PROTOCOL TITLE
CLINICAL STUDY PROTOCOL

Interventional clinical trial to assess efficacy and safety of the extemporaneous combination of zofenopril calcium and amlodipine in grade 1-2 hypertensive patients versus each monotherapy – (MASOLINO Study)	
Protocol Code	MEIN/20/ZoAm-Hyp/001
EudraCT (or National Clinical Trial Identified Number)	2021-000745-40
Protocol Phase (if applicable)	IV
Study type and design	Interventional, multi-centre, open-label study
Protocol Version Number	1.0
Protocol Version Date	23 April 2021
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SUMMARY OF CHANGES FROM PREVIOUS VERSION

Affected Section(s)	Summary of Revisions Made	Rationale

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
ACE	Angiotensin Converting Enzyme
ACE-i	Angiotensin Converting Enzyme inhibitors
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AML	Amlodipine
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
CCBs	Calcium Beta Blocker
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CV	Cardiovascular Event
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
FDC	Fixed Dose Combination
FPI	First Patient In
IMP	Investigational Medicinal Product
ISCR	Individual Case Safety Report
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive Web Response System
MACE	Major Adverse Cardiovascular Events
NSAE	Non-Serious Adverse Events
PP	Protocol Population
PDE	Phosphodiesterase inhibitors
RCT	Randomized controlled trial
SAE	Serious Adverse Events
SBP	Systolic Blood Pressure
SD	Standard deviation
SS	Sample Size
SUSAR	Suspected Unexpected Serious Adverse Reaction

TEAE	Treatment Emergent Adverse Event
UNL	Upper Normal Limit
UPT	Urine Pregnancy Test
ZOF	Zofenopril

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2 PROTOCOL SYNOPSIS

Title Acronym Sponsor Study Code	Interventional clinical trial to assess efficacy and safety of the extemporaneous combination of zofenopril calcium and amlodipine in grade 1-2 hypertensive patients versus each monotherapy MASOLINO Study MEIN/20/ZoAm-Hyp/001
Study product, Dosage and Regimen: -Investigational Product -Reference Therapy (comparator)	Extemporaneous combination of Zofenopril (ZOF) 30 mg (ATC code: C09AA15) with Amlodipine (AML) 5 mg (ATC code: C08CA01) or Amlodipine (AML) 10 mg (ATC code: C08CA01) will be administered orally once daily.
Study Type and Design	This study is a phase IV, open-label, multicentre, multinational study with two study periods, treating patients with grade 1-2 hypertension, blood pressure (BP) ranging from ≥140/90 mmHg to ≤179/109 mmHg while on treatment with any angiotensin converting enzyme-inhibitors (ACE-i) or Calcium Channel Blockers (CCBs) including ZOF 30 mg or AML 5 mg respectively. The study is designed with a run-in period of 4 weeks and an assessment period of 8 weeks.
Phase	Phase IV
Objectives*	Primary Objective: To assess the anti-hypertensive efficacy of the extemporaneous combination of ZOF 30 mg with AML 5 mg or AML 10 mg in lowering the sitting diastolic BP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP

	previously treated with ZOF (30 mg) or AML (5 mg) monotherapies for at least 4 weeks. Secondary objectives: ●To assess the antihypertensive efficacy of the extemporaneous combination of ZOF 30 mg in combination with AML 5 mg or AML 10 mg in lowering sitting systolic BP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with ZOF 30 mg or AML 5 mg monotherapies for at least 4 weeks. ●To assess the antihypertensive efficacy of the extemporaneous combination of ZOF/AML 30/10 mg vs. ZOF/AML 30/5 mg, in lowering sitting DBP and SBP between Visit 3 (Week 4) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with ZOF or AML 5 mg monotherapies for at least 4 weeks. ●To evaluate the total number and percentage of patients who achieved the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8). ●To assess the compliance to the treatment (percentage of actual doses taken versus doses to be taken) at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8). ●To evaluate the safety and tolerability of the monotherapies (ZOF 30 mg and AML 5 mg) and of the extemporaneous combinations (ZOF 30 mg and AML 5 mg or AML 10 mg) after 8 weeks of treatment.
Endpoints*	Primary Efficacy Endpoint: ●Change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8). Secondary Efficacy Endpoint: ●Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8).

	●Change in mean sitting DBP and SBP between Visit 3 (week4) and 4 (Week 8) in patients on combination of ZOF/AML 30/5 with uncontrolled BP at Visit 3 and up titrated to the extemporaneous combination of ZOF/AML 30/10 mg ●Number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8). ●Adherence to the treatments (% of doses taken/ doses to be taken) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8). ●Safety and tolerability of the monotherapies (ZOF 30 mg and AML 5 mg) and of the extemporaneous combination (ZOF 30 mg and AML 5 mg or AML 10 mg) after eight weeks of treatment. Exploratory Efficacy Endpoint: ●Change in mean sitting SBP and DBP between Visit 1 (week -4) and Visit 2 (Week 0), visit 3 (Week 4) and Visit 4 (Week 8).: o in the group of patients who were on ZOF and AML 5 mg at Visit 1 and started ZOF 30 mg or continued the same therapy AML 5 mg at Visit 1 o in the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 ●Change in mean sitting SBP and DBP for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4) ●Number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0) and Visit 3 (Week 4): o in the group of patients who were on and AML 5 mg at Visit 1(Week -4) and started ZOF 30 mg or continued the same therapy AML 5 mg o in the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week- 4) ●Number and proportion of patients divided in subgroup by the hypertension grade, the presence of diabetes and/or of

	hypercholesterolemia achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8) o in the group of patients who were on ZOF and AML 5 mg at Visit 1 (Week -4) and continued AML 5 mg and started ZOF 30 mg o in the group of patients, who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week 4)
Study Population: Subjects characteristics Number of Subjects	●Male or female, Grade 1-2 uncontrolled hypertensive patients ≥18 and ≤65 years of age ●Considering a screening failure and a drop-out rate of 25%, the overall number of patients to be screened is 290. ●216 patients are needed to complete the run- in period and start the assessment period to guarantee powered results *Inclusion Criteria* A patient will be considered eligible for inclusion in the study only if all the following criteria are met: 1. Male or female Grade 1-2hypertensive patients: with mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥ 90 mmHg and ≤109 mmHg at Screening, with ≥18 and ≤65 years of age, in monotherapy either with ZOF 30 mg or AML 5 mg, or any other ACE-I or CCBs (Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine) for at least 1 months before Visit 1 (Screening). 2. Patients who are able to understand and give written informed consent at Screening 3. Patients who are available for the entire trial period and willing to adhere to the protocol requirements 4. Ability to take oral medication and willing to adhere to the drug regimen

5. Female patients are eligible to participate if not pregnant, or not breastfeeding and must refrain from donating or storing eggs. For females of reproductive potential: use of highly effective contraception (e.g., method of birth control throughout the study period and for 4 weeks after study completion defined as a method which results in a failure rate of less than 1% per year) such as:
    - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner (performed at least 2 months before screening) (if partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success)
6. A male patient must agree to use contraception during the whole study period and for at least 1 week after the last dose of study treatment and refrain from donating sperms during this period

Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. Known contraindications, presence of not recommended / contraindicated concomitant therapy allergies, or significant history of hypersensitivity to zofenopril, amlodipine, other ACE-

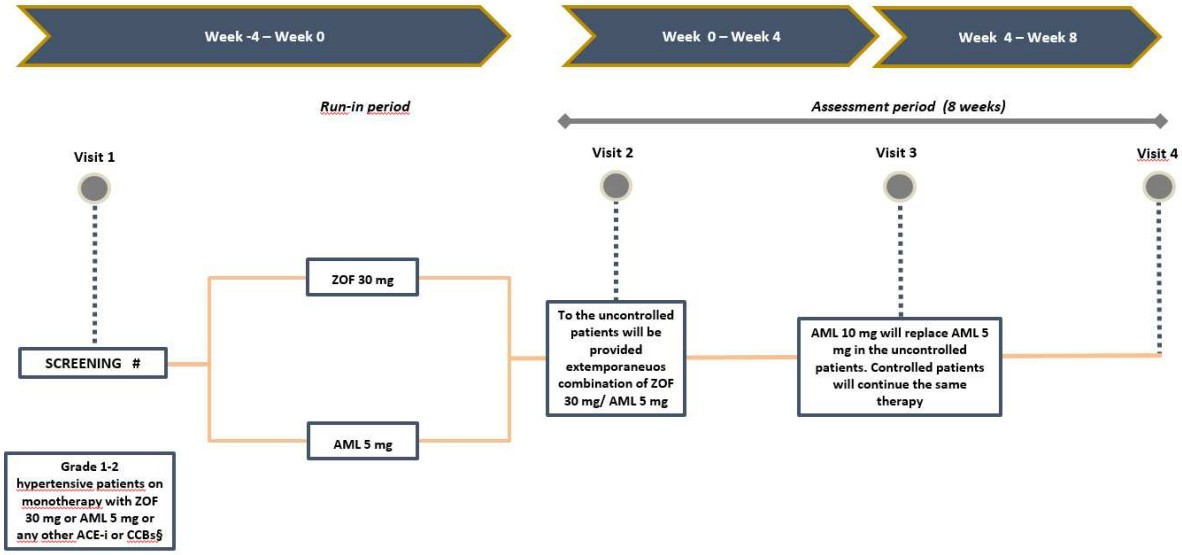
	inhibitors or dihydropyridines calcium channel blockers, or any related products (including excipients of the formulations as outlined in the Investigator's Brochure [IB]) or), summary of product characteristics (SmPCs) or local package inserts for AML and ZOF 2. Patients with serious disorders (in the opinion of the Investigator) which may limit the ability to evaluate the efficacy or safety of the tested medications, including cerebrovascular, cardiovascular, renal, respiratory, hepatic, gastrointestinal, endocrine/ or metabolic, haematological, or oncological, neurological, and psychiatric diseases. The same applies for immunocompromised and/or neutropenic patients 3. Patients having a history of the following within the last 6 months: myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, bypass surgery, valve replacement (transcatheter aortic valve implantation, MitraClip), cerebrovascular accident (stroke, heart failure, hypertensive encephalopathy, cerebrovascular accident (stroke), or transient ischemic attack. Patients with who have undergone other surgery that in the in the opinion of the Investigator may limit the ability to evaluate the efficacy or safety of the tested medications. 4. Patients with secondary hypertension of any aetiology such as renal diseases, pheochromocytoma, Cushing's syndrome hyperaldosteronism, renovascular disease, thyroid disorders 5. Patients with severe heart failure (New York Heart Association classification III-IV), a narrowing of the aortic or bicuspid valve, an obstruction of cardiac outflow (obstructive, hypertrophic cardiomyopathy) or symptomatic coronary disease 6. Patients with clinical evidence of renal disease as per the Investigator's judgement (including renovascular occlusive disease, nephrectomy and/or renal transplant, bilateral renal artery stenosis or unilateral renal artery stenosis in a solitary kidney, or severe renal impairment)

	7. Patients with history of angioneurotic oedema 8. Patients with clinically relevant hepatic impairment 9. Patients with sick sinus syndrome, including sino-atrial block 10. Patients with second- or third-degree heart block (without a pacemaker) 11. Participation in any other interventional drug trial or exposure to other investigational agents within 30 days before Screening (Visit 1) 12. Inability to cooperate or any condition that, in the opinion of the Investigator, could increase the patient's risk of participating in the study or confound the outcome of the study 13. Patients with conditions that, in the opinion of the Investigator, would prevent a careful adherence to the protocol 14. Patients with severe hypotension 15. Patients who suffer from shock (including cardiogenic shock) 16. Patients treated with Amlodipine 10 mg and Zofenopril (other than 30 mg)
Clinical Sites Number of Centres	• Approximately 28 clinical sites
List of Countries	Russia, Hungary, Italy
Study Duration (specify different study phases):	• Screening Visit 1, (Week -4) • Run-in period from Visit 1(Week -4) to Visit 2 (Week 0) • Assessment period from Visit 2 (Week 0) to Visit 4 (Week 8):
Subject Study Phases Duration	The overall duration of the study will be 12 weeks. Screening Visit 1, (Week -4): Grade 1-2 hypertensive patients with blood pressure [BP] ranging from ≥140/90 mmHg to ≤179/109 mmHg) in treatment with any ACE-i or CCBs*, including ZOF 30 mg or AML 5 mg (only dosage allowed) for at least one month prior to Visit 1 will be screened for eligibility. Run-in period from Visit 1(Week -4) to Visit 2 (Week 0): eligible patients will enter a 4 weeks run-in period on the same day of the

	screening visit. Patients previously receiving ZOF 30 mg or AML 5 mg will continue the same treatment, patients receiving other ACE-i will be switched to ZOF 30 mg, while patients receiving CCBs will receive AML 5 mg. Patients entering this phase in therapy with ZOF 30 mg or AML 5 mg should be in a 1:1 ratio. Assessment period from Visit 2 (Week 0) to Visit 4 (Week 8): patients having uncontrolled BP at Visit 2, will be assigned to the extemporaneous combination of ZOF 30 mg and AML 5 mg. After 4 Weeks ± 2 days the BP will be assessed again (Visit 3): controlled patients (SBP/DBP ≤ 130/80 mmHg) will continue the same extemporaneous combination, while uncontrolled (SBP/DBP >130/80 mmHg) patients will be up-titrated from extemporaneous combination ZOF/AML 30/5 mg to extemporaneous combination of ZOF/AML 30/10 mg for further 4 weeks ± 2 days (Visit 4, Week 8). At Visit 2 and Visit 3 patients with SBP/DBP value classified as Grade 3 (SBP ≥ 180 or DBP ≥ 110 mmHg) hypertension will be withdrawn from the study. *To be enrolled in the study, patients could be in monotherapy with one of the listed CCBs: felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine.
Statistical Assumptions	The primary endpoint will be assessed before and after assessment period at Week 8, by a paired t-test using the Intention-to-treat (ITT) population and the Per-Protocol (PP) population. All the other continuous secondary/exploratory endpoints will be assessed before (Week 0) and after treatment (at Week 8) by a paired t-test. All secondary/exploratory endpoints related to proportion of patients achieving the BP goal at Week 4 and Week 8 will be analysed descriptively producing also the relative 95% CI to assess if there is a significant difference from Week 0 where all patients were uncontrolled.

