysis.

Per protocol (PP) dataset: All randomized patients who received at least one dose of IMP have baseline and final time point measurement, and have no major protocol deviations.

11.3 Demographic and Other Baseline Characteristics

The following demographic variables will be summarized by treatment group: age, sex, race, height, weight, and BMI. Smoking history will also be summarized by treatment group. No statistical hypothesis testing of demographic or baseline data will be performed.

History of disease and other diagnostic information will be summarized. Other baseline characteristics collected in the eCRF will be summarized as appropriate.

Concomitant medications taken during the study will be summarized.

11.4 Variables

11.4.1 Definition of Primary Endpoint

The first occurrence of any component of the following composite endpoint, as adjudicated by the Clinical Events Committee:

- Any nonfatal type 1 myocardial infarction
- Any nonfatal ischemic stroke
- Any urgent coronary revascularization
- Cardiovascular death

Nonfatal myocardial infarction: defined by the presence of electrocardiographic changes or at least 1 elevated biomarker measurement of a troponin T level ≥ 0.1 ng/mL

Nonfatal ischemic stroke. Acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue, not resulting in death.

Urgent coronary revascularization: Episode/s of persisting or increasing chest pain (with or without ST-T changes or elevated biomarkers) requiring urgent hospitalization and urgent coronary revascularization (PCI or CABG), during the same hospitalization.

Cardiovascular death: includes any death resulting from acute myocardial infarction, sudden cardiac death, heart failure, stroke, or any other cardiovascular causes

11.4.2 Definition of Secondary Endpoints

Efficacy Endpoints

1. The first occurrence of any component of the following composite endpoint: CV death, MI, stroke
2. The first occurrence of the individual components of the primary endpoint CV death:
    - Nonfatal type 1 myocardial infarction.
    - Nonfatal ischemic stroke.

- Urgent coronary revascularization

3. Treatment adherence, measured by MMAS-8.
4. Patient satisfaction measured by TSQM.
5. Risk factor control at 2 years defined as LDL-cholesterol and blood pressure values (SBP and DBP)
6. Regional differences in performance

Safety Endpoints
All-cause mortality: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.
Safety and tolerability of the treatments, defined by adverse events and percentage of the patients who discontinue the treatment in both arms.

Health Economic Endpoints
1. Costs
2. QALYs
3. Incremental cost-effectiveness ratios (ICERs)
4. Occurrence of the following events:
   - **Scheduled Revascularization (non-urgent)**: defined as Coronary revascularization (either PCI or CABG) of a lesion or lesions with diameter stenosis >50% by QCA triggered by the presence of clinical or functional ischemia with severe ischemic signs and symptoms not being an urgent hospitalization and intervention
   - **Angina**
   - **Atherosclerosis**: defined as Hospitalization for atherosclerosis of the coronary arteries, including: atherosclerosis heart disease of native coronary artery, atherosclerosis of coronary artery bypass graft(s), atherosclerosis of bypass graft of coronary artery of transplanted heart, old myocardial infarction, ischemic cardiomyopathy, silent myocardial ischemia, chronic total occlusion of coronary artery, coronary atherosclerosis due to lipid rich plaque, chronic ischemic heart disease, cardiomegaly, heart disease (unspecified), abnormal findings on diagnostic imaging of heart and coronary circulation; excluding angina, myocardial infarction or surgical intervention.
   - **Other Cardiovascular Hospitalizations or Cardiovascular interventions** (excluding myocardial infarction, stroke, urgent revascularization, scheduled revascularization, hospitalization for ischemic heart disease or atherosclerosis of the coronary arteries or angina.)
   - **Emergency room visits** for cardiac atherosclerosis-related causes without hospital admission.

11.5 Methods of Analysis

For the primary endpoint first the non-inferiority will be tested using Cox proportional hazards regression with the pre-specified non-inferiority margin of HR = 1.373. If this non-inferiority hypothesis is confirmed, it will be preceded with the superiority testing using a log-rank test.

Secondary endpoints defined as time to event will be analyzed using a log-rank test.
Treatment adherence between groups will be compared by a Mann-Whitney test.

Between-group differences in SBP, DBP and lipid profile variables after treatment will be analyzed by ANCOVA, including fixed terms for treatment, center and baseline SBP or LDL-cholesterol

accordingly as covariate. A point estimate will be constructed using the error variance obtained from the ANCOVA.

Adaptive Design
The trial will use an adaptive sample size re-estimation[23]. In brief, an unblinded interim analysis of the primary endpoint will take place after 70% of the initial sample size have been recruited and followed for a minimum of 6 months. If the conditional power lies in a "promising zone" then the sample size and length of follow-up will be increased.
Full details of the adaptive sample size re-estimation design, including definition of the favorable, promising and unfavorable zones and rules regarding the sample size inflation, will be provided in an Adaptive Charter and in the Statistical Analysis Plan (SAP), both of which will be agreed and signed off before the trial data are unblinded.

