CLINICAL STUDY PROTOCOL

Open-label, **M**ulticenter, multinational, interventional clinical trial to **A**ssess effectiveness and **SA**fety of the extemporaneous **C**ombination of nebivolol and zofenopril Calcium in grade 1 to 2 hypertensive pat**I**ents versus each m**O**notherapy – **MASACCIO study**

Sponsor name and address	Menarini International Operations Luxembourg SA Registered Offices: 1, Avenue de la Gare L-1611 Luxembourg Operative Offices: 5D, Rue Eugene Ruppert L-2453 Luxembourg Ph. (+352) 2649761 - Fax (+352) 26497649
Protocol Code	MEIN/19/ZoNe-HYP/001
EudraCT (or National Clinical Trial Identified Number)	2020-002340-23 ClinicalTrials.gov: NCT05257148
Protocol Phase (if applicable)	IV
Study type and design:	Multicenter, open-label, interventional study
Protocol Version Number	Version 1
Protocol Version Date	16 July 2020
Coordinating Investigator	Professor Massimo Volpe
CRO	IQVIA

CONFIDENTIALITY STATEMENT

The information in this document contains information that are privileged or confidential and may not be disclosed unless such disclosure is required by law. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

Summary of Changes from Previous Version

Affected Section(s)	Summary of Revisions Made	Rationale
	N/A	**First emission**

Sponsor: **Menarini International Operations Luxembourg** **Protocol Version_1 *of 16/07/2020***
Study Code: MEIN/19/ZoNe-HYP/001

TABLE OF CONTENTS

1. *RESPONSIBILITIES*

Sponsor:	Name: Menarini International Operations Luxembourg SA
	Address: 1, Avenue de la Gare L-1611 Luxembourg
	Phone: +352 2649761 Fax: +352 26497649
Clinical Trial Coordinator:	Name: Eleonora Droghetti
	Address: Via Sette Santi 1-3, 50131, Firenze
	Phone: +39 055 56809665 Fax: + 39 055 56809961
	e-mail: edroghetti@@menarini.it
Study Medical Expert (SME):	Name: Marco Salvatore
	Address: via dei sette santi 1-3, Firenze
	Phone: (055) 56809581 Fax: (055) 56809710
	e-mail: msalvatore@menarini.it
Study Drug Safety Manager (SDSM):	Name: Jaleh Khabirinejad
	Address: 5D, Rue Eugene Ruppert L-2453 Luxembourg
	Phone: +352 26497696 Fax: +352 26497649
	e-mail: jkhabirinejad@menarini.lu
Coordinating Investigator	Name: Professor Massimo Volpe
	Address: Via Di grottarossa, 1035 Roma
	Phone: 06 33775654
	e-mail: massimo.volpe@uniroma1.it
CRO	Name: IQVIA
	Address: 3 Forbury Place, 23 Forbury Road, Reading, RG1 3JH, United Kingdom
Statistician	Name: Susmita Sanyal
	Address: IQVIA, 2nd Floor, iSprout, Purva Summit Building, Whitefield, Kondapur, Hyderabad, India
	e-mail: susmita.sanyal@quintiles.com

Sponsor Statistician	Name: Andrea Nizzardo
	Address: Via Sette Santi 1-3, 50131, Firenze
	Phone: + 39 055 5860 7243
	e-mail: anizzardo@menarini-ricerche.it

2. PROTOCOL SYNOPSIS

Title	Open-label, multicenter, multinational interventional clinical trial to assess effectiveness and safety of the extemporaneous combination of nebivolol and zofenopril calcium in grade 1 to 2 hypertensive patients versus each monotherapy
Sponsor Study Code	MEIN/19/ZoNe-HYP/001
Study product, Dosage and Regimen: -Investigational Product	Extemporaneous combination of nebivolol (NEB) 5 mg tablets (Anatomical Therapeutic Chemical [ATC] code: C07AB12) with zofenopril calcium (ZOF) 30 mg tablets (ATC code: C09AA15)
Study Type and Design	This is a phase IV, open-label, multicenter, multinational study with 2 study periods (a run-in period of 4 weeks and an assessment period of 8 weeks). 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) or beta blockers (BBs) including ZOF 30 mg or NEB 5 mg respectively will be screened for eligibility (Visit 1). On the same day, the eligible patients will enter into a run-in period after Screening, during which: • Patients on ZOF 30 mg or NEB 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 while patients on any other BB will be assigned to monotherapy with NEB 5 mg, respectively, for 4 weeks After the 4 weeks of monotherapy in the run-in period, if BP at Visit 2, remains uncontrolled (sitting SBP/DBP >130/80 mmHg) despite an adherence to the treatments ranging from 80% to 120%, the patients will