	A total sample size of 216 patients is required to achieve 90% power at a 5% significance level assuming a difference in mean DBP from baseline (Visit 2) to 8 weeks (Visit 4) of 4 mmHg and a standard deviation (SD) for this difference of 10 mmHg. The mean change in DBP for the null hypothesis is set equal to 2 mmHg.

2.1 Study Scheme



 # There is not a randomization procedure

§Allowed CCBs at screening: Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine.

Subjects treated with Amlodipine 10 mg or Zofenopril other than 30 mg will not undergo screening procedures.

Grade 1-2 hypertensive patients mean: Blood pressure [BP] ranging from ≥140/90 mmHg to ≤179/109 mmHg)

Uncontrolled patients with Grade 1-2 hypertension mean: Sitting SBP/DBP >130/80 mmHg. Patients with Grade 3 (SBP ≥ 180 or DBP ≥ 110 mmHg) hypertension will be withdrawn from the study at Visit 2 and Visit 3

Controlled patients mean: SBP/DBP ≤130/80 mmHg

2.2 Study Flow Chart

The assessment schedule lists all the assessments and when they are performed. All data obtained from these assessments mut be supported in the subject's source documentation. Subjects who prematurely discontinued the study for any reason should be scheduled for a visit as soon as possible. All the assessments listed for the final visit (Visit 4) will be performed. At this final visit, all dispensed investigational treatment should be reconciled, and the adverse events and concomitant medications recorded in the eCRF.

Informed consent must be signed prior to any study-related procedure.

	VISIT 1 / WEEK -4	VISIT 2 / WEEK 0± 2 days	VISIT 3 / WEEK 4± 2 days	VISIT 4 / WEEK 8± 2 days
Informed consent submitted	✓			
IWRS[f] registration	✓	✓	✓	✓
Inclusion/exclusion criteria	✓			
Medical history	✓			
Prior medications	✓			
Demographic information (for more details see section 8)	✓			
Concurrent diseases and medical conditions	✓	✓	✓	✓
Monotherapy of ZOF 30 mg or AML 5 mg dispensing[a]	✓			
Extemporaneous combination of ZOF/AML 30/5 mg dispensing		✓	✓[b]	
Extemporaneous combination of ZOF/AML 30/10 mg dispensing			✓[c]	
Study drug return/accounting (Compliance assessment)		✓	✓	✓
Concomitant medications	✓	✓	✓	✓
Urine Pregnancy test	✓	✓	✓	✓
Physical examination (for more details see section 8)	✓	✓	✓	✓
Vital signs (for more details see section 8)	✓	✓	✓	✓
Laboratory tests[d]	✓			✓
Blood pressure assessment	✓	✓	✓	✓
ECG	✓			✓
AE/SAE assessment[e]	✓	✓	✓	✓

BP device provided to patients[h]	✓			
Patient diary provided to patients[g]	✓	✓	✓	
Patient diary to be returned by patient if used [g]			✓	✓
BP device returned to site[i]				✓

a. Patients on ZOF 30 mg or AML 5 mg will continue the same therapy for 4 weeks. Patients on any other ACE-i will be assigned to monotherapy with ZOF 30 mg and the patients on other CCBs (the allowed CCBs are: felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine) will be assigned to monotherapy with AML 5 mg
b. Only patients controlled at Visit 3 will receive ZOF/AML 30/5 mg
c. Only patients uncontrolled at Visit 3 will receive ZOF/AML 30/10 mg.
d. To ensure patient safety, the patients will be contacted over phone within 24 hours, in case of any abnormality and clinically relevant laboratory test according to the Investigator's judgement at any visit
e. The Investigator is expected to also record any AE which was ongoing at the last treatment dose and a follow-up phone call should be made after 2 weeks from the last study visit.
In case AE was ongoing, the Investigator is expected to follow-up until the outcome of the AE has been determined.
f. IWRS- Interactive Web Response System
g. The following procedure is applied only in case of COVID-19 restrictions.
h. Patients will be provided with an automatic blood pressure device to be used in case they are not able to go to the study centre due to Covid-19 pandemic situation.
i. The patient will return the device at the last visit at the site

3 STUDY RATIONALE AND BACKGROUND INFORMATION

The global prevalence of hypertension was estimated to be 1.13 billion in 2015, with a prevalence of over 150 million in central and eastern Europe. The overall prevalence of hypertension in adults is around 30 - 45%[1]. Elevated blood pressure (BP) was the leading global contributor to premature death in 2015, accounting for almost 10 million deaths and over 200 million disability-adjusted life years[2].

There are two well-established strategies to lower BP: lifestyle interventions and drug treatment[3].

The drug treatment of hypertension is founded on very solid evidence, supported by the largest number of outcomes based RCTs in clinical medicine. Meta-analyses of RCTs including several hundred thousand patients have shown that a 10 mmHg reduction in SBP or a 5 mmHg reduction in DBP is associated with significant reductions in all major CV events (MACE) by 20%, all-cause mortality by 10 - 15%, stroke by 35%, coronary events by 20%, and heart failure by 40%[4,5].

Guidelines have generated a variety of different strategies to initiate and escalate BP-lowering medication to improve BP control rates. In previous 2013 Guidelines, the emphasis was on initial use of different monotherapies, increasing their dose, or substituting for another monotherapy[3].

However, increasing the dose of monotherapy produces little improvement in lowering the BP and may increase the risk of adverse effects, whilst switching from one monotherapy to another is frustrating, time consuming, and often ineffective. Due to these reasons, 2018 ESC/ESH Guidelines have increasingly focused on the stepped care approach, initiating treatment with different monotherapies and then sequentially adding other drugs until BP control is achieved[3].

Despite this, BP control rates have remained poor worldwide, only 40% of patients with hypertension being treated and of these, only 35% being controlled to a BP of <140/90 mmHg[1].

This has become an even more pressing matter because, based on new evidence, current guidelines are recommending more stringent BP targets (on-treatment values of <130/80 mmHg in the general population and <140/90 mmHg in older hypertensive people), which will make the achievement of BP control even more challenging[3].

Patients with hypertension are generally treated with multiple pharmaceutical products, Fixed Dose Combinations (FDC) have generated increasing interest and have been recommended in treatment guidelines due to advantages in dosing and compliance, leading to improved treatment outcomes [10,11].

One of the main reasons why the current treatment strategy has failed to achieve better BP control rates is the insufficient use of the combination treatment[10,11].
Blood Pressure is a multi-regulated variable depending on many compensating pathways. Consequently, combinations of drugs, working through different mechanisms, are required to reduce BP in most people with hypertension. Thus, monotherapy is likely to be inadequate therapy in most patients. Indeed, almost all patients in RCTs have required combinations of drugs to control their BP[6].
Zofenopril has been widely investigated for the treatment of patients with hypertension and its BP lowering effect has been compared with either placebo or with all the classes of antihypertensive drugs currently recommended for the treatment of hypertension. Although there are data in literature showing an added antihypertensive effect of Amlodipine or Zofenopril to other antihypertensive treatment,[9] there is scarce evidence at the moment on the antihypertensive effect of the extemporaneous combination of ZOF and AML versus each monotherapy. The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.
Amlodipine (a CCB) and Zofenopril (an ACE inhibitor) are antihypertensive drugs widely prescribed as monotherapies in the real world, according to treatment guidelines. Both drugs have specific benefit-risk profiles with different mechanism of action[9].
Amlodipine belongs to the dihydropyridine class of calcium channel blockers[7]. Amlodipine, like other calcium channel blockers, acts primarily by inhibiting extracellular calcium influx through cardiac and vascular smooth muscle cell membranes; this inhibition is achieved mainly by blockade of L-type 'voltage operated' calcium channels. Its main site of action is the peripheral vasculature, although it also produces vasodilation in coronary vascular beds. In patients with mild to moderate essential hypertension, amlodipine had a sustained and gradual onset of antihypertensive effect, when assessed by 24-hour ambulatory or intra-arterial blood pressure monitoring[7].

3.1 Assessment of Potential Risks and Benefits

Extemporaneous combination of ACE-i and CCBs are often prescribed to control BP without major reported risks. Several clinical studies have demonstrated how this combination is effective in lowering BP[12,13]. Furthermore, the combination does not significantly increase the incidence of adverse events compared with either agent alone[12,13]. In many cases, combination therapy improves rates of BP control and requires less time to achieve target BP with equivalent or better tolerability than higher dose monotherapy[15]. Hypertension to goal blood

pressure (BP) is an important objective. Approximately, 70% of patients with hypertension require 2 or more agents to achieve their target BP[16]. Beyond improving compliance, combination therapy in the setting of hypertension management allows for decreased BP variability. Variability in SBP and DBP is associated with an increased risk of myocardial infarction and stroke[17].

4 TRIAL OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
• To assess the anti-hypertensive efficacy of the extemporaneous combination of ZOF 30 mg in combination with AML 5 mg or AML 10 mg in lowering the sitting diastolic BP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with Zofenopril or Amlodipine (5 mg) monotherapies for at least 4 weeks.	• Change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8)	• The association between elevated DBP and increased mortality risk has been reported several times in literature[15],
Secondary		
• To assess the antihypertensive efficacy of the extemporaneous combination of ZOF 30 mg in combination with AML 5 mg or AML 10 mg in lowering sitting systolic BP (SBP) between Visit 2 (Week 0) and Visit 4 (Week	• Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8).	• Change in SBP after 8 weeks of treatment is intended to show the added efficacy of the extemporaneous combination also on SBP considering its link to the cardiovascular disease (CVD)

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
8) in patients with uncontrolled BP previously treated with ZOF or AML 5 mg monotherapies for at least 4 weeks.		
• To assess the antihypertensive efficacy of the extemporaneous combination of ZOF/AML 30/10 mg vs. ZOF/AML 30/5 mg, in lowering sitting DBP and SBP between Visit 3 (Week 4) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with ZOF or AML 5 mg monotherapies for at least 4 weeks	• Change in mean sitting DBP and SBP between Visit 3 (Week 4) and 4 (Week 8) in patients on combination of ZOF/AML 30/5 with uncontrolled BP at Visit 3 and up titrated to the extemporaneous combination of ZOF/AML 30/10 mg	• The number and proportion of patients with uncontrolled BP following the shift from ZOF/AML 30/5 mg to ZOF/AML 30/10 mg is very important to assess the contribution by AML 10 mg in reaching the BP target
• To evaluate the total number and percentage of patients who achieved the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8)	• Number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).	• The proportion of patients at target is a very important clinical indicator of therapeutic success
• To assess the compliance to the treatment (percentage of actual doses taken versus doses to be taken) at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8).	• Adherence to the treatments (percentage (%) of doses taken/ doses to be taken) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).	• Monitoring compliance is extremely important to better understand the efficacy and tolerability of the extemporaneous combination
• To evaluate the safety and tolerability of the monotherapies (ZOF 30 mg and AML 5 mg) after 4	• Safety and tolerability of the monotherapies (ZOF 30 mg and AML 5 mg) after 4 weeks of therapy and of the	• Incidence of ADRs, AEs, SAEs, vital signs, physical examination, ECG, and

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
weeks of therapy and of the extemporaneous combinations (ZOF 30 mg and AML 5 mg or AML 10 mg) after 8 weeks of treatment. These objectives should be the same as the objectives contained in the body of the protocol.	extemporaneous combination (ZOF 30 mg and AML 5 mg or AML 10 mg) after eight weeks of treatment.	concomitant medications needs to be studied to address safety and tolerability of the extemporaneous combination for a safe and optimal use of the treatment
Exploratory objective		
• To assess change in mean sitting SBP and DBP between Visit 1 (week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8):	• Change in mean sitting SBP and DBP between Visit 1 (week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8): In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 and continued the same therapies at Visit 1 o In the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 o Change in mean sitting SBP and DBP, for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4) • Number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0) and Visit 3 (Week 4):	• Evaluation of the antihypertensive efficacy of monotherapies and combination therapy in patients with different associated CV risk factors (Hypertension grade, presence of diabetes, and/or hypercholesterolemia) •

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	o In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 (week -4) and continued with the same therapies o In the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (week -4)	
• To assess the antihypertensive efficacy at different time points in patients who (1) received ZOF or AMLO monotherapies before the run-in period, (2) received any other ACE-i or CCB monotherapies before the run-in period	• Number and proportion of patients divided in subgroup by the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8) o In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 (Week -4) and continued on the same therapies o In the group of patients, who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week 4)	

5 STUDY DESIGN

This is a phase IV, open-label, multicentre, multinational study with 2 study periods: a 4-week run-in period and an 8-week assessment period.
Approximately 290 patients are planned to be screened to ensure at least 216 patients complete the run-in period and start with the assessment period.
Patients with Grade 1-2 hypertensive patients (blood pressure [BP] ranging from ≥140/90 mmHg to ≤179/109 mmHg) on treatment with any angiotensin converting enzyme inhibitors (ACE-i) including Zofenopril 30 mg or with calcium channel blockers (CCBs) including Amlodipine 5 mg will be screened for eligibility (Visit 1).
Allowed CCBs: Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine. Patients treated with other dosages of Zofenopril (other than 30 mg) are not allowed to be screened.
After screening, on the same day, eligible patients, will enter into a 4-week run-in period, during which patients on other ACE-i will be assigned to monotherapy with ZOF 30 mg while patients on CCBs[§] will be assigned to monotherapy with AML 5 mg for 4 weeks. Patients with on-going treatment zofenopril 30 mg and amlodipine 5mg will continue on the same treatment for 4 weeks.