Health Economic Analysis
As part of a sub study a within-trial health economic evaluation will be conducted comparing Cardiovascular Combination Pill AAR with usual care using a third party payer perspective. For this purpose data on health service resource use alongside the clinical trial will be collected.
The sub study will include the following analyses:

1. An intention-to-treat comparison of health service resource use and costs associated with Cardiovascular Combination Polypill AAR and usual care at different time points. Costs will be compared using nonparametric bootstrapping.
2. A cost-effectiveness analysis will be conducted using the third party payer perspective to estimate the incremental cost-effectiveness ratio (ICER), expressed as the cost per QALY gained of the Cardiovascular Combination Polypill AAR versus usual care. Different time horizons will be explored using discount rates for costs and benefits applicable for each country. Costs and outcomes will be discounted at rates appropriate for country level analyses. Cost-effectiveness analyses will be performed for each country separately to incorporate differences in cost data.
3. Several sensitivity analyses will be carried out to investigate the robustness of the results with respect to parameter uncertainty. In addition, the effect of different cost-effectiveness ratio thresholds for the willingness-to-pay will be explored to show the probability the Cardiovascular Combination Polypill AAR has to be cost-effective relative to standard care.

A detailed description of the statistical analysis in used in the cost comparisons and cost-effectiveness analysis will be provided in the Statistical Analysis Plan.

11.6 Safety Variables

Exposure and Compliance
Exposure and compliance to IMP will be summarized.

Adverse Events
Reported AEs will be coded by the pharmocovigilance company using the MedDRA dictionary (most recent version), by system organ class and preferred term. Only treatment emergent AEs (ie commencing after dosing with the IMP) will be included in the summary tables. Treatment emergent AEs will be assigned to the treatment received preceding event onset. All reported AEs, whether treatment emergent or not will be included in the data listings.
IMP-related AEs will be defined as events considered to have a probable, possible, or unlikely causal relationship to the IMP. AEs leading to withdrawal will be defined as events where the IMP

was withdrawn as a result of the AE. If the intensity or causal relationship to the IMP of an AE is missing, a worst-case scenario will be assumed (ie it will be set to severe or probably related).
The denominator used for the calculation of percentages will be the number of patients in the safety dataset (N) for the treatment group.
The following summary of treatment emergent AEs will be provided.

Overall Summary of AEs
The number and percentage of patients reporting AEs, serious AEs, IMP-related AEs, AEs leading to withdrawal and AEs leading to death will be presented.
In addition, the following summary tables will be presented.
Summary of AEs by system organ class and preferred term.
Summary of AEs by intensity of event.
Summary of AEs by seriousness
Summary of IMP-related AEs.
Summary of AEs by causal relationship to the IMP.

Laboratory Variables
Laboratory variables (hematology and clinical chemistry) will be summarized at baseline and final timepoint including changes from baseline. Shift tables from baseline to final timepoint (with respect to the number and percentage of patients with values below, within, or above the reference range) will also be presented. Values outside the reference ranges will be flagged in the data listings.

Vital Signs
Vital signs data will be summarized at each timepoint, including changes from baseline (i.e. predose).

Physical Examination
Physical examination data will be summarized over the course of the study.

11.6.1 Determination of Sample Size

The planned total sample size in this study is 2514 patients (1257 per group). The initial assumptions for the determination of sample size are as following:

- A composite primary endpoint event rate of 7.7% per year in the population to be recruited
- A true hazard ratio of 1
- A planned accrual period for the study of 3 years
- A minimum follow-up and treatment period of 2 years
- An estimated loss to follow-up of 1%

Based on these assumptions, it is anticipated that 420 composite primary events will be accrued during the follow-up period.
A non-inferiority margin of 1.373 for the upper limit of the 95% confidence interval for the hazard ratio is set for this study. With the total sample size of 2514 patients (1257 per group) a non-inferiority test at 0.025 one-sided significance level with have a 90% power to reject the null hypothesis of inferiority.
With this sample size, the study will have 78% power at a two-sided alpha of 0.05 to demonstrate a relative risk reduction of 21%, which corresponds to a hazard ratio 0.79.

11.6.2 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in a protocol amendment and/or in a statistical analysis plan and/or in the final report, as appropriate.

12 INVESTIGATOR/SPONSOR RESPONSIBILITIES

12.1 Ethics

12.1.1 Ethics Committee

Before initiating the study, the investigator must have written and dated approval from the Ethics Committee (EC) for the study protocol, written informed consent form, patient recruitment procedures (e.g. advertisements), and any other written information to be provided to patients. Approval from the EC must be documented in a letter to the investigator specifying the protocol number, protocol version, documents reviewed, date on which the EC met, date the EC granted the approval, the date of approval expiration and the EC membership list. A list of all ECs will be included in the Trial Master File.