	start treatment (Week 0, Visit 2) with the extemporaneous combination of NEB 5 mg/ZOF 30 mg (NEB/ZOF) and will be assessed for further 8 weeks (assessment period). If the patients, at Visit 2 after the Run-In period, have controlled BP (sitting SBP/DBP ≤130/80 mmHg), and/or do not tolerate the treatment, and/or do not maintain the adherence to the therapy (range from 80% to 120%), these patients will not be continued further in the study. At the end of the assessment period (Visit 3) the antihypertensive effect of the extemporaneous combination of NEB 5 mg and ZOF 30 mg will be evaluated. A total number of 290 patients will be screened considering 25% of drop-out rate, to obtain approximately 216 completed patients at the end of the study.
Phase	IV
Objectives	<u>Primary objective</u>: ● To assess the antihypertensive effect of the extemporaneous combination of NEB 5 mg and ZOF 30 mg in lowering sitting DBP after 8 weeks of treatment, in patients with uncontrolled BP who were previously treated with NEB or ZOF monotherapies for at least 4 weeks <u>Secondary objectives</u>: ● To assess the antihypertensive effect of the extemporaneous combination of NEB 5 mg and ZOF 30 mg in lowering sitting SBP after 8 weeks of treatment in patients with uncontrolled BP, after at least 4 weeks of treatment with NEB or ZOF monotherapies ● To evaluate the total number and percentage of patients who achieved the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3 ● To assess compliance to the monotherapy and extemporaneous

	combination (actual doses taken versus planned doses to be taken) • To evaluate the safety and tolerability of the ZOF and NEB monotherapies, and the extemporaneous combination of NEB 5 mg and ZOF 30 mg after 8 weeks of treatment <u>Exploratory objective</u>: • To assess the antihypertensive efficacy at different time points in patients who (1) received NEB or ZOF monotherapies before the run-in period, (2) received any other ACE-i or BB monotherapies before the run-in period • To assess the antihypertensive effect on patients, based on their hypertension grade, presence or absence of hypercholesterolemia, presence or absence of diabetes at Visit 2 and Visit 3
Endpoints	<u>Primary endpoint</u>: • Change in mean sitting DBP between Week 0 (Visit 2) and Week 8 (Visit 3) <u>Secondary endpoint</u>: • Change in mean sitting SBP between Week 0 (Visit 2) and Week 8 (Visit 3) • Total number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Week 0 (Visit 2) and Week 8 (Visit 3) • Adherence to treatment will be measured through treatment compliance which is 100 × (actual doses taken versus planned doses to be taken) from Visit 1 to Visit 2 for the monotherapies and from Visit 2 to Visit 3 for the extemporaneous combination • Safety and tolerability of the NEB and ZOF monotherapies, as well as extemporaneous combination between NEB 5 mg and ZOF 30 mg will be measured by adverse events (AEs), SAEs, AEs of special interest (AEOSI), vital signs, physical examination,

	electrocardiogram (ECG), and concomitant medications at Week 0 (Visit 2) and Week 8 (Visit 3) <u>Exploratory endpoint:</u> ● Change in mean sitting SBP and DBP between Visit 1 and Visit 2 : (a) in the group of patients who were on ZOF 30 mg and NEB 5 mg at Visit 1 and continued on the same treatment until Visit 2 and (b) in the group of patients, who switched to ZOF 30 mg or NEB 5 mg from any other ACE-i or BB at Visit 1 until Visit 2. ● Change in mean sitting SBP and DBP between Visit 1 and Visit 3: (a) in the group of patients who were on ZOF 30 mg and NEB 5 mg at Visit 1 and continued on the same treatment until Visit 2 and (b) in the group of patients who switched to ZOF 30 mg or NEB 5 mg from any other ACE-i or BB at Visit 1 until Visit 2. ● Number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3 evaluated in the patients: (a) who were on ZOF 30 mg and NEB 5 mg at Visit 1 or (b) who switched to ZOF 30mg or NEB 5 mg from any other ACE-i and BB at Visit 1 ● Number and proportion of patients, divided in subgroups based on the hypertension grade, the presence or absence of diabetes, the presence or absence of hypercholesterolemia achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3
Study Population: Patients characteristics Number of Patients	Approximately, 290 male or female Caucasian uncontrolled hypertensive patients between ≥18 and <65 years of age, who are on treatment with ZOF or NEB, or, on any other ACE-i or BBs, for at least 1 month, will be screened for eligibility. A total drop-out rate of 25% from Visit 1 to Visit 3, has been considered. A