After the run-in period (4 weeks ± 2 days), BP will be further assessed (Visit 2), if BP levels are over the defined controlled target goal (sitting SBP/DBP >130/80 mmHg), treatment is well tolerated and adherence to the treatments ranges from 80% to 120%, patients will enter the assessment period, where they will be assigned to the extemporaneous combination of ZOF 30 mg and AML 5 mg. At Visit 2 patients with SBP/DBP values classified as Grade 3 (SBP ≥ 180 or DBP ≥ 110 mmHg) hypertension will be withdrawn from the study.

If patients, at Visit 2, after the run-in period, have a controlled BP (sitting SBP/DBP≤130/80 mmHg) or do not tolerate the treatment or have an adherence range below 80% or superior to 120%, they will be withdrawn from the study.

The patients will be assessed for further 8 weeks (assessment period).
After 4 weeks ± 2 days from Visit 2,during the assessment period patients receiving the extemporaneous combination of ZOF 30 mg and AML 5 mg, will be further evaluated (Visit 3): controlled patients (sitting SBP/DBP ≤130/80 mmHg) will continue the same

extemporaneous combination for additional 4 weeks ± 2 days, while uncontrolled patients (sitting SBP/DBP >130/80 mmHg) will be up-titrated from ZOF/AML 30/5 mg to ZOF/AML 30/10 mg for further 4 weeks ± 2 days.
At Visit 3 patients with SBP/DBP values classified as Grade 3 (SBP ≥ 180 or DBP ≥ 110 mmHg) hypertension will be withdrawn from the study.
If patients at Visit 3, do not tolerate the extemporaneous combination treatment or they have an adherence range below 80% or superior to 120%, they will be withdrawn from the study.
At the end of the assessment period (8 weeks ± 4 days) at Visit 4, the anti-hypertensive effect of the extemporaneous combination (ZOF/AML 30/5 mg and ZOF/AML 30/10 mg) will be evaluated.
Efforts will be made to achieve 1:1 ratio in the enrolment of patients receiving any ACE-i or allowed CCBs (refer to section Subject Study Phases Duration for allowed CCBs). At Visit 2, a minimum of 45% of uncontrolled patients receiving treatment with ZOF 30 mg or AML 5 mg are required to enter the assessment period, in order to maintain a balance between the 2 treatments during the assessment period.

5.1 Procedures and Study Visits

Patients will attend a total of four visits during the study for a duration of 12 weeks. A total number of 290 patients will be screened considering 25% of drop-out rate, to obtain at least 216 patients complete the run-in period and start with the assessment period. The description of the activities, procedures, and tests to be performed at each visit is detailed below:

Screening Visit 1 (Week -4)

The following procedures/assessments will be performed during the Screening Visit 1:

- Informed consent
- Interactive Web Response System (IWRS) registration to register the treatment allocation
- Verification of inclusion and exclusion criteria
- Collection and review of Medical history
- Collection and review of Prior and concomitant medications
- Collection of Demographic data
- Recording of concurrent diseases and medical conditions

- Physical Examination
- Vital sign measurements
- BP Measurement
- ECG
- Perform Urine Pregnancy Test (UPT) to female of child-bearing potential
- Perform Local Laboratory Tests
- Adverse Event (AE) and Serious Adverse Event (SAE) Assessment
- Paper instruction to use automatic blood pressure device, including patient's diary provided to the patient
- Automatic blood pressure device provided to patients: to be used in case of Covid-19 pandemic situation emergency procedures (Section 2.3)

Patients meeting all inclusion criteria and none of the exclusion criteria will enter the run-in period on the same day and will receive monotherapy of ZOF 30 mg or AML 5 mg.

- Patients who are already on therapy with ZOF 30 mg or AML 5 mg will be provided with the same medication
- Patients taking any other CCBs (refer to section Subject Study Phases Duration for allowed CCBs) will be provided with AML 5 mg, and patients taking any other ACE-i will be provided with ZOF 30 mg. Patients entering this phase in therapy with ZOF 30 mg or AML 5 mg should be as close as possible to a 1:1 ratio.

Visit 2 (Week 0 ± 2 days):

The following procedures/assessments will be performed at Visit 2:

- Recording of concurrent diseases and medical conditions
- Concomitant medications
- Vital sign measurements
- Physical Examination
- BP Measurement
- Urine pregnancy test (UPT)

- Study Drug Compliance assessment by return of monotherapy ZOF and AML tablets (also empty blister) and IP accountability
- AEs and serious adverse events (SAEs) assessment
- IWRS update
- Patient's instruction to use the automatic blood pressure device, including patient's diary to be returned at site by the patient

The patients with uncontrolled BP (SBP/DBP >130/80 mmHg), who tolerated the treatment and whose adherence to the therapy ranges from 80% to 120%, will enter the assessment period and at this visit will be dispensed with extemporaneous combination of ZOF 30 mg and AML 5 mg.

To correctly evaluate the additional effect of the combination therapy, the number of patients with uncontrolled BP on AML or ZOF monotherapy needs to be balanced at Visit 2. In order to maintain a 1:1 ratio during the assessment period, a cap of 110 patients for each arm (i.e., AML and ZOF) will be included at Visit 2 in order to maintain a balanced number of uncontrolled patients entering the assessment period for each drug (please refer to section 8 IWRS registration). The evaluation will be done every 50 patients. If the rate of entrance in the assessment period for one of the 2 tested drugs will deviate more than 5%, a corrective measure will be initiated: according to the enrolment site statistics, one or more sites will be informed to enrol a greater number of patients being treated with the least represented drug in the assessment period.

Visit 3 (Week 4 ± 2 days)

The following procedures/assessments will be performed at Visit 3:

- Recording of concurrent diseases and medical conditions
- Concomitant medications
- Vital sign measurements
- Physical Examinations
- BP Measurement
- Urine pregnancy test (UPT)
- Study Drug Compliance assessment (Study Drug Compliance assessment extemporaneous combination of ZOF 30 mg and AML 5 mg) return (also empty blisters) and IP accountability

- AEs and serious adverse events (SAEs) assessment
- IWRS updates
- Patient's instruction to use the automatic blood pressure device, including patient's diary to be returned at site by the patient

At Visit 3, BP will be assessed, and controlled patients will continue the same extemporaneous combination from ZOF/AML 30/5 mg, while uncontrolled patients (SBP/DBP >130/80 mmHg) will be up titrated to ZOF/AML 30/10 mg for a further 4 weeks

Visit 4 (Week 8 ± 2 days)

The following procedures/assessments will be performed at Visit 4:

- Recording of concurrent diseases and medical conditions
- Concomitant medications
- Vital sign measurements
- Physical Examinations
- BP Measurement
- ECG
- Perform Urine Pregnancy Test (UPT)
- Perform Local Laboratory Tests
- Patient's instruction to use the automatic blood pressure device, including patient's diary to be returned at site by the patient
- Patients return of the automatic BP device to the site
- Study Drug Compliance assessment [extemporaneous combination of ZOF 30 mg and AML 5 mg/10 mg) return (also empty blisters) and IP accountability]
- AEs and serious adverse events (SAEs) assessment:
  In case of any patients having an ongoing AE or SAE at the end of the treatment, there will be a follow-up telephone call after 2 weeks to ensure patient safety

The Investigator is expected to record any AE which was ongoing at the last treatment dose and a follow-up phone call should be made after 2 weeks from the last study visit.
In case of an ongoing AE, the Investigator is expected to follow-up until the outcome of the AE has been determined.

The details of the study visits are described in the Study Flow Chart Section 2.3.

6 SELECTION OF SUBJECTS

The following subject will be screened:

- Male or female, (Grade 1-2), uncontrolled hypertensive patients ≥18 and ≤65 years of age
- Considering a screening failure and a drop-out rate of 25%, the overall number of patients to be screened is 290.
- 216 patients needed to complete the run-in period and enter the assessment period to guarantee powered results

6.1 Informed Consent Process

Prior to the subject's enrolment into the study and before performing any study-related procedures, the Investigator - or its authorized delegate - shall obtain the subject's written, dated and signed informed consent to participate into the study and process personal data for processing and transferring necessary documentation of the subject's health and personal data to the CRO, Sponsor and its Affiliates, the competent Health Authorities and any other institutions, as legally required and in accordance with the local applicable privacy laws (for the Privacy information to be reported on the ICF refer to Section 17 PERSONAL DATA PROTECTION).
Institution and Investigator undertake to duly inform subjects about personal data processing and the relevant applicable privacy rights before their participation into the study.

After being duly informed and interviewed by the Investigator, . The subject freely has to date and sign the ICF before being enrolled into the study and before undergoing any study procedure. The Investigator must store the originally signed ICF in the Investigator's File, and the subject will be provided with a copy of it.
If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to EC for approval.
The Investigator will ensure that this new consent form is signed by all subjects subsequently entered in the study and those currently in the study, if affected by the amendment.

6.2 Inclusion and Exclusion Criteria

6.2.1 *Inclusion Criteria*

A patient will be considered eligible for inclusion in the study only if all the following criteria are met:

1. Male or female Grade 1-2 hypertensive patients: with mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥ 90 mmHg and ≤109 mmHg at Screening, with ≥18 and ≤65 years of age, on monotherapy either with ZOF 30 mg or AML 5mg or any other ACE-I or CCBs (Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine) for at least 1 month before Visit 1 (Screening).
2. Patients who are able to understand and give written informed consent at Screening
3. Patients who are available for the entire trial period and willing to adhere to the protocol requirements
4. Ability to take oral medication and willing to adhere to the drug regimen
5. Female patients are eligible to participate if not pregnant, or not breastfeeding and must refrain from donating or storing eggs. For females of reproductive potential: use of highly effective contraception (e.g., method of birth control throughout the study period and for 4 weeks after study completion defined as a method which results in a failure rate of less than 1% per year) such as:
    - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner (performed at least 2 months before screening) (if the partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success)
6. A male patient must agree to use contraception during the whole study period and for at least 1 week after the last dose of study treatment and refrain from donating sperms during this period

6.2.2 *Exclusion Criteria*

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. Known contraindications, presence of not recommended/contraindicated concomitant therapy allergies, or significant history of hypersensitivity to zofenopril, amlodipine, other ACE-inhibitors or dihydropyridines, or any related products (including excipients of the formulations as outlined in the Investigator's Brochure [IB]), or summary of product characteristics (SmPCs) or local package inserts for AML and ZOF
2. Patients with serious disorders (in the opinion of the Investigator) which may limit the ability to evaluate the efficacy or safety of the tested medications, including cerebrovascular, cardiovascular, renal, respiratory, hepatic, gastrointestinal, endocrine/ or metabolic, haematological, or oncological, neurological, and psychiatric diseases. The same applies for immunocompromised and/or neutropenic patients
3. Patients having a history of the following within the last 6 months: myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, bypass surgery, valve replacement (transcatheter aortic valve implantation, mitraclip),cerebrovascular accident (stroke, heart failure, hypertensive encephalopathy, cerebrovascular accident (stroke), or transient ischemic attack. Patients with who have undergone other surgery that in the in the opinion of the Investigator may limit the ability to evaluate the efficacy or safety of the tested medications.
4. Patients with secondary hypertension of any aetiology such as renal diseases, pheochromocytoma, Cushing's syndrome hyperaldosteronism, renovascular disease, thyroid disorders
5. Patients with severe heart failure (New York Heart Association classification III-IV), a narrowing of the aortic or bicuspid valve, an obstruction of cardiac outflow (obstructive, hypertrophic cardiomyopathy) or symptomatic coronary disease
6. Patients with clinical evidence of renal disease as per the Investigator's judgement (including renovascular occlusive disease, nephrectomy and/or renal transplant, bilateral renal artery stenosis or unilateral renal artery stenosis in a solitary kidney, or severe renal impairment)
7. Patients with history of angioneurotic oedema
8. Patients with clinically relevant hepatic impairment
9. Patients with sick sinus syndrome, including sino-atrial block
10. Patients with second- or third-degree heart block (without a pacemaker)
11. Participation in any other interventional drug trial or exposure to other investigational agents within 30 days before Screening (Visit 1)
12. Inability to cooperate or any condition that, in the opinion of the Investigator, could increase the patient's risk of participating in the study or confound the outcome of the study

13. Patients with conditions that, in the opinion of the Investigator, would prevent a careful adherence to the protocol
14. Patients with severe hypotension
15. Patients who suffer from shock (including cardiogenic shock)
16. Patients treated with Amlodipine 10 mg and Zofenopril (other than 30 mg)

6.2.3 *Screening Failures*

All patients who have signed an informed consent form but do not enter into the Run-in period (failure to meet at least one of the inclusion criteria and/or met at least 1 of the exclusion criteria) will be classified as a screening failure. Screening failures need to have the screening completion eCRF for run-in period, demographics, inclusion / exclusion criteria and any SAE collected. There will be no re-screening allowed for screening failure patients.