In the event the EC approval/favorable opinion requires a change(s) in any aspect of the study (e.g. modification to the protocol), the sponsor must be provided with a copy of all requested modification(s). If the sponsor is in agreement with the requested modification(s), the sponsor will provide an investigator-specific protocol amendment to the investigator for submission to the reviewing EC. Dated documentation must then be provided to the sponsor upon approval/favorable opinion of the protocol based upon the investigator-specific protocol amendment by the EC.

12.1.2 Ethical Conduct of the Study

The study will be conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the Declaration of Helsinki as adopted by the World Medical Assembly, 1996 (and subsequent revisions).

12.1.3 Patient Information and Consent

The investigator is responsible for ensuring that no patient undergoes any study-related examination or activity before that patient has given written informed consent to participate in the study. The written consent must be given by the patient of the patient, after detailed information about the study has been given as in accordance with any national provisions on the protection of clinical study patients. The verbal explanation will cover all the elements specified in the written information provided for the patient.

The investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The patient must be given every opportunity to clarify any points he/she does not understand and, if necessary, ask for more information. At the end of the interview, the patient will be given time to consider the study if this is required, or if the patient requests more time. Patients will be required to sign and date the informed consent form. After signatures are obtained, the informed consent form will be kept and archived by the investigator in the investigator's study file for possible inspection by regulatory authorities, the EC and sponsor.

It should be emphasized to the patient that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study.

12.2 Patient Records and Source Data

There may be data that are recorded only in the eCRF. In these circumstances, the Investigator would not be expected to duplicate information. With information of this type, in which the clinical data are associated with protocol-specific procedures and not with clinical care practice, the eCRFs will stand as the source documents.
The origin of source data in the study will be further specified in a separate document ("Origin of Source Data").
It is the responsibility of the Investigator to record essential information in the medical records in accordance **with national regulations and requirements**. The following information should be included as a minimum:

- Study code
- Patient screening number and/or patient number
- Date when informed consent was obtained
- Diagnosis
- All visits during the study period
- All reportable AEs
- Treatments and medications (including dosage)
- Date of study termination
- Patient health service identification number

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs.

12.2.1 Archiving

All documents compiled in the Trial Master File (TMF) and Investigator Site File (ISF) will abide to the principles and guidelines of good clinical practice and with the applicable requirements and, in particular with Annex I of Directive 2001/83/EC.

The sponsor and each investigator (participating sites) shall retain the essential documents relating to a clinical trial for at least fifteen years after the completion or discontinuation of the clinical trial. Investigator must also obtain approval from Sponsor prior to destroying any study essential documents within the fifteen year period after the completion or discontinuation of the clinical trial.

Retention of documents for a longer period shall occur, if so required by other applicable requirements.

Essential documents shall be archived in a way that ensures they are readily available, upon request to the competent authorities.

The medical files of trial subjects shall be retained in accordance with national legislation and accordance with the maximum period of time permitted by the hospital, institution, or private practice.

Access to archives shall be restricted to the named individuals responsible for the archives.

Any alteration to records shall be traceable.

12.3 Monitoring

The study sites will be visited on a regular basis to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any study specific documents such as eCRF completion guidelines.

Monitoring visits will be conducted to confirm e.g. that:

- The investigational team is adhering to this study protocol
- Informed consent has been obtained for all participants
- AEs have been collected and reported according to the protocol requirements
- Data are being accurately recorded in the eCRFs
- Investigational products have been stored correctly and that drug accountability has been performed
- Facilities are and remain acceptable
- The Investigator and the site receive sufficient information and support

Moreover, during monitoring visits the data recorded in the CRFs, source documents and other study-related records will be compared against each other in order to ensure accurate data that reflects the actual existence of the patient in the study i.e. source data verification.

Deviations to the study protocol will be documented in the Protocol Deviation Log.

12.4 Access to Source Data and Documentation

All personnel involved in the study at the site are bound to professional secrecy under the national official secrecy act.

An individual secrecy agreement will be established for all Sponsor and CRO representatives (including study monitors), independent auditors, and representatives from Competent Authorities (if applicable) that will have access to the information in the medical records for the participating patients.

The Investigator should guarantee access to source documents for the monitor and auditors, as well as for inspection by appropriate regulatory agencies.

12.5 Quality Assurance and Audit

A quality assurance system has been implemented to ensure that the study is performed and the data are generated, documented (recorded), and reported in compliance with GCP as defined in ICH E6 guidelines and the applicable regulatory requirement(s).