	patient will be considered eligible to be enrolled in the study only if he/she meets all of the inclusion criteria and none of the exclusion criteria. **Inclusion criteria:** 1. Male or female Caucasian uncontrolled hypertensive patients (see definition in criterion 3) ≥18 and <65 years of age, in monotherapy either with ACE-i or BBs since at least 1 month, at Screening (Visit 1) 2. Patients are able to understand and have freely given written informed consent at Screening 3. Patients with mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥ 90 mmHg and ≤109 mmHg at Screening (Visit 1) 4. Patient who are able to comply with all study procedures and who are available for the duration of the study 5. Ability to take oral medication and willing to adhere to the drug regimen 6. A female patient of childbearing potential is eligible to participate if she is not pregnant, or not breastfeeding. A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Women of childbearing potential must agree to use of highly effective contraception (eg, 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) and also must refrain from donating or storing eggs during this time. Highly effective contraception methods can be: • 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 (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success)

7. A male patient with female partner 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:

Patients who meet any of the following criteria will not qualify for entry into the study:

1. Known contraindications, allergies, or hypersensitivities to any of the study medications or excipient as outlined in the investigators brochures (IBs), summary of product characteristics (SmPCs) or local package inserts for NEB 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, hematological, 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, heart failure, hypertensive

	encephalopathy, cerebrovascular accident (stroke), or transient ischemic attack 4. Patients with secondary hypertension of any etiology such as renal diseases, pheochromocytoma, or Cushing's syndrome 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. History of angioneurotic edema 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. History of bronchospasm and bronchial asthma 12. Patients with bradycardia (heart rate <60 bpm) 13. Patient with metabolic acidosis 14. Patients with severe peripheral circulatory disturbances 15. Participation in another study within the last 4 weeks 16. Patients with diseases that, in the opinion of the Investigator, prevent a careful adherence to the protocol 17. Pregnant and breastfeeding women. NOTE: a pregnancy test will be performed on all women of childbearing potential at each study visit
Clinical Sites	15 investigational clinical sites

Number of Centers	
List of Countries	European Union countries
Study Duration (specify different study phases):	This study will last 12 weeks. **<u>Screening Visit (Visit 1, week -4)</u>** Uncontrolled hypertensive patients receiving treatment with any ACE-i or BBs including ZOF 30 mg or NEB 5 mg will be screened for eligibility. **<u>Run-in period (4 weeks): from Visit 1 (Week-4) to Visit 2 (Week 0)</u>** Eligible patients from Screening will enter the run-in period on the same day. Patients previously receiving ZOF or any other ACE-i will enter into the run-in period with ZOF monotherapy while patients receiving NEB or any other BBs will enter into the Run–in period with NEB monotherapy in a 1:1 ratio. **<u>Assessment period (8 weeks): from Visit 2 (Week 0) to Visit 3 (Week 8)</u>** Patients experiencing uncontrolled BP after 4 weeks of monotherapy, will be given the extemporaneous combination of NEB 5 mg and ZOF 30 mg at Week 0 (Visit 2) and will be assessed for 8 weeks (assessment period). Patients with controlled BP (sitting SBP/DBP ≤130/80 mmHg) and/or patients who do not tolerate the treatment at Week 0 (Visit 2) will be withdrawn from the study. Only uncontrolled BP patients, whose adherence to the treatment (actual doses taken compared to planned doses to be taken) ranges from 80% to 120%, will enter the assessment period.
Patient Study Phases Duration	For patients completing the study, participation will last up to 12 weeks: • 4 weeks of run-in period (monotherapy) • 8 weeks of assessment period (extemporaneous combination)