7 STUDY TREATMENT

7.1 Study Treatment Formulation, Appearance, Packaging, and Labeling

Zofenopril calcium will be provided as 30 mg film coated tablets

Amlodipine (as besylate) will be provided as 5 mg and 10 mg tablets

The treatments administered during the run-in period of the study are AML 5 mg tablets or ZOF 30 mg film-coated tablets. The patients who are eligible (uncontrolled hypertension with sitting BP of SBP/DBP >130/80 mmHg, who tolerated the treatment and whose adherence to the therapies ranges from 80% to 120%) for the assessment period will be given a combination of AML 5 mg and ZOF 30 mg or AML 10 mg and ZOF 30 mg. Details on the study design is provided in Section 5.

Study Treatment Name:	Amlodipine **Marketing Authorisation Holder**: EG S.p.A. Via Pavia, 6 20136 Milano Italy	Zofenopril calcium **Marketing Authorisation Holder**: Laboratori Guidotti S.p.A. - Via Livornese 897, PISA – La Vettola Concessionario per la vendita: A. Menarini Industrie Farmaceutiche Riunite s.r.l., Via Sette Santi, 3 – Firenze, Italy
Dosage Formulation:	Tablets	Film-coated tablets
Unit Dose Strength(s)/Dosage Level(s):	5 mg once daily 10 mg once daily	30 mg once daily
Route of Administration:	Oral	Oral
Dosing Instructions*:	1 tablet of study medication to be administered with water, once daily and according to instructions provided by Principal Investigator	1 tablet of study medication to be administered with water, once daily and according to instructions provided by Principal Investigator
Packaging and Labelling:	Study medication will be provided in its original marketed PVC//Aluminium blisters	Study medication will be provided in its original marketed a PVDC/PVC//Aluminium blisters
Storage Conditions:	All study treatment must be stored in its original packaging and kept in a secure area (in a dry place and protected from light and in accordance with the label's instructions) with access limited to the Investigator and authorized site staff. No other special storage conditions are needed.	All study treatment must be stored in its original packaging and kept in a secure area (in a dry place and protected from light and in accordance with the label's instructions) with access limited to the Investigator and authorized site staff. No other special storage conditions are needed.

Study treatment dosage form, strength, formulation:
Amlodipine 5 mg: AML 5 mg is white, round, tablet
Amlodipine 10 mg: AML 10 mg is white, round, tablet with one break on one side

Zofenopril calcium 30 mg: ZOF 30 mg is white, oblong film-coated tablet with break marks on both sides.

Study treatment manufacturing

The AML 5/10 tablets and ZOF 30 mg film-coated tablets will be sourced as authorized EU marketed products from a commercial supplier in the European market.
Marketing Authorization Holders (MAH) are reported in relative SmPC[7,8].

Study treatment packaging and labelling

The study treatment packaging and labelling operations are performed by A. Menarini Manufacturing Logistics and Services S.R.L. (Menarini Group), Via Sette Santi, 3 50131-Florence (Italy).

The study treatment packaging and labelling operations will be performed in compliance with all applicable regulatory requirements and Good Manufacturing Practice guidelines, as well as any additional national requirement and Standard Operative Procedures (SOPs).
The label wording will be in the local language for each country and will report the contents of the boxes and the instructions on how to administer and store the study medication.

Study treatment packaging description

Both ZOF 30 mg and AML 5/10 mg will be provided in dedicated treatment Patient Kits to be dispensed at Visit 1 (Run In) and at Visit 2 and Visit 3 (Assessment).

Visit 1 (Screening- start Run In)

- ZOF 30 mg: each trial participant is provided with one labelled Patient Kit (blue label) containing 42 film-coated tablets (3 blisters of 14 tablets each) of zofenopril calcium 30 mg.
- AML 5 mg: each trial participant is provided with one labelled Patient Kit (yellow label) containing 42 tablets (3 blisters of 14 tablets each) of amlodipine 5 mg.

Trial participant must be instructed by Investigator to take one tablet of ZOF 30 mg or AML 5 mg, according to Study Protocol.

Visit 2 (start of Assessment)
Participants with uncontrolled BP (>130/80 mmHg) will be provided with ZOF 30 mg and AML 5 mg while participants with controlled BP (≤130/80 mmHg) will be withdrawn from the study
Each trial participant is provided with one treatment Patient Kit made up by

- ZOF 30 mg: one labelled box (white label) containing 42 film-coated tablets (3 blisters with 14 film coated tablets each) of zofenopril calcium 30 mg
- AML 5 mg: one labelled box (white label) containing 42 tablets (3 blisters with 14 tablets each) of amlodipine 5 mg.

The two white labelled boxes are then sealed together into a transparent plastic film to realize the treatment Patient Kit.
Trial participant must be carefully instructed by Investigator to take simultaneously (at the same time): ZOF 30 mg (zofenopril calcium 30 mg) as one oblong film-coated tablet and AML 5 mg (amlodipine 5 mg) as one round tablet, according to Study Protocol.

Visit 3 (Assessment)
Participants **with controlled BP (≤130/80 mmHg)** are provided with one treatment kit made up by:

- ZOF 30 mg: one labelled box (white label) containing 42 film-coated tablets (3 blisters with 14 film coated tablets each) of zofenopril calcium 30 mg
- AML 5 mg: one labelled box (white label) containing 42 tablets (3 blisters with 14 tablets each) of amlodipine 5 mg.

The two white labelled boxes are then sealed together into a transparent plastic film to realize the treatment kit.
Trial participant must be carefully instructed by Investigator to take simultaneously (at the same time): ZOF 30 mg (zofenopril calcium 30 mg) as one oblong film-coated tablet and AML 5 mg (amlodipine 5 mg) as one round tablet, according to Study Protocol.

Participants with SBP/DBP values classified as Grade 3 hypertension will be withdrawn from the study
Participants **with uncontrolled BP (>130/80 mmHg**) are provided with one treatment Patient Kit made up by:

o ZOF 30 mg: one labelled box (green label) containing 42 film-coated tablets (3 blisters with 14 film coated tablets each) of zofenopril calcium 30 mg
o AML 10 mg: one labelled box (green label) containing 42 tablets (3 blisters with 14 tablets each) of amlodipine 10 mg.
The two green labelled boxes are then sealed together into a transparent plastic film to identify the treatment Patient Kit.
Trial participant must be carefully instructed by Investigator to take simultaneously (at the same time): ZOF 30 mg (zofenopril calcium 30 mg) as one oblong film-coated tablet and AML 10 mg (amlodipine 10 mg) as one round tablet (with one break on one side), according to Study Protocol

7.2 Study Treatment Distribution and Return / Destruction

All the study drugs must be retained at the investigational site for accountability, destruction and return of study supplies.
The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition.
Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained.
The investigator is responsible for ensuring the retrieval of all study supplies from patients.

At the conclusion of the study, any unused investigational product will either be destroyed at the investigator site or be returned to the Sponsor or its designee for destruction and destruction will be documented appropriately.
If no supplies remain, this fact will be documented appropriately
Destruction of returned investigational products must carried out after written authorization of the Sponsor

7.3 Product Storage and Stability

No special storage conditions are required. However, the verification of the storage conditions along with the relevant records will be monitored at the trial site.

All study treatment must be stored in its original packaging and kept in a secure area (in a dry place and protected from light and in accordance with the label's instructions) with access limited to the Investigator and authorized site staff.

7.4 Study Product Compliance

The investigator must promote compliance by instructing the patient to the study treatment exactly as prescribed and by stating the compliance is necessary for the patient's safety and the validity of the study. The investigator has to instruct patients to return the study treatment (if any or empty boxes for accountability) at each visit.

Investigator should instruct the patient to take the study drug at the same time every day, in the morning. On the days of the patient's visits, the investigator should instruct the patient to not take the study drug at home.

In case a patient forgets to take a dose, he/she can by take the study drug the same day. Patients should not take the study drug after 16.00 (4 pm) on the visit days. The investigator should instruct the patient to not take the dose at home.

The compliance to the treatment (percentage of actual doses taken versus doses to be taken) will be assessed by the investigator and/or study personnel at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8). This information should be captured in the source document and in the eCRFs at each visit.

Adherence to treatment will be measured through treatment compliance which is 100 × (actual doses taken/planned dose).
A patient who has taken at least 80% and no more than 120% of the required study medication intake since the last visit will be considered as compliant.

7.5 Concomitant Therapy(ies)

The investigator must instruct the patient to notify the study site about any new medication he/she takes after being enrolled into the study. All medication, procedures and significant non-drug therapies administered after the patient was enrolled at the study must be recorded in the

appropriate eCRF. Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If the patient is already enrolled, please contact BIORASI to determine if the patient should continue participation in the study.

7.6 Not permitted medications

Blood pressure modifying drugs, even though used for other indications like alpha receptor blockers and agonists, beta receptor blockers and agonists, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, diuretics, centrally acting antihypertensives (e.g. clonidine, methyldopa, guanfacine), reserpine, moxonidine, chronic nitrate treatment (e.g. isosorbide dinitrate or isosorbide mononitrate), potassium sparing diuretics, potassium supplements, potassium-containing salt substitutes or other agents that increase serum potassium, PDE - inhibitors and angiotensin II antagonists will be prohibited during the study.

The Investigator has to instruct patients to refer to the study doctor before they administer any medicinal substances or products listed in section 4.5 of the Zofenopril and Amlodipine SmPC[7,8].

7.7 Rescue Medicine

Not Applicable.

8 STUDY ASSESSMENT AND PROCEDURES

The following study assessment and procedures will proceed according to the Study Flow Chart in Section 2.3.

Informed Consent

A signed and dated, study-specific, Independent Ethics Committee (IEC) approved consent form must be obtained from each patient at the Screening Visit and prior to performing any study related procedures. No study related procedures or activities may be performed until each patient is fully informed and the consent form is duly read, understood, signed and dated. All patients will be given a copy of the signed and dated consent form. The Investigator must store

the originally signed ICF in the Investigator's File, and the patient will be provided with a copy of it. For more details, please refer to Section 6.

Inclusion/Exclusion Criteria

All patients who sign the ICF will be evaluated for inclusion and exclusion criteria to determine patient eligibility as described in Section 6.1. If the patient is determined to be ineligible prior to enrolment, the reason(s) for ineligibility must be documented by the Investigator. Verification of all inclusion and exclusion criteria, including all baseline assessments, will take place at the Screening Visit.

Medical History

A complete medical history for each patient will be recorded at the Screening Visit. A complete review of all current diseases, history of hypertension, and their respective durations and treatments will be conducted, and the relevant documentations will be filed in the Source Documentation.

Prior medication

At the Screening Visit, all medications taken within the 30 days prior to the start of the study will be recorded as Prior Medication with the corresponding indication, start and stop dates. Prior medications may include prescription, over-the counter (OTC) and all dietary supplements. A particular focus will be on prior medication to treat hypertension including zofenopril or amlodipine status and dosage.

Demography

After the informed consent has been signed and the patient's eligibility to participate in the study has been determined at the Screening Visit, basic demographic information, including age, gender, race, height, and weight. The BMI (kg/m^2) will be calculated will be recorded. Smoking status will be documented in the source documents and Ecrf. For female patients, the menopausal status would also be documented.

IWRS registration:

At Visit 1 all screened patients will be registered via Interactive (IWRS) to one of the allocated treatments: zofenopril 30 mg and amlodipine 5 mg. The investigator or his/her delegate will contact the IWRS after confirming that the patient fulfils all the inclusion /exclusion criteria. The percentage of enrolled patients coming from each monotherapy treatment, Zofenopril 30 mg / Amlodipine 5 mg will be capped at 50% at Visit 2.
IWRS must be updated at each visit, registering the status of the patient (failure, ongoing and which therapy the patient's is administering)

Concurrent diseases and medical conditions

At each of the study visits (1, 2, 3, and 4) current diseases and medical conditions will be recorded including their date/time of diagnosis, duration, and treatment. Adverse event will be conditions arising after the start of the study, which should be recorded as adverse events as described in Section 9.1.

Monotherapy of zofenopril 30 mg or amlodipine 5 mg dispensing

- At the Screening Visit (Visit 1):
  - Patients who are currently being treated with zofenopril (ZOF) 30 mg or amlodipine (AML) 5 mg will continue the same therapy for 4 weeks.
  - Patients on any other ACE-i will be assigned to monotherapy with ZOF 30 mg for 4 weeks.
  - Patients on other CCBs (the allowed CCBs are: felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine) will be assigned to monotherapy with AML 5 mg for 4 weeks.