SOPs have been created to ensure that clinical studies are conducted in compliance with regulatory requirements and GCP. Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Authorized representatives of CNIC, the Sponsor and/or a Competent Authority and/or the EC may visit the center to perform audits/inspections, including source data verification.

12.6 Protocol Amendments

Unless otherwise agreed, substantial protocol amendments will be approved by the same persons that approved the study protocol. All substantial protocol amendments to the protocol will be submitted to the EC and Competent Authorities. Substantial protocol amendments become effective first when the Competent Authorities and/or EC have provided written approval. Non-substantial amendments will be approved by appropriate persons.

12.7 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement.

12.8 Report and Publication

After completion of the study, a clinical study report will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3) by CNIC in collaboration with the SECURE consortium.

The results of the study will be published in a peer review journal.

All publications and presentations must be based upon the clinical study report.

All information supplied by the Sponsor in connection with this study will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this study.

If an Investigator wishes to publish results from this clinical study, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the investigational product and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript prior to their submission to journals, meetings or conferences.

The Sponsor will publish and present data from this study. If an Investigator is offered first authorship, he/she will be asked to comment and approve the publication.

13 ANNEXES TO CLINICAL PROTOCOL

Annex 1: Participating Organization

Organization Name	Country
Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) Valentín Fuster, MD, PhD –PI [redacted]	ES
IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri" (IRFMN) [redacted]	IT
Charité, Universitätsmedizin Berlin (CHAR) [redacted]	DE
University Hospital of Besançon (UHB) [redacted]	FR
Wroclaw Medical University (UM Wroclaw) [redacted]	PL
Semmelweis University (SE) [redacted]	HU
General University Hospital in Prague (GUHP) [redacted]	CZ
Servicio Madrileño de Salud (SERMAS) [redacted] Fundación Investigación Biomédica Hospital Clínico San Carlos, Third party	ES
London School of Hygiene and Tropical Medicine (LSHTM) [redacted]	UK
ARTTIC (ARTTIC) [redacted]	FR
Ferrer (Ferrer) [redacted]	ES

Annex 2: The Data Safety and Monitoring Board (DSMB)

Purpose Overview

The purpose of an independent Data and Safety Monitoring Board (DSMB) has been convened to safeguard the interests of trial participants and to safeguard the scientific integrity of the trial. The DSMB will review accumulating safety and efficacy data throughout the trial as well as other data related to the overall conduct of the trial. The DSMB will make recommendations concerning continuation, modification or termination of the trial to the Executive Committee.

Independence of the DSMB

The DSMB will be independent of the sponsor, national competent authorities, ethics committees, and investigators. Such independence of the DSMB is essential to maintain subject's safety, preserve the integrity of the study, and ensure members are objective and capable of an unbiased assessment of the study's safety and efficacy data. A set of strict criteria will be used in evaluating the independence of the DSMB.

Responsibilities of the DSMB

All DSMB members will review the study protocol, amendments, planned analysis, investigator brochure (IB), and summary of product characteristics (SmPC) to ensure a complete understanding of the study's objective and its design in order to anticipate interim safety review and possible early stopping rules. The responsibilities of the DSMB and its members are:

- To evaluate, on an ongoing basis, the accumulating safety assessments to ensure the ongoing safety of study subjects
- To consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study
- To review all documents provided in the DSMB data review packets upon receipt
- To review the conduct of the study, including protocol violations
- To review data on participant recruitment, accrual, and retention, as well as assessments of data quality, completeness, and timeliness
- Protect the confidentiality of the study data and the DSMB discussions
- Review specific interim analyses for efficacy
- To make recommendations to continue, modify, or terminate the study depending upon these analyses
- Operate according to the procedures described in the DSMB charter
- Follow conflict of interest guidelines as detailed in the charter
- Maintain documentation and records of all activities.

Responsibilities of the Sponsor

- Ensuring resources are available to the DSMB as required to perform its designated functions
- Promptly reviewing and responding to the DSMB recommendations
- Deciding whether to continue or terminate the trial, and determining whether amendments to the protocol or changes in study conduct are necessary

- Communication of all pertinent DSMB information to Regulatory Authorities
- Forward special requests from any national regulatory authority requiring input from the DSMB

Recommendations from the DSMB

The DSMB will transmit the recommendations in writing, to the Executive Committee. At each of their meetings, one of the following will be recommended:

- continue the trial until the next meeting
- continue the trial with recommendations (e.g., modify the informed consent form, disseminate information to study Investigators, seek additional expert review/analysis)
- modify the trial (amend the protocol)
- temporarily suspend subject enrollment or dosing to obtain additional data or resolve an issue, or
- stop the trial early because of undue safety risks to subjects or compelling benefits to the subjects

Recommendations to modify or terminate the trial will be accompanied by the DSMB's justification for the recommendation. The Executive Committee will review the recommendations made by the DSMB, discuss them as appropriate with the DSMB, and accept or reject the DSMB's recommendations in writing together with some members of the Executive Committee. In the event that the DSMB's recommendations are not agreed upon by the TSC and DSMB, the TSC will discuss this further with the DSMB; however, the final decision for study continuation, modification, suspension or discontinuation rests solely with the TSC and Executive Committee. The recommendations and final decision will be disseminated to all study Investigators.