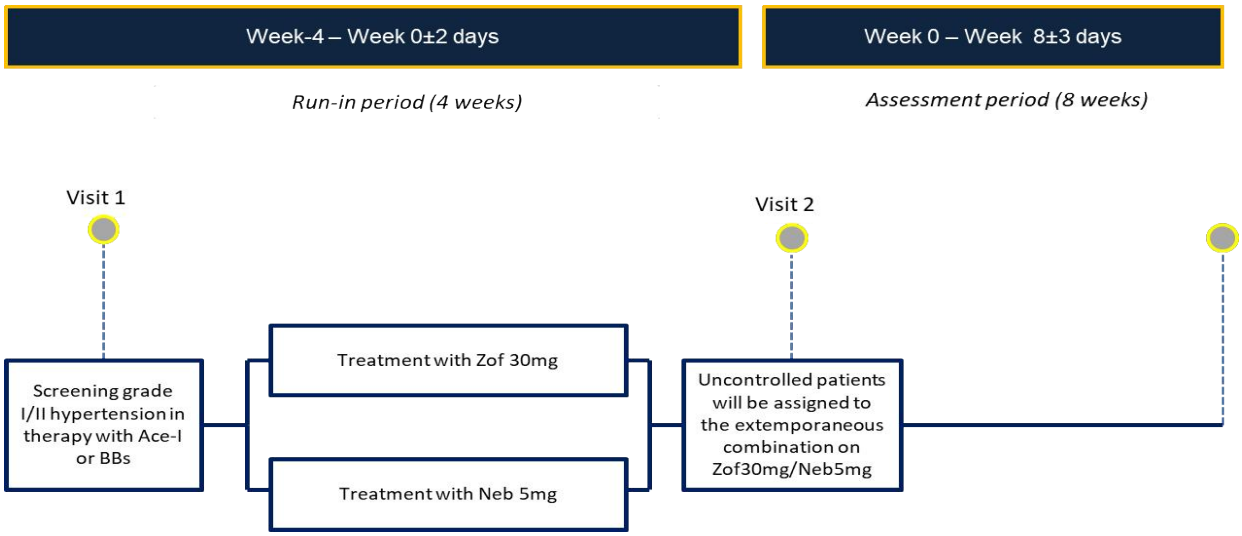
Statistical Assumptions	The primary endpoint will be assessed before and after assessment period at Week 8, by a paired t-test using the ITT population and the Per protocol (PP) population. All other secondary endpoints will be assessed before (Week 0) and after treatment (at Week 8). A total sample size of 216 patients is required to achieve 90% power at a 5% significance level assuming a difference in mean DBP from baseline to 8 weeks 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.

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
ACE-i	angiotensin converting enzyme-inhibitors
ADR	adverse drug reaction
AE	adverse Event
AEOSI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BB	beta blocker
BP	blood pressure
CRO	contract research organization
DBP	diastolic BP
EC	ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FDC	Fixed-dose combination
GCP	good clinical practice
HA	health authority
ICF	informed consent form
ICH	International Council for Harmonisation
ICSR	individual case safety report
ITT	Intent-to-treat
NEB	Nebivolol
NSAE	Nonserious AE
PI	Principal Investigator

PP	per protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic BP
SD	standard deviation
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TMF	trial master file
ULN	upper limit of normal
ZOF	zofenopril calcium

4. STUDY SCHEME



BP: Blood pressure, NEB: Nebivolol, ZOF: Zofenopril calcium, ACE-i: Angiotensin converting enzyme-inhibitors, BB: Beta blockers

- Patients meeting the eligibility criteria at Screening (Visit 1), will enter the run-in period on the same day
- Patients who were on ZOF or NEB treatment at Screening, will continue to receive the same drugs; the patients on any other ACE-i will start ZOF and patients who were on any other BB will start NEB from the same day
- Only patients with uncontrolled BP (sitting SBP/DBP >130/80 mmHg) and whose adherence to the treatment ranges from 80% to 120%, will enter the assessment period to receive the extemporaneous combination of NEB and ZOF; while the patients with controlled sitting BP (SBP/DBP ≤130/80 mmHg) and/or the patients who do not tolerate the treatment and patients with uncontrolled BP whose adherence to the therapy do not range from 80% to 120%, will be withdrawn from the study.

4.1 Study Flow Chart

Study Procedures/ Assessments	Visit 1 (Week -4)	Visit 2 (Week 0)[a]	Visit 3 (Week 8)[a]
	Screening + Start of Run-in Period[b]	Start of Assessment Period	End of Assessment Period
Informed consent	X		
Inclusion/exclusion criteria	X		
Medical history	X		
Prior medication	