The study drugs will be dispensed such that patients have sufficient supply to last until the next visit (Visit 2). All patients will be counselled to keep the packaging and any remaining drug to be surrendered during Visit 2.
Extemporaneous combination of ZOF/AML 30/5 mg dispensing

At Visit 2 (after the run-in period (4 weeks ± 2 days) of monotherapy) if BP remains uncontrolled (sitting SBP/DBP >130/80 mmHg), treatment is well tolerated and adherence to

the treatments ranges from 80% to 120%, patients will enter the assessment period, where they will be assigned to the extemporaneous combination of ZOF 30 mg and AML 5 mg. The study drugs will be dispensed such that patients have sufficient supply to last until the next visit (Visit 3). All patients will be counselled to keep the packaging and remaining drug to be collected during Visit 3.
At Visit 2 patients with SBP/DBP values classified as Grade 3 hypertension (SBP ≥ 180 or DBP ≥ 110 mmHg) will be withdrawn from the study.

At Visit 3, if BP is controlled (≤130/80 mmHg), patients will continue the same extemporaneous combination ZOF/AML 30/5 mg for additional 4 weeks ± 2 days (Visit 4).

Extemporaneous combination of ZOF/AML 30/10 mg dispensing

At Visit 3, if BP is controlled, patients will continue the same extemporaneous combination for additional 4 weeks ± 2 days (Visit 4). Uncontrolled patients (sitting SBP/DBP >130/80 mmHg), will be up titrated from AML 5 mg to AML 10 mg for further 4 weeks ± 2 days (Visit 4).
At Visit 3 patients with SBP/DBP values classified as Grade 3 (SBP ≥ 180 or DBP ≥ 110 mmHg) hypertension will be withdrawn from the study

Study drug return/accounting (Compliance assessment)

The study drugs will be dispensed on site such that patients have sufficient supply to last until the next visit. All patients will be counselled to keep the packaging and remaining drug to be returned to the site staff at the subsequent visit. Site staff will collect the unused drug and packaging and provide an assessment of compliance at Visits 2, 3, and 4.

Concomitant medications
Any medication that the patient was receiving at the time of enrolment, and the other regular or occasional use of any concomitant medication during the study will be recorded in the source documents and in the eCRF. The concomitant medications will be recorded at the Screening Visit and each subsequent visit during the study.

8.1 Assessment of Efficacy

The primary objective of this study is to assess the anti-hypertensive efficacy of the extemporaneous combination of ZOF 30 mg in combination with AML 5 mg or AML 10 mg in lowering the sitting diastolic BP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with Zofenopril or Amlodipine (5 mg) monotherapies for at least 4 weeks. The primary efficacy endpoint is change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8). To achieve this objective, the efficacy parameter BP will be measured at all visits as described below.

Blood Pressure (BP)

BP will be measured in both arms at the screening visit (Visit 1) to detect possible between-arm differences. The arm with the higher value of mean DBP will be identified as the reference arm and will be used at all subsequent visits for BP monitoring. Blood pressure measurements should be performed as nearly as possible at the same time of the day (7:00 – 12:00 a.m.), on the same arm, and using the same calibrated equipment at each visit.
All BP measurements will be performed after at least 10 minutes rest in sitting position in triplicate (spaced by at least 1 minute) and once standing using an automatic device provided by MENARINI. The mean of the three recordings in sitting position will be used as the BP value for that visit and recorded in the source document and in the eCRF. All BP measurements during the treatment phase will be performed as through readings (i.e. 24 + 2 h after the last drug intake). Thus, the study drug should be taken at morning time Post-BP measurement.
For this purpose, patients will be instructed to take study treatment at the same time each day except on the days of study visits when study treatment will be taken after all visit evaluations have been performed.

8.2 Assessment of Safety

Safety will be assessed through collection of treatment-emergent AEs, serious AEs (SAE), , that started after the first dose of study treatments (incidence, severity, seriousness, treatment causality), and physical examination (, vital signs, BP, and heart rate). Safety assessments will be performed at time points as described in Section 9.

Urine Pregnancy test

Study medication should not be given to pregnant female. Therefore, Urine Pregnancy tests will be performed in all females of childbearing potential at Screening and each subsequent visit during the study.

Physical examination

The Investigator (or site staff) must perform a complete physical examination at Screening and each subsequent visit during the study. At the Screening visit height, weight (in indoor clothing but without shoes) and body mass index [BMI] calculation will be recorded. At all visits, the physical examination will include general appearance, skin, head, neck, ear-nose-throat (ENT), heart, lungs, abdomen, extremities, neurological, musculoskeletal and lymph nodes. Information pertaining to physical examinations must be included in the source documentation at the study site. Any new finding, or worsening of a previous finding, should be reported as a new AE.

Vital Signs

Body temperature (°C) and heart rate will be measured under the same conditions at Screening and all subsequent visits (Visit 2, Visit 3, and Visit 4). If possible, vital sign assessment should be performed by the same study site staff member using the same validated device throughout the study. Blood pressure will also be measured at all visits as described above.
Vital signs should be performed prior to taking the blood samples.

Electrocardiograms

In this study, Local ECG will be used and will be performed by a qualified clinical site physician. All 12-lead electrocardiogram (ECG) will be standardized recordings. Single 12-lead ECGs will be performed at Screening (Visit 1) and at Visit 4. Additional 12-lead ECG will be performed at other times if judged to be clinically appropriate or if the on-going review of the data suggests a more detailed assessment of ECG is required. ECGs will be performed in triplicate at Visit 1 and Visit 4.

The patient must rest in a supine position for 5 minutes before the ECG is obtained. ECG tracings (paper or electronic) should be reviewed and interpreted by the Investigator or a qualified clinician. ECG parameters including ventricular rate, RR-Interval [ms], PR-Interval [ms], Rhythm (sinusal - other), PR, QRS, QT, QTcF, and QTcB intervals will be recorded.

If QTcF > 450 ms, it should be evaluated and used for clinical decision: another triplicate ECG is indicated and if required should be discussed with the Sponsor and/or medical monitor.

The original ECGs must be appropriately signed, collected and archived at the study site. Printouts and related copies for each ECG will include date, time, initials of the technician/nurse, and initials of the Investigator who reviewed the printout and should be properly archived at site.
Clinically relevant abnormalities should be recorded first on the source documents by the PI and then on the relevant section of the eCRFs.

Laboratory tests

A local laboratory will be used for laboratory evaluation. Clinical laboratory tests (chemistry and haematology) will be conducted at Screening (Visit 1) and Visit 4. Blood and urine samples for pregnancy test will be collected, processed, and analysed locally and in accordance to the research site's SOPs.

The maximum volume of blood to be taken is approximately 40 mL, which will be the total blood collected during the study.

The results should be evaluated for criteria defining AE and reported as such if the criteria are met. In all cases, the investigator must document in the source documents, the clinical considerations (i.e. results were or was not was clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

To ensure patient safety, the patients will be contacted over phone within 24 hours, in case of any abnormality and clinically relevant laboratory test according to the Investigator's judgement at any visit. The results of laboratory tests will be returned to the Investigator, who is responsible for

reviewing and filing these results. Note: Patients who will be reported with an abnormal renal function (creatinine clearance <30 mL/min) and/or abnormal liver enzyme parameters (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level of >2.5 × upper limit of normal [ULN] or bilirubin level >1.5 × ULN) will be withdrawn from treatment and study.

The following parameters Haematology and Serum Chemistry parameters will be assessed:

Haematology	Serum Chemistry
Red blood cell	ALT
White blood cell	Albumin
Haemoglobin	Alkaline phosphatase
Haematocrit	AST
Platelets	Direct bilirubin
Neutrophils	Total bilirubin
Lymphocytes	Total protein
Monocytes	Creatinine
Eosinophils	Blood urea nitrogen
Basophils	Creatine kinase
Neutrophils absolute	GGT
Lymphocytes absolute	Triglycerides
Monocytes absolute	Cholesterol
Eosinophils absolute	High- and low-density lipoprotein
Basophils absolute	Chloride
	eGFR
	Blood glucose
	Potassium
	Uric acid

AE/SAE Assessments

The assessment of adverse events (AEs) by seriousness and relationship will be performed at all visits. AEs that occur after a patient has signed the ICF and prior to exposure to study drug will be recorded on the case report form and will not be considered treatment emergent adverse events (TEAEs).

Management of clinical trial during Pandemic COVID-19

Since December 2019, an outbreak of respiratory disease caused by a novel coronavirus, first detected in Wuhan City, Hubei Province, China, has been detected in nearly all countries of the world. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On 08 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic.

The COVID-19 public health emergency may impact the conduct of clinical trials of medical products. In response to the pandemic, various health authorities have issued guidelines to maintain the integrity of ongoing clinical studies

Summary of Changes in Study-Related Procedures as a Result of the COVID-19 Pandemic

To assure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity, if necessary, the method of assessments may be changed at the discretion of the Sponsor. In addition, site visits may be replaced with home visits, telephone, or internet-based video-conferencing applications. For this study, except in an urgent situation, changes in study conduct need to be approved by the Sponsor before being initiated. The specific changes to be implemented will be based on the current conditions in the country/region and will be reassessed on an ongoing basis. Not all countries or all sites in a country may be impacted. Normal procedures, as described in this protocol, will be resumed as soon as possible thereafter.
This section describes the COVID-19 mitigation plans for MASOLINO study. The following mitigation measures will be implemented in study-related procedures as a result of the COVID-19 pandemic.
Clinical investigators should document in site files and in source documents as appropriate how restrictions related to COVID-19 originated changes to the study conduct, duration of changes, and which participants were affected by such changes. Communications with Sponsor regarding the implementation of the herein described mitigation measures should be documented in the source documents.

Informed consent

This paragraph is applicable only in case a patient needs to re-consent in study participation.
Initial informed consent signature must be provided at site during Visit 1 (Screening)
Each participant must be provided with new information that might impact their willingness to participate in the study in a timely manner. Should the participant need to re-consent if permitted by investigative site procedures and local regulations, the informed consent form can be mailed to the participant.
The participant can sign the consent form at home and mail it to the study site. Alternatively, the PI or designee can visit the participant at home to present the changes to the study and obtain the informed consent form signature at the participant's home. If the participant has any questions about the changes to the study prior to providing their signature, they will be provided with an opportunity to discuss these questions with the PI or designee.
After having obtained the consent, a copy of the signed consent must be sent to or stay with the participant.

Study Treatment Distribution and Return

This paragraph is not applicable for Visit 1 (screening) but only for the subsequent visits.
Due to social restriction measures, the participant may not be able to reach the study site. In such cases, the study treatment will not be dispensed to the participants at the site. Instead, the study treatment may be distributed to the participants' home at the times defined in the Study flow chart by the designated site staff or by a distributor independent from and acting on behalf of the sponsor in line with national law or temporary national emergency measures. Participants will be informed and trained on the new dispensing procedures. Participants will be instructed to keep unused study treatment, which will be collected by the designated site staff on the earliest possible time or agreed with the participant to return to site via courier.

Study assessment and procedures

The Screening visit is a mandatory in clinic/hospital visit and therefore should be performed at the site. The Principal Investigator continues to be responsible for reviewing all study -related assessments.
The participant may not be able to reach the site to perform blood pressure (BP) measurement for primary and secondary analysis, clinical laboratory tests, vital sign and physical examination, electrocardiogram (ECG), or other assessments required by the study flow chart

In such cases, these assessments will be performed by the health care professionals (study staff or qualified designee) at participant's home, if allowed per country regulations.

At Visit 1 patients will be provided with an automatic BP device, instructions, on how to measure BP, and a diary to record the relevant BP values. In the case of COVID-19 restrictions, all patients will be able to measure BP themselves. All patients will be fully trained by the investigator or delegated site staff and training will be recorded in the relevant source documentation. Patients will note the BP measurements in the diary and communicate it to the appropriate site staff. The diary will be returned at the first on-site visit if possible or it will be delivered via mail/e-mail.

9 SAFETY DATA MANAGEMENT

9.1 Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

9.2 Drug Relationship

The relationship between an AE and study drugs will be judged according to the following categories:

- **Certain**: The AE occurs in a plausible time relation to the administration of the drug and cannot be explained by a concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- **Probable:** The AE occurs in a reasonable time relation to the administration of the drug, it is unlikely to be attributed to a concurrent disease or other drugs or chemicals and it follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge

information (AE reappearance after drug reintroduction) is not required to fulfil this definition.

- **Possible**: The AE occurs with a reasonable time relation to the administration of the drug, but it could also be explained by a concurrent disease or other drugs or chemicals. Information on drug withdrawal (dechallenge) may be lacking or unclear.
- **Unassessable:** The relationship cannot be judged, because of the information is insufficient or contradictory and cannot be supplemented or verified.
- **Unlikely**: A causal relationship cannot be definitively ruled out, but:
- other drugs, chemicals, or underlying disease provide plausible explanations and / or
- the temporal relation to the administration of the drug makes a causal relation improbable.
- **Not Related**: Any of the following are present:
  - existence of a clear alternative explanation, and / or
  - unreasonable temporal relationship between Drug and Event, and / or
  - non-plausibility.

9.3 Adverse Drug Reaction (ADR)

An ADR is any untoward and unintended response to an investigational medicinal product related to any dose administered.
The definition implies a reasonable possibility of a causal relationship between the event and the Investigational Medicinal Product (IMP). This means that there are facts (evidence) or arguments to suggest a causal relationship.
An ADR is considered any AE for which the relationship is considered as:

1. Certain
2. Probable
3. Possible
4. Un-assessable

An AE is not considered as ADR when the relationship is judged as:

1. Unlikely
2. Not related

9.4 Seriousness

An AE/ADR is considered Serious when:
1. Results in death;
2. Is life-threatening.