Confidentiality

DSMB members are bound by confidentiality disclosure agreements to refrain from disclosing study-related material to any person without prior approval from CNIC. The DSMB members must ensure that no other individuals involved with the conduct, editing, entry, or analysis of data are informed of study results.

Annex 3: Definition of Myocardial Infarction[24, 25]

All myocardial infarctions (MIs) will be counted as events whether they represent the reason for the hospitalization or occurred during a hospitalization. In addition, they will be counted as events whether they occurred spontaneously or as the direct consequences of an investigation/procedure or operation. The definition of MI as an endpoint will take into account whether a subject had a recent MI or has undergone revascularization with PCI or CABG surgery. In cases where both cardiac troponin and CK-MB are available (drawn at similar time points) and are discordant, biomarker criteria will be applied using cardiac Troponin except in cases of peri-procedural infarction. The definitions of MI are as follows for the 4 clinical settings in which it may occur:

1. **Spontaneous MI (normal biomarkers)**- For patients with no recent revascularization in whom biomarkers were never elevated or have been documented to return to normal after a qualifying (or recent) MI, criteria a & b or criterion c or criterion d must be met:

a) Typical cardiac biomarker rise and/or fall with the following degrees of elevation accepted as biochemical evidence of myocardial necrosis (either one or both):

- Troponin T or I: maximal concentration greater than the MI decision limit
- CK-MB: maximal concentration greater than the ULN

AND

b) At least 1 of the following additional supportive criteria:

- Ischemic discomfort at rest lasting >10 minutes or
- ECG changes indicative of ischemia (ST elevation > 0.1 mV or ST depression > 0.05 mV, or new T-wave inversions)

OR

c) Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction

OR

d) Pathologic findings of an acute MI.

2. **Spontaneous MI (Elevated biomarkers)** - For patients with no recent revascularization in whom biomarkers from a qualifying (or recent) MI remain elevated, criteria a and b, or criterion c, or criterion d must be met:

a) Cardiac biomarker re-elevation defined as:
   i. Increase by at least 20% of the previous value; and
   ii. Documentation that the biomarker assayed was decreasing prior to the suspected new MI

AND

b) At least 1 of the following additional supportive criteria:
   i. Ischemic discomfort at rest lasting >10 minutes; or
   ii. ECG changes indicative of ischemia (ST elevation > 0.1 mV or ST depression > 0.05 mV, or new T-wave inversions)

OR

c) Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction

OR

d) New elevation of ST-segments > 0.1 mV in > 2 contiguous precordial or adjacent limb leads

AND

   i. Ischemic discomfort at rest lasting > 20 minutes; or
   ii. Ischemia-mediated new hemodynamic decompensation requiring pharmacologic or mechanical support; or
   iii. Angiographic evidence of acute coronary occlusion

3. Within 24 hours after PCI a patient must have EITHER:

a) CK-MB >3× ULN and, if the pre-PCI CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

OR

a) Pathologic findings of an acute MI.

Note: symptoms are not required.

4. Within 24 hours after CABG a patient must have EITHER:

a) CK-MB >5× ULN and, if the pre-CABG CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI;

AND

b) At least one of the following supportive criteria:
   i. Development of new, abnormal Q waves (>30 msec in duration and >1 mm in depth) in >2 contiguous precordial leads or >2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction, or
   ii. Angiographically documented new graft or native coronary occlusion, or
   iii. Imaging evidence of new loss of viable myocardium

OR

c) Pathologic findings of an acute MI.

Note: symptoms are not required.

5. **Sudden Cardiac Death -** Sudden cardiac death may represent an acute MI, but typically occurs before blood samples can be obtained. In the absence of cardiac biomarkers, a patient who experiences sudden death will be considered to have had an acute MI if either of the following 2 criteria is met:

a) Pathologic findings of an acute MI (if no recent prior MI), or
b) Presence of at least 2 of the following 3 criteria:
   i. Ischemic discomfort
   ii. New ST segment elevation at the J point in ≥2 anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (>0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads, new left bundle branch block, or new, abnormal Q waves (>30 msec in duration and ≥0.1 mV in depth) in ≥2 contiguous leads or new abnormal R waves (≥30 msec in duration and > depth of the S wave) in V1 and V2 consistent with posterior infarction
   iii. Angiography with evidence of fresh coronary thrombus