Note: Life-threatening is considered any AE 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.

- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability / incapacity;
- is a congenital anomaly/birth defect;
- is another medically important condition that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Any suspected transmission of an infectious agent via a medicinal product is considered serious and should be assessed under the category of medically important events in the absence of other seriousness criteria.

An AE / ADR is considered non-serious when it does not fulfil the conditions for the definition of Serious AE / ADR.

9.5 Adverse Event / Adverse Drug Reaction Intensity

The intensity level of a Serious or a Non-serious AE or ADR is attributed according to the following definitions:
- **Mild:** does not interfere with routine activities; in case of laboratory tests, when there is a mild abnormality.
- **Moderate**: interferes with the routine activities; in case of laboratory tests, when there is a moderate abnormality.
- **Severe**: makes it impossible to perform routine activities; in case of laboratory tests, when there is a significant abnormality.

9.6 Adverse Event / Adverse Drug Reaction Expectedness

An AE/ADR is considered Unexpected when the nature, severity, or outcome of the AE/ADR is not consistent with the information provided in the Reference Safety Document (summary of product characteristics for Zofenopril and Amlodipine)[7,8].

9.7 Serious Unexpected Adverse Drug Reaction (SUSAR)

Any SAE judged by the Investigator or the Sponsor as drug-related (see Section 9.3) and considered as unexpected qualifies as a SUSAR.
SUSARs are subject to expedited reporting, as specified in Section 9.10, as having a "Reasonable Possibility" of relationship with the IMP.

9.8 Individual Case Safety Report (ICSR)

Format and content provided to describe one or several AEs or a disease experience that occur to an individual subject at a particular point of time.

9.9 Collection, Recording and Reporting of AEs

At each visit the Investigator will collect and assess any occurred subjective or objective AE occurred to each subject after his / her signature of the informed consent.
The Investigator should manage as AE any laboratory test abnormality (newly occurring after the IMP administration or worsening of previously known abnormalities) considered as clinically relevant: i.e. values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the IMP discontinuation.
Any AE communicated by the subject or by the subject's relatives or delegates through phone calls, letters or e-mails will also be collected and assessed.
The Investigator shall record on the respective eCRF AE recording pages / AE form any recognised AE identifying an ICSR, both serious and non-serious, whether or not thought to be drug-related, observed in or reported by the subject (or relatives / delegates), specifying the judgement on the causal relationship with the study treatment.
Any available information and diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall be recorded in and / or attached to the concerned eCRF pages / sections.

The Investigator is expected to also record any AE which was ongoing at the last treatment dose and a follow-up phone call should be made after 2 weeks from the last study visit.
The Investigator is expected to follow up any AE occurred during the study, including the follow-up period, until the outcome of the AE has been determined.
The Investigator must report all the collected information on any ICSR with Serious and Non Serious AE (whether or not thought to be related to the investigational drug), providing the *concerned eCRF-AE pages/ by alert email)*, after the first knowledge of the occurrence of the case, to:

CRO Pharmacovigilance Officer:
Email: MEIN/20/ZoAm-Hyp/001-safety@biorasi.com
Fax: +1 (786) 221-3531
Tel: +1 (786) 388-0700
Mobile: N/A

When relevant, also the eCRF pages concerning medical history, concomitant medication, and laboratory tests will be placed at Sponsor disposal by email.

9.10 Management of Serious AEs (SAEs) including laboratory abnormalities

9.10.1 Reporting Duties of the Investigator

The Investigator must report all the collected information on any eCRF with SAE (whether or not thought to be related to the investigational drug), as above specified, **no later than 24 hours** after the first knowledge of the occurrence of the case.
Any further information and supporting documentation that become available (copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall be provided **no later than 24 hours** after the knowledge, by the Investigator to the CRO by email (MEIN/20/ZoAm-Hyp/001-safety@biorasi.com) to be forwarded to the Sponsor.
The Investigator must also comply with the local applicable obligation(s) on the reporting of ADRs to the local concerned Regulatory Authority/Ethics Committee.

9.10.2 Reporting Duties of the Sponsor

The Sponsor shall ensure that all relevant information about any SUSAR, is expeditiously reported to the competent Authorities and Ethics Committees as required, with these deadlines

after the first knowledge, intended as the day when the CRO receives the notification of the SUSAR:

– Fatal and life-threatening unexpected cases, no later than 7 days.
– Other unexpected serious cases, no later than 15 days.

The Sponsor shall ensure that all relevant information and supporting documentation that subsequently becomes available, is also expeditiously reported as follow-up information according to the above-mentioned deadlines.

Furthermore, the following safety issues will be subjected to expedited management for the identification of possible necessary actions:

– SAEs associated with the trial procedures.
– Potential clinically significant findings emerging from non-clinical studies.
– An anticipated end or suspension for safety reasons of another trial with the same study drug.

When appropriate and applicable the Sponsor will arrange the adequate information also to the Investigators.

9.11 Management of Non-serious AEs (NSAEs) including laboratory abnormalities

9.11.1 Reporting Duties of the Investigator

The Investigator must report all the collected information on any eCRF with NSAE (whether or not thought to be related to the investigational drug), as above specified, no later than **5 Calendar days** after the first knowledge of the occurrence of the case.
Any further information and supporting documentation that become available (copies of laboratory reports, tests, procedures, etc.) shall be provided **no later than 24 hours** after the knowledge, by the Investigator to the CRO by email, to be forwarded to the Sponsor.

9.12 Management of any laboratory abnormality

Any laboratory test abnormality which is considered by the Investigator as AE is to be managed as above detailed (refer to Section 9.9).
However, all "out of range" values should be collected and reviewed periodically every 2 months by the CRO and the Sponsor.

9.13 Management of pregnancy exposure cases

The Investigator is expected to record in the provided form (Pregnancy Exposure Form)any case of pregnancy exposure occurring in a female subject or in a male subject's partner during the treatment and follow-up periods, sending it within 5 days after being made aware of the pregnancy, to the CRO *by email*, to be forwarded to the Sponsor.
The Investigator is requested to follow each case of pregnancy exposure until the outcome.
If the pregnancy results in an abnormal outcome, this will be recorded in the eCRF as a SAE and managed as above described.

Eligibility of a woman of childbearing potential (WOCBP) will be considered as described in Section 6.2.

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile as described below.

Women in the following categories are not considered WOCBP if:

- Premenarchal
- Premenopausal female with one of the following:
    - o Documented hysterectomy.
    - o Documented bilateral salpingectomy.
    - o Documented bilateral oophorectomy.

Note: Documentation can come from the study centre personnel's: review of the patient's medical records, medical examination, or medical history interview.

Postmenopausal female: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH)

level to 30 mIU/mL or higher may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10 WITHDRAWAL CRITERIA

Patients are free to discontinue the trial at any time without giving their reasons without losing the right to future medical care. Patients who withdraw from the trial will also be withdrawn from the investigational medicinal product.
Patients who voluntarily withdraw their consent can do so for any of the following reasons:

- Does not want to participate in the study anymore
- Does not permit further collection of personal data

The investigator should make a reasonable effort to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study participants may, at any moment, be withdrawn by the Investigator, if considered appropriate. Patients can be withdrawn for any of, but not limited to, the following reasons:

- If the patient meets an exclusion criterion (newly developed or not previously recognized) that precludes further study participation
- Adverse events: when during the conduct of the study, adverse events occur that, in the Investigator's judgement, are of such a nature or severity to recommend treatment withdrawal
- Failure to comply with requirements of the protocol including, but not limited to evidence of non-compliance with inclusion/exclusion criteria during the study or patient non-compliance with key study procedures

- By request of the patient including explicit withdrawal of patient's consent to participate
- Patient's failure to report to study visits
- Patient's loss to follow-up (for guidance see Section 11)
- Withdrawal by Investigator's judgement: Investigator may choose to withdraw a patient from the study if the Investigator deems it in the best interest of the patient to discontinue.

Patients who satisfy the following criteria will also be withdrawn from the study:

- If at Visit 2 patients have a controlled BP (sitting SBP/DBP ≤130/80 mmHg) or do not tolerate the treatment or have an adherence range below 80% or superior to 120%.
- If at Visit 3 the patients do not tolerate the extemporaneous combination treatment or have an adherence range below 80% or superior to 120%.
- Patients with abnormal renal function (creatinine clearance <30 mL/min) and/or abnormal liver enzyme parameters (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level of >2.5 × upper limit of normal [ULN] or total bilirubin level >1.5 × ULN).

If a patient has been withdrawn due to an AE, the Investigator must immediately contact the relevant pharmacovigilance contact (see Safety Data Management section). The reason for patient withdrawal must be well-documented in the Electronic Case Report Form (eCRF). The eCRF should capture the date and specific underlying reason for discontinuation of study product or patient discontinuation/withdrawal. Study treatment must be discontinued, and no further assessment conducted, and the data that would have been collected at subsequent visit will be considered missing. Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up. All effort should be made to complete the assessment prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Early termination visit scheduled assessment.
Patients who discontinue from the study early will complete an early termination visit.

Subjects who prematurely withdrawn from study medication or from the study will not be replaced. These subjects will not be considered lost to follow-up.

11 LOST TO FOLLOW UP

A patient will be considered lost to follow-up if he or she fails to return for 2 or more scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a patient fails to return to the clinic for a required study visit.
The site staff will attempt to contact the patient and reschedule the missed visit within 2 business days. Site staff will counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study.

Before a patient is deemed lost to follow-up, the investigator or designee will make every effort (e.g. letters, telephone calls) to regain contact with the patient. Each contact attempt should be documented in the patient's medical record or study file.

12 STATISTIC

This section outlines the major features of statistical analyses. More detailed methodology for summary and statistical analysis of data collected in this study will be documented in the statistical analysis plan (SAP), which will be maintained by the sponsor and completed prior to locking the database. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Any additional or supplemental data analyses performed independently by the investigator should be submitted to the Sponsor.

12.1 Statistical Methods (Blinding and Randomization)

This is a non-randomized, unblinded study. Unless specified otherwise, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05.

12.2 Determination of Sample Size

A total sample size of 216 patients is required to achieve 90% power at a 5% significance level assuming a difference in mean DBP from baseline (Visit 2) to 8 weeks (Visit 4) of 4 mmHg and a standard deviation (SD) for this difference of 10 mmHg. The mean change in DBP for the null hypothesis is set equal to 2 mmHg. To achieve this, a total of 290 patients will be enrolled, allowing for a 25% withdrawal rate.

12.3 Analysis Populations

A total of three populations will be used for all summaries and analyses. Study participants who have satisfied the population criteria will be classified in the designated population and will only be included in analyses for which they have available data.

Data analysis will be performed using the following analysis sets.

The Safety Population
The Safety population is defined as all study participants who sign the informed consent, meet all screening criteria, are enrolled, and receive at least one dose of the assigned treatment during the run-in period. This population will be used for safety analyses.

The Efficacy Population
The Efficacy population is defined as all study participants in the Safety population who complete the 4-week run-in period and the Visit 2 blood pressure assessment. This will be population for efficacy analysis.

The Per-Protocol Population
The Per-Protocol (PP) population is defined as all study participants in the Efficacy population who were dosed according to protocol, complete the required study visits, and do not experience any major protocol deviations that may impact the primary efficacy assessment through end of treatment.

12.4 Analysis Variables

The primary endpoint (i.e. change in sitting Diastolic Blood Pressure from Visit 2 to Visit 4) and primary statistical analysis specifications will be detailed in 12.5.2. Secondary endpoints and their respective statistical analyses are summarized in 12.5.4 while safety analyses in 12.5.7. Data handling and imputation methods are reported in 12.5.9.

12.5 Statistical Analysis

12.5.1 *Descriptive statistics*

Descriptive statistics for categorical variables (such as gender, race, and ethnicity) will include the number and percent of study participants with each characteristic. Percentages will be based on the number of study participants with non-missing values. Descriptive statistics for ordinal and continuous variables will include the number of study participants with non-missing values, mean, median, standard deviation, minimum value, and maximum value. Intervals representing 95% confidence will be presented when appropriate. Graphical displays will be present when appropriate.

All relevant data collected in the eCRF will be shown for each study participant in the individual study participant data listings.

Disposition

A tabulation of the disposition of study participants will be presented, including the number enrolled, the number treated, and the reasons for study discontinuation. Summaries of the number in each analysis set will be presented. Entry criteria violations and protocol deviations will be listed.

Demographics and Baseline

Demographic and baseline characteristic data summarization will be performed. Data to be tabulated will include study site, gender, age, race, and ethnicity, as well as baseline characteristics related to medical history.

12.5.2 *Primary (efficacy) analysis*

For the primary efficacy analysis of the primary endpoint, the change in sitting Diastolic Blood Pressure (DBP) from Visit 2 to Visit 4 will be assessed using a paired t-test. A Type I error

threshold of 0.05 will be used to test the null hypothesis that the mean reduction in DBP is 0 mmHg against a two-sided alternative. The Efficacy population will be used to analyse the primary endpoint.