6. **Silent MI -** A patient must meet one of the following 3 criteria to qualify for a silent MI:

a) New, abnormal Q waves (>30 msec in duration and ≥0.1 mV in depth) in ≥2 contiguous leads, or new abnormal R waves (≥30 msec in duration and > depth of the S wave) in V1 and V2 consistent with posterior infarction, or

b) Imaging evidence of a new (post-randomization) region (ie, must have a prior study) of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause

c) Pathological findings of acute MI (eg acute myocardial necrosis or fresh coronary thrombosis) that are clearly distinct from prior known MIs and which does not otherwise meet the criteria for any other category as described above

Note: If cardiac troponin measurements are the only cardiac biomarker data available, they may be used by the CEC, along with the ECG and clinical scenario, in the adjudication of suspected MI after revascularization (PCI or CABG).

The reviewers should also consider the clinical features (e.g., renal insufficiency), possible alternative diagnoses (e.g., pericarditis), pattern of marker release (e.g., absence of a rise and/or fall), and known sensitivity/specificity of the various cardiac markers in the adjudication of infarction, particularly when there is discordance in the results of multiple markers.

Universal Definitions of MI Criteria

Myocardial infarctions will be also be classified according to the following universal definition of MI criteria:

Type 1: Spontaneous Myocardial Infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe Coronary Artery Disease (CAD) but on occasion non-obstructive or no CAD.

Other definitions of myocardial infarction not encompassed in the inclusion criteria

- Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

- Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

- Type 4b: Myocardial infarction related to stent thrombosis as documented by angiography or at autopsy.

- Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG).

ST-Segment Elevation MI versus Non-ST-segment Elevation MI
All events meeting criteria for MI* will also be classified as either ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), or unknown.

- **STEMI** – To be classified as a STEMI the event must meet all of the above criteria for myocardial infarction and one of the four criteria below.

    - New ST segment elevation at the J point in ≥2 contiguous leads, defined as: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads. Subjects must have an interpretable ECG (i.e., without evidence of left ventricular hypertrophy or pre-existing left bundle branch block), *or*

    - New left bundle branch block

- **NSTEMI** – To be classified as a NSTEMI the event must meet all of the above criteria for myocardial infarction and not meet criteria for classification as STEMI. In order to be classified as NSTEMI there must be adequate interpretable ECG documentation associated with the event.

- **Unknown** – Events which meet criteria as specified above for MI but do not meet criteria for STEMI or NSTEMI. All cases where ECG documentation of the acute event is missing, inadequate, or uninterpretable should be classified as Unknown.

***All events adjudicated as MI will be classified as STEMI, NSTEM, or Unknown; however, it is acknowledged that a significant proportion of peri-procedural (PCI or CABG) events may have missing, inadequate or uninterpretable ECG documentation.*

Annex 4: Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials[25]

13.1.1 Definition of Cardiovascular Death

1. **Death due to Acute Myocardial Infarction**
   Refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days1 after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. We note that there may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the myocardial infarction, it will be considered a death due to myocardial infarction.

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis.

   Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

   Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. **Sudden Cardiac Death**
   Refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
   - Death witnessed and occurring without new or worsening symptoms.
   - Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI.
   - Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review).
   - Death after unsuccessful resuscitation from cardiac arrest (e.g., implantable cardioverter-defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest).
   - Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology.
   - Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

3. **Death due to Heart Failure**
   Refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

4. **Death due to Stroke**
   Refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. **Death due to Cardiovascular Procedures**
   Refers to death caused by the immediate complications of a cardiac procedure.

6. **Death due to Cardiovascular Hemorrhage**
   Refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. **Death due to Other Cardiovascular Causes**
   Refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

13.1.2 Definition of Noncardiovascular Death

Non-cardiovascular death is defined as any death with a specific cause that is not thought to be cardiovascular in nature, as listed above. Detailed recommendations on the classification of non-CV causes of death are beyond the scope of this document. The level of detail required and the optimum classification will depend on the nature of the study population and the anticipated number and type of non-CV deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS) / Immune (including autoimmune) (may include anaphylaxis from environmental (e.g., food) allergies)
- Hemorrhage that is neither cardiovascular bleeding or a stroke (see Chapter 1, Section 6, and Chapter 6)
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose (may include anaphylaxis)
- Neurological (non-cardiovascular)
- Malignancy
- Other non-CV, specify: _____

13.1.3 Definition of Undetermined Death

Undetermined Cause of Death: refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is “patient died”) or when there is insufficient

supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death; therefore, should be discouraged and should apply to few patients in well-run clinical trials.
A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the CV category (e.g., presumed CV death, specifically "death due to other CV causes"). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, and the disease process. The approach should be prespecified and described in the protocol and other trial documentation such as the endpoint adjudication procedures and/or the statistical analysis plan.

13.1.4 Definition of Urgent Coronary Revascularization.

Coronary revascularization (either PCI or CABG) of a lesion or lesions with diameter stenosis >50% by QCA triggered by the presence of clinical or functional ischemia with severe ischemic signs and symptoms leading to urgent hospitalization and intervention.

13.1.5 Definition of Transient Ischemic Attack and Stroke

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.

Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, documented by imaging technique (CT or MRI).

Stroke Classification

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.
Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, but with insufficient information to allow categorization as A or B.

Annex 5: Safety Measures – Bleeding Definition[22]

BLEEDING ACADEMIC RESEARCH CONSORTIUM DEFINITION FOR BLEEDING

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.

Type 3
Type 3a:
Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding.
Type 3b:
Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed).
Cardiac tamponade.
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid).
Bleeding requiring intravenous vasoactive agents.
Type 3c:
Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal).
Subcategories confirmed by autopsy or imaging or lumbar puncture.
Intraocular bleed compromising vision.

Type 4: CABG-related bleeding
Perioperative intracranial bleeding within 48 h
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding
Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.
Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.

Annex 6: Notes on Use of Atorvastatin 40mg on the Elderly in a Post MI setting

Standard care for post-acute MI recommends high doses of statin to be use (Atorvastatin 80mgs, Rosuvastatin 40mg) which could potentially throw back investigators from enrolling patients in SECURE.

However, according to the European Society of Cardiology (ESC) Guidelines for Management of STEMI, "the use of **lower intensity statin** should be considered in patients at increased risk of side effects (e.g. **the elderly**, patients with hepatic or renal impairment, with previous side effects to statins or the potential for interaction with essential concomitant therapy)."[26]

Furthermore, the recently published 2013 guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults,[27] Atorvastatin 40 mgs, is indeed considered high intensity treatment. (Table 1).

Table 3. High- Moderate- and Low-Intensity Statin Therapy

High- Intensity Statin Therapy	**Moderate-Intensity Statin Therapy**	**Low-Intensity Statin Therapy**
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin 40–80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1

Annex 7: Drug Equivalence

No differences in efficacy have been demonstrated between different doses of AAS from 75 to 325 mg. So, the FDC (100mg) could replace any preparation of AAS within that range. In addition, the 100mg AAS preparation provided by the study (control group) can replace other AAS previously prescribed to the patient.

Atorvastatin 40 mg, the dose included in Cardiovascular Combination Polypill AAR, is equivalent Rosuvastatin 10mg. Atorvastatin 20mgs is equivalent to Lovastatin 80, Pitavastatin 4, Pravastatin 80, Rosuvastatin 5, Simvastatin 40 in LDL lowering.

Ramipril 10 mg, the maximal dose included in Cardiovascular Combination Polypill AAR is equivalent to Perindopril 8 mg, Trandolapril 4 mg, Enalapril 20 mg and Captopril 150 mg/day.

Annex 8: The Morisky-Medication Adherence Scale (8 item) Questionnaire

MMAS – 8	Points
Do you sometimes forget to take your heart attack medication(s)?	1
People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your heart attack medication(s)?	1
Have you ever cut back or stopped taking your heart attack medication(s) without telling your doctor, because you felt worse when you took it?	1
When you travel or leave home, do you sometimes forget to bring along your heart attack medication(s)?	1
Did you take your heart attack medication(s) yesterday?	1
When you feel like your heart attack is under control, do you sometimes stop taking your medication(s)?	1
Taking medication(s) every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your heart attack treatment plan?	1
How often do you have difficulty remembering to take all you medicine?* ___A. Never/rarely ___B. Once in a while ___C. Sometimes ___D. Usually ___E. All the time	1

Adherence	Score
High adherence	8
Medium adherence	6-7
Low adherence	0-5

Each response carries a score: yes=0 and no=1, except for question 5, where yes=1 and no=0; and question 8, where never/rarely= 1, once in a while= 0.75, sometimes= 0.50, usually= 0.25, all the time= 0.

Annex 9: Treatment Satisfaction Questionnaire for Medication (TSQM)

TSQM *(Version 1.4)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

☐$_1$ Yes
☐$_0$ No (if No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?

☐1 Extremely Bothersome
☐2 Very Bothersome
☐3 Somewhat Bothersome
☐4 A Little Bothersome
☐5 Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

9. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Annex 10: European Quality of Life- 5 Dimensions (EQ-5D) Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Annex 11: Identification of a Protocol Deviation or Violation

The Chief Investigator of a research project is responsible for ensuring their appropriate oversight systems in place to monitor research activity and identify any deviations from the study protocol. This responsibility may be shared with other members of the research team, e.g. a Trial Steering Committee.