12.5.3 *Sensitivity analysis*

A sensitivity analysis for the primary endpoint will be conducted by replicating the primary endpoint analysis under each of the following:

1. Per-protocol population
2. Imputation of missing data using last-observation-carried-forward (LOCF)
3. Analysis stratified by study site
4. Analysis stratified by gender
5. Analysis stratified by age group

Further details of these analyses will be presented in the SAP

12.5.4 *Secondary (efficacy) analysis*

The secondary efficacy endpoints are derived from the primary objective and will be used to support the conclusion of the primary efficacy endpoint, provided that the primary efficacy endpoint is met. The secondary endpoints will be analysed as follows:

1. Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8).
   Endpoint (1) will be analysed using a paired t-test with the null hypothesis that the mean change in SBP is 0 mmHg from Visit 2 to Visit 4.

2. Change in mean sitting DBP and SBP between Visit 3 (week4) and Visit 4 (Week 8) in patients uncontrolled at Visit 3 and up titrated to the extemporaneous combination of ZOF/AML 30/10 mg.
   Endpoint (2) will be analysed using paired t-test for DBP and SBP with null hypotheses of 0 mmHg mean change from Visit 3 to Visit 4.

3. Number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).
   Endpoint (3) will be analysed using a 95% binomial confidence interval for adherence for each visit.

4. Adherence to the treatments (% of doses taken/ doses to be taken) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).
   Endpoint (4) will be analysed using a 95% binomial confidence interval for adherence for each visit.

In addition, all continuous efficacy variables will be summarized for all study visits using descriptive statistics for both actual values and change-from-baseline values. The Efficacy population will be used to analyse the secondary endpoints.

12.5.5 *Exploratory (efficacy) analysis*
The exploratory efficacy endpoints assessing change-from-baseline BP will be analysed using mixed models for repeated measured (MMRM). The models will include treatment subgroup, analysis visit, treatment subgroup-by-visit interaction, the baseline BP value as a covariate, and patient as a random effect. An unstructured covariance structure was used to model the within-patient errors. The exploratory efficacy endpoint for proportion of patients achieving controlled BP will be analysed using a logistic MMRM with similar terms.

Additional details will be summarized in the Statistical Analysis Plan.

12.5.6 *Subgroup analysis*
Further subgroups analyses besides those described in the exploratory endpoints will be defined in the Statistical Analysis Plan.

12.5.7 *Safety analysis*
Safety and tolerability of the monotherapies (ZOF 30 mg and AML 5 mg) and of the extemporaneous combination (ZOF 30 mg and AML 5 mg or AML 10 mg) will be evaluated using the Safety population. The variables for this safety endpoint are laboratory tests, physical examination, vital signs, 12-lead ECG, and incidence of AEs and SAEs.

12.5.8 *Interim analysis and stopping rules*
There will be no interim analyses for this study.

12.5.9 *Data imputations*
Missing BP values that occur after baseline will be imputed for the sensitivity analysis using LOCF (see 12.5.3). Any missing data for BP at baseline will not be imputed. No other standard

imputations of missing efficacy data will be applied unless it is described later in the SAP in the respective data section.

12.6 Protocol Deviations and Protocol Amendments

No deviations from the Protocol should be initiated without prior approval by EC/HA of a Protocol Amendment according to applicable Regulations, except in case of emergency or when the change involves only logistical or administrative aspects of the trial.
Any deviation from the Protocol, SOPs, GCP and applicable Regulatory Requirements should be immediately reported to the Sponsor.
Changes in the study protocol will require a protocol amendment. Such amendments will be agreed upon and approved in writing by all signatories of the protocol.
If amendments are substantial, i.e. are likely to have an impact on the safety of the subjects, or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the ECs and the CAs in the participating countries have to approve these amendments before implementation, according to applicable Regulatory Requirements.
Changes which have no significant impact on medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the EC will be notified of this protocol amendment.
Any substantial amendments of the protocol will be integrated in an updated study protocol.
The Principal Investigator must ensure full compliance with the updated study protocol.

12.7 End of Study Visit

The final subject last visit that occurs on Week 8 ± 2 days will be considered to be end of study.

12.8 Statistical Analysis Plan

The statistical analysis plan (SAP) will be finalized before the study. The SAP will describe in detail study endpoints and statistical analyses, including the analysis of the primary as well as additional endpoints. In case changes of the original primary endpoint or of the original primary analyses will occur during the study, these changes will be the subject of a substantial protocol amendment.
All statistical analyses not pre-specified and run after additional/exploratory analyses.

13 STUDY DISCONTINUATION AND CLOSURE

Menarini International Operations may discontinue this study prematurely for reasonable cause. Possible reasons for early termination or temporary suspension of the study include, but is not limited to:

- Study closure based on PI decision and/or
- Study closure based on Sponsor decision and/or
- Study closure based on Regulatory or other oversight bodies initiation and/or
- Review of serious, unexpected, and related AEs and/or
- Non-compliance.

In case this study was temporarily suspended or prematurely terminated, written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party at a reasonable time in advance of the intended termination.

The Investigator may also discontinue this study at his/her site for reasonable cause after notifying the IEC and providing written notice to Menarini International Operations at a reasonable time in advance of the intended termination.

Please note advanced notice is not required by either party if the study is stopped due to safety concerns.

Menarini International Operations and the Investigator should take the following steps to follow up on patient safety and ensure data integrity:

- Immediately notify the pharmacovigilance officer at Biorasi
- Notify the IEC within 24 hours
- Contact all patients by phone and distribute written communication that the study has been stopped
- Advise all patients to report for an early termination visit
- Make plans to follow all patients for AEs for two months after the study has been stopped or for as long as it takes for any AE/SAEs to resolve, whichever is longer
- Instruct study staff to enter all data in the case report form and ensure their completion

14 DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The Investigator and/or Institution will permit trial related monitoring, audits, EC review, and regulatory inspections, providing direct access to source data/documents upon request.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study Monitoring / Data Quality Control

Site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol / amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

The monitoring of the conduct of the study and progress of the clinical investigation will proceed in accordance to the Monitoring Plan. The purpose of the Monitoring Plan is to establish guidelines for managing, monitoring, and working with Investigational Sites for this study.
The Monitoring Plan provides information that will be used by Clinical Research Associates (CRAs) to ensure the quality of the data including the type, frequency, and extent of monitoring, who will be provided reports of monitoring and whether independent audits of the monitoring activities will be conducted. The Monitoring Plan also provides detailed information about the number of study sites, Site Initiation Visits (SIVs), Study Site Visits (SSVs), Interim monitoring visits (IMVs), and close-out visits.

The Investigator will be contacted by the study monitor on a regular basis. The monitor will have the responsibility of reviewing the ongoing study with the Investigator to verify adherence to the protocol and to deal with any problems.

Quality checks that will be performed on trial documents and on the collected data include, but is not limited to, ICF review and source data verification. Detailed information can be found in the Monitoring Plan.

The Investigator agrees to allow access to all study materials needed for the proper review of study conduct. The Investigator agrees to assist the monitor in resolving any problem that may be detected during the monitoring visit or data cleaning process.

15.2 Case Report Forms

Patient data will be entered into the IBM Clinical Development electronic data capture (EDC) system.

Menarini International Operations, or its designee, will supply to the site personnel access to the electronic case report forms. These forms will be used to transmit information collected during the study to Menarini International Operations or its designee and regulatory authorities, as applicable. The Investigator may formally designate authority to complete eCRFs to qualified staff by completing the signature log and requesting access rights to the EDC system for the designee. Every user of the system will be made aware of the fact that username and password should never be shared, and their electronic signature constitutes the legally binding equivalent of a hand-written signature.
Electronic CRFs (eCRFs) must be completed for each patient who signs the ICF for the study. Screening study data will be collected on the eCRF for all patients only. The system automatically records all changes in an electronic audit trail and requires a “reason for change” to be picked from a pre-defined list. If the reason for the correction is not obvious, a brief explanation (e.g. transcription error) should accompany the change. All information recorded on the eCRF forms must reflect the information in the patient source documents.
For screen failed patients, the Investigator or designee will capture in source the patient’s demographic data, data collected from all completed screening procedures, and reason for screen failure. Only the patient’s demographic data, informed consent, reason for screen failure and SAEs will be entered in the EDC.

Data collected during the study will be recorded in the eCRF. Data reported on the eCRF have to be consistent with the source documents. The Investigator must ensure the accuracy, the completeness and the consistency of the data entered in the eCRF.

The Investigator will review the eCRFs for completeness and accuracy and electronically sign each set of eCRFs. Menarini International Operations personnel (or their representatives) will

periodically review the eCRFs for completeness and accuracy. Menarini International Operations personnel (or their representatives) will be allowed access to all source documents in order to verify eCRF entries.
On the eCRF, patients will be identified by the patient number/code, assigned at the Screening Visit. The patient number/code will be assigned as stipulated in the Data Management Plan.
During the conduct of the clinical part of the study, the eCRF must be available and up to date, so that it always reflects the latest observations on the respective patient. The data entry expectations are that the eCRFs will be entered within 5 business days of a patient's visit. Any eCRF queries should be answered by the site within 5 business days. SAE/Coding queries must be answered by the site within 3 business days.
The Investigator will be responsible for entering study data into the eCRF in accordance to the eCRF user guidelines.

15.3 Quality Assurance

Quality Control will be performed according to applicable SOPs. The study may be audited by Quality Assurance representatives of Menarini International Operations (or their designee). All necessary related data and documents will be made available for inspection.

All clinical activities conducted under this protocol is subject to GCP regulations. This includes audits / inspections by the Sponsor, and / or by national / international Health Authority representatives at any time. Principal Investigators must agree to the inspection of the study site, facilities, and of study related records by the Health Authority representatives and / or by the Sponsor, and / or its delegates, which must be performed in accordance with national laws concerning personal data protection.

16 ETHICS ASPECTS

This study will be conducted in compliance with this study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, International Conference of Harmonisation – Good Clinical Practices (ICH-GCP) Guidelines, EU-Directives and Regulations and national requirements for the participating countries.

16.1 Ethics Committees

Before starting the study in a study site, Study Protocol and relevant documentation (Subject information leaflet, Informed Consent Form and the Investigator's Brochure and other documents, according to National Regulations) must be submitted to and approved by the Ethics Committees (EC) and the Health Authorities (HAs) of the participating countries.
In addition, all local national legal requirements for the conduct of a clinical study have to be followed. Any amendment to the protocol will be submitted to the ECs and HAs before implementation.
Furthermore, the HAs and ECs of the participating countries will be informed about the study start, the end of the study, or the premature study termination as appropriate and within the requested time period.

16.2 Subject's Insurance

For subjects participating in the study, Sponsor will issue an insurance policy in accordance with local regulatory requirements.
Details on the insurance company, the insurance number and conditions will be made available to subjects in the ICF and / or provided as a separate document, in accordance with national requirements. Insurance policy will be submitted for approval to the ECs along with the other study documents.
A copy of the insurance certificate will be provided to each Investigator and will be filed in the Investigator's File at the sites and in the study's Trial Master File (TMF).
The Investigator must notify to Sponsor immediately upon notice of any claims or lawsuits.

17 PERSONAL DATA PROTECTION SECTION

17.1 General Principles on Personal Data Compliance

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the patients shall remain protected in accordance with the applicable law on personal data protection such as the EU General Data Protection Regulation 679/2016, the EU Regulation on clinical trials on medicinal products for human use 536/2014,

laws applicable in countries where the data subject is based –i.e.., Russian privacy laws, particularly Data Protection Act No. 152 FZ dated 27 July 2006 ("DPA") and various regulatory acts adopted to implement the DPA". This section defines the appropriate technical and organisational measures that shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfilment of subjects' privacy rights.

17.2 Acknowledgment

The Site, the Principal investigator, the Local Laboratory, the CRO - as well as their appointed staff and service providers acknowledge that: (a) the performance of the study will imply processing of sensitive personal data; (b) personal data processing is regulated by the applicable European (i.e. the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014) and laws applicable in countries where the data patient is based –i.e.., Russian privacy laws, particularly Data Protection Act No. 152 FZ dated 27 July 2006 ("DPA") and various regulatory acts adopted to implement the DPA and local laws (i.e. the laws of all the countries where the study is conducted) as well as by the Sponsor's national legislation. In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Luxemburg law, it has to mandatorily comply with Luxemburgish and EU laws on data protection: therefore The Site, the Principal investigator, the Local Laboratory, the CRO - shall cooperate with the Sponsor to allow the fulfilment of such obligations; (c) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the Site, the Principal investigator, the Local Laboratory, the CRO

17.3 Data Controllers and Data Processors

The Sponsor, the Site, the Principal investigator and the CRO - acknowledge that according to the applicable privacy laws, Sponsor and Site - will act as independent data controllers while CRO and the Principal investigator will act as data processors respectively of the Sponsor and of Site. Before the beginning of the study, the Site - will instruct in writing, the Principal Investigator - as its data processor. However, if specific local laws or regulations mandate a different definition of the privacy roles, the Sponsor, the Site, the Principal

investigator and the CRO - will implement the relevant legal instruments (e.g. if pursuant to the local laws the Site is a data processor of the Sponsor, a Data Processing Agreement will be finalised; if pursuant to the local laws Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalised).

For clinical trials where the Principal Investigators are the owners of the Site, this provision may not apply. In such cases, the Principal Investigator might be considered as a Data Controller

17.4 Duties of the Parties involved in the performance of the study

Collection and use of patient's date will be carried out in full respect of the provisions of the information notices submitted to patients, as well as the privacy rights, the fundamental freedoms and the dignity of data patients. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws. *The Site, the Principal investigator, the Sponsor, the CRO and the Local Laboratory* as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the study- use the same protocol terminology/definitions], shall implement the following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the patients involved in the *study*. In particular:
(i) DATA SAFETY. *The Site and/or the Principal Investigator* shall adopt all the necessary measures to prevent or minimise the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorised access to patient's data or Sponsor's proprietary confidential information; to this extent, before the beginning of the *study, the Site and/or the Principal Investigator* shall ensure that the actual measures they have implemented are fit-for purpose and law-compliant, and in particular:
- in order to minimise the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at

least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least three "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her , such as name and year of birth (e.g. “johnbrown80”) or easily predictable strings of characters (e.g. “qwerty”, “12345”, “admin”, “user”, etc.);

- adequate cryptographic protection measures shall be put in place for data “at rest” and “in transit” (these include, for example, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorised to access them);

-high level security measures shall be implemented also on the files or databases which contain the “key” to match the patients’ personal data (i.e. name, surname, etc.) with their respective “Patient IDs” (as defined at point *(iv)* below);

- Backup processes and other measures that ensure rapid restoration of business-critical systems shall be implemented;

- Updated Antivirus and firewall programs shall be installed on the IT devices.

The *Site* shall, regularly test and update the measures listed above. The *Site* shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above. The *CRO* shall ensure that the selected sites for the study have implemented the above listed measures.

(ii) TRANSMISSION OF DATA. All the parties that transfer data through internet and/or to the centralised database(s) used to process study’s data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.

(iii) SECURITY OF THE CENTRALISED DATA BASE. The centralised database held by the Sponsor shall have the following safeguards in place: - appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of patients' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study; - appropriate measures to ensure that the authentication credentials are periodically updated (i.e. password change);

(iv) PSEUDONYMIZATION. All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymisation" process). The *Principal investigator* shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to a an alphanumerical code ["Patient ID"], whose format shall not make it possible to identify the patient directly or indirectly, so as to ensure that only anonymous data are transmitted to the *Sponsor, the Local Laboratory and /or the CRO, Site/Principal Investigator* shall securely store a separate list (e.g.: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.
The subject code pairing list (i.e. the list that where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived by the Principal Investigator.

(v) TRAINING. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues. All actions related to the implementation of the afore mentioned measures shall be provided by the Sponsor, the *Centre and/or the* to the competent authorities (including data protection authorities) and Ethics Committees if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, *The Site, the Principal investigator, the CRO and the Local Laboratory* undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

17.5 Archiving of the clinical trial master file and code pairing list

Unless other EU laws require archiving for a longer period, the Centre and the Principal Investigator shall archive the content of the clinical trial master file, including the relevant patients' personal data, for at least 25 years after the end of the clinical trial. However, medical records shall be archived in accordance with the national laws of the country where the study is performed. The patient code pairing list (i.e. the list that where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived care of the Principal Investigator.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.

The content of the Investigator's File shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.
If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility.
The Sponsor must be notified in writing of the name and address of the new custodian.
Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall undertake the responsibilities set out in this protocol. The Sponsor appoints Clinical Operations Director as responsible person/s for archives. Access to archives shall be restricted to those individuals.Once mandatory data retention time for the clinical trials master file has elapsed, the Centre/Principal Investigator shall seek the authorisation of the Sponsor to destroy the clinical trial master file.

Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Site, sponsor, CRO, Principal Investigator, Vendor etc data loss is when the data may still exist, but the Site, sponsor, CRO, Principal Investigator , Vendor etc has lost control or access to it, or no longer has it in its possession; damage is where personal data has been altered, corrupted, or is no longer complete; data unavailability is where, following a data incident (such as a network outage, a natural or manmade disaster, etc.), personal data become temporarily inaccessible to the, Vendor Site, sponsor, CRO, Principal Investigator.
Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (e.g. an unauthorised access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (e.g. cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability, alteration, theft, copy or dissemination of personal data. Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach

(see definitions above –) affecting the patients' personal data and/or personal data collected in the context of the study, shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the Menarini Clinical Operations Director the sponsor's Data Protection Officer (dpo@menarini.com), the Site and the Biorasi's Data Protection Officer (DPO@biorasi.co) for data breach incidents and shall provide the following information:

(i) Anomalous Event / Data Breach Type (e.g. data loss, unauthorized access, loss of company device, etc.).

(ii) Person or source that first reported the Anomalous Event/Data Breach;

(iii) Date and Time when the person who first reported the Anomalous Event / Data Breach became aware of it;

(iv) Anomalous Event / Data Breach Date and Time (actual or presumed);

(iv) Place (specify if actual or alleged) where the Anomalous Event / Data Breach occurred;

(v) Anomalous Event / Data Breach Description;

(vi) Indicate the source of the Anomalous Event / Data Breach (e.g. I.P. source) - (if relevant);

(viii) Indicate the affected infrastructure / system / application / cloud/ software / hardware / database and their location;

(ix) List or describe the processing/storage systems affected by the Anomalous Event/Data Breach (if relevant);

(x) Number of data patients involved (if known);

(xi) Amount of allegedly breached data

(xii) Other relevant information.

Once all the above information have been provided, the Sponsor and/or the Site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

Then, as appropriate, Sponsor and Site, each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.

For Data Breach affecting personal data of patients enrolled within the European Union, Sponsor and Site -autonomously or jointly depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. Collect the necessary evidence and information;
2. Categorise the breach;

3. Determine the risk probability and level to the rights and freedom of the concerned patients;
4. Identify and put in place appropriate remedies to minimise the impact of the Data Breach
5. Determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned patients.

17.6 Information notice on personal data protection and pseudo-anonymisation

Prior to patients' enrolment in the study, the Principal Investigator and/or the Site (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The Principal Investigator is responsible to archive the signed ICF in accordance with the security measures described above. Among other things, the ICF (or the separate form) shall inform patients about:
(i) the applicable data protection legislation
(ii) what kind of data shall be collected during the study listing them in detail or by category;
(iii) the purpose of data processing e.g. performance of the study, pharmacovigilance, registration of new drugs and the legal basis;
(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study;
(v) the use of data for future scientific researches / secondary use of data (if any). In such a case the future scientific purposes / secondary use shall include the future/further scientific processing activities/purposes (vi) the pseudonymisation procedure and scope;
(vii) who can access patients' data and under what circumstances Principal Investigator, Site, Sponsor during monitoring activities, audit, etc., regulatory authorities during inspection etc, Ethics Committee];
(viii) the period of data retention/storage as defined in Paragraph 19;
(ix) to which entities/countries outside the EU patients' data will be transmitted [list here the non-EU countries] (if applicable), as per Paragraph 18.7.
(x) patients' data protection rights as defined by the [EU General Data Protection Regulation 679/2016, and laws applicable in countries where the data patient is based –i.e.., Russian

privacy laws, particularly Data Protection Act No. 152 FZ dated 27 July 2006 ("DPA") and various regulatory acts adopted to implement the DPA].
(xi) Data Controllers / Data Processors and the relevant contact details
(xii) Sponsor's Data Protection Officer contacts (DPO)

17.7 Genetic Data

Not applicable

17.8 Transfer of subjects' data outside the European union

The study performance entails transferring patients 'personal data (coded data) outside the EU. To this extent, the Sponsor, the Site, the Principal investigator, the Local Laboratory, the CRO undertake to export such data in compliance with adequate safeguards/legal basis as required by the Regulation 679/2016 including the Commission Decisions, the Standard Contract Clauses, the Privacy Shield, patients' specific consent only where permitted under Chapter V of the GDPR, on one of the basis set out under art. 49 GDPR.

LIST HERE THE NON-EU COUNTRIES/ENTITIES WHERE DATA CAN BE EXPORTED:
USA,
RUSSIA

Nevertheless, if Sponsor registers and markets the: Amlodipine and Zofenopril calcium in non-EU countries, data may have to be submitted to the Authorities in charge of monitoring the safety and reliability of medicines in those countries. The updated list of foreign countries is available upon request.

17.9 Exercise of subjects' data privacy rights

Each study patient has the right to contact the Sponsor, the Site, the Principal investigator, the Local Laboratory, the CRO to exercise the rights afforded to the patient by the law, including the ones afforded under articles 15 to 22 of Regulation (EU) 2016/679 or under Data Protection Act No. 152 FZ dated 27 July 2006 and implementing acts,, namely: knowing whether or not any data referring to his/her is being processed in the context of the study - access his/her data; verify the data's content, origin, exactness, location (including, where

applicable, the non-EU countries where the data might be); obtain a copy of the data including their transmission to another entity indicated by the patient; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/her data for legitimate reasons. Each patient- has the right to lodge a complaint with his/her local supervisory authority and/or to notify to the Data Protection Officer any use of his/her personal data the patient- regards as inappropriate. Each study patient is free to withdraw at any time from the study. In such case, each study patient may ask the Sponsor, the Site, the Principal investigator, the Local Laboratory, the CRO - to destroy/delete his/her personal data (including his/her biological samples), thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study. If he Site, the Principal investigator, the Local Laboratory, the CRO receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by email at dpo@menarini.com]. The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, the Principal investigator, the Local Laboratory, the CRO - shall implement adequate organisational measures to reply to patients within the above-mentioned deadline

17.10 Future research

In the context of additional research activities, patients' data will be processed, anonymised and transferred abroad, and may be shared with future research partners –this will take place in a format that prevents patients' identification.

18 PUBLICATION POLICY AND RESULTS

By signing the study protocol, the Investigator (and his / her appointed staff) ensures that any information and all the study documents provided by the Sponsor will be maintained strictly confidential.
None of this material may be disclosed to any party not directly involved in the study without written permission from the Sponsor.
All information concerning the study, the drug as well as data and results of the study are confidential and property of the Sponsor.

The Sponsor will prepare the clinical trial report, including the statistical and clinical evaluations, and trial results will be posted and made public, according to applicable Regulatory Regulations. The Investigator's agreement and signature will be obtained, and a copy will be provided to the Investigator.
Sponsor reserves the exclusive right to publish and present data and results of the present study at scientific meetings, or to submit these clinical trial data to national and international Regulatory Authorities. The Investigator may not use the results of this study for publication or presentation without written authorization from Sponsor.

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20 PROTOCOL APPROVAL PAGE

Study Title: Interventional clinical trial to assess efficacy and safety of the extemporaneous combination of zofenopril calcium and amlodipine in grade 1-2 hypertensive patients versus each monotherapy (MASOLINO Study)

Code: MEIN/20/ZoAm-Hyp/001

EUDRA-CT number: 2021-000745-40

The signers confirm that they have read and approved the protocol

Study Medical Expert: MARCO SALVATORE

Signature & Date: _____ 27/04/2021

Corporate Medical Director/: LORENZO MELANI

Signature & Date: _____ 26/04/2021

Coordinating Investigator: PROFESSOR MASSIMO VOLPE

Signature & Date: _____ 27/04/2021

Medical Writer: SHWETA DEHERKAR

Signature & Date: DocuSigned by Shweta Deherkar / 23 April 2021

Signer Name: Shweta Deherkar
Signing Reason: I approve this document
Signing Time: 23 April 2021 | 3:23:39 AM PDT
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Statistician: JOHN REBER

Signature & Date: DocuSigned by: John Reber / 27 April 2021

Signer Name: John Reber
Signing Reason: I approve this document
Signing Time: 27 April 2021 | 10:29:05 AM PDT
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21 INVESTIGATOR'S APPROVAL PAGE

I understand that all information concerning the product that Menarini supplied Zofenopril and Amlodipine in connection with this study protocol are confidential information. This information includes: Protocol, Investigator's Brochure, Case Report Form etc.

I understand that any change in this study protocol must be approved in writing by Menarini International Operations Luxembourg and the Co-ordinating Investigator, submitted to the Ethics Committee and Health Authorities before implementation, except where necessary to eliminate apparent immediate hazard to patients.

I confirm that I will conduct the study according to this protocol, the Good Clinical Practice (GCP), the Declaration of Helsinki and laws and regulations in the Country where the study is to be conducted.

I confirm that I will record and report all adverse events occurring during the study, according to this protocol.

I confirm that I am informed about the need of data records retention, according to current regulations and that no data can be destroyed without the written consent of Menarini International Operations Luxembourg

I confirm that I will transfer adequate ownership of my responsibilities for the trial and will inform the Sponsor, in case I retire from my PI role.

I confirm that in case the Trial Centre File is stolen or anyhow damaged, I will promptly inform the Sponsor and declare it to the Competent Authorities

Principal Investigator: _____

Signature & Date: _____

22 APPENDICES

Appendix 1: Declaration of Helsinki

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
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, 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 patients.
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 patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, 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 patients set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises 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 patients.

15. Appropriate compensation and treatment for patients 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 minimise 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 non-vulnerable 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 patients 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 patients 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 patients and the confidentiality of their personal information.

11 Informed Consent

25. Participation by individuals capable of giving informed consent as patients 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 patient 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 patient 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 patients as well as to the methods used to deliver the information.

After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient'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 patients 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 patient 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 patient who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised 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 patient, 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 patient 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 authorised representative. The potential patient's dissent should be respected.

30. Research involving patients 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 authorised 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 patients 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 patient or a legally authorised 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 patient 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 authorised 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.