1. All deviations identified must be reviewed by the Chief Investigator (CI) to assess whether participant safety or study integrity has been affected by the deviation and to what extent the deviation has affected the project.
2. The CI will notify the sponsor if a deviation has an impact on safety or research integrity. The sponsor will advise whether the event is a protocol violation and take appropriate measures to address the occurrence which may include audit of the research project and defining a corrective action plan to be implemented by the CI.
3. Where a protocol deviation is not judged to impact on safety or research integrity, a file note should be added to the Trial Master File and/or CRF and source documents explaining the action taken and its justification.
4. If the CI is unsure whether an occurrence is a deviation or violation they should seek advice from the sponsor to ensure appropriate action is taken.

Reporting a Protocol Violation

When a protocol violation is identified it is essential to inform the appropriate parties of the occurrence and any corrective actions that have been implemented.

1. The CI must notify the sponsor of the violation immediately upon identifying the issue. The sponsor will advise on what action is required and may initiate a triggered audit of research activity to assess the extent of the violation and its relation to any other protocol compliance issues.

2. If the sponsor identifies a protocol violation during routine audit the process described in the Audit SOP will be followed. For IMP trials requiring MHRA approval, should the violation be identified as a serious breach of good clinical practice or the trial protocol, the sponsor will follow the procedure by SOP – Notification of Serious Breaches of GCP or the Trial Protocol, and inform the Regulatory Authorities of the incident within seven day of being notified of the event.

3. Once a violation has been identified it may be necessary to inform the ethics committee and/or regulator of the incident and any corrective actions. The sponsor will inform the CI of reporting requirements and direct them to submit a report explaining the event. Key areas to include in a report are:
   a) An overview of the incident and its cause
   b) Description of corrective action
   c) An assessment of likelihood of reoccurrence
   d) Outline of any changes to the protocol that may be required
   e) Time line for corrective action and amendment approval (if applicable)

4. If the protocol violation is deemed to be of a serious nature the sponsor will suspend the research project until all necessary corrective actions have been taken.

Annex 12: Management of Urgent Safety Measures (Clinical Trials)

Under the Medicine for Human Use (Clinical Trials) Regulations the sponsor, Chief Investigator or Principal Investigator may carry out urgent safety measures (USM) to protect trial subject from immediate harm.

1. Any urgent safety measure relating to an IMP trial must be notified to the sponsor, ethics committee and RA (Regulatory Authorities) within three days of the action being taken. The notification should describe the event, the measures taken and justification for the measures taken. The ethics committee will need to be informed in writing with a copy to the sponsor,

2. The sponsor must be notified of the USM before submitting to the RA and ethics to advise on content and process, and to ensure the sponsor is aware of the event should the ethics committee or regulator contact for further information.

Annex 13. DECLARATION OF HELSINKI 1996

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly,
Helsinki, Finland, June 1964,

and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient." The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.
In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human being to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the word. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subject unless they are satisfied that the hazard involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazard of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should the obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any-should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).
6. the physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to patient's illness.
3. The investigator or the investigating team should discontinue the research if in his /her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Annex 13.2. DECLARATION OF HELSINKI 2013

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a nonvulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.
Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such

representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention (s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in

the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Annex 14: Withdrawal of Consent Checklist

WITHDRAWAL OF CONSENT CHECKLIST
PRINCIPAL INVESTIGATOR SIGNATURE REQUIRED

Instructions: Going forward, this form must be signed by a Principal Investigator for any patient who withdraws consent to participate in all trial activities and refuses any method of follow-up. Notify National Coordinator and Sponsor. Fill-out the corresponding eCRF and file the original form in the patient's binder.

Site Number: _____ PI Name: _____

Patient ID: _____

The following list of follow-up choices must be reviewed with the patient prior to determining that the patient has withdrawn consent. If the patient agrees to any of the following, then the patient has **not** withdrawn consent for follow-up.

Patient refused all of the following methods of follow-up (all boxes must be checked for the patient to have withdrawn consent for any follow-up):

- □ Regular telephone follow-up according to the original visit schedule
- □ Less frequent telephone follow-up (1-2 times per year)
- □ One telephone contact at the end of the study
- □ Telephone follow-up through family or friends
- □ Follow-up for study endpoints through the patient's local clinician
- □ Follow-up through patient's medical records

If the patient has refused all of these options, please provide a reason below for their withdrawal of consent:

I confirm that all of these options were reviewed with the patient and all of the options for follow-up have been declined. The patient has confirmed that he/she wants to withdraw consent to participate in ALL trial activities and will not allow alternate methods of follow-up.

_____ _____
Signature of Principal Investigator Date of Signature

_____
Printed name of Principal Investigator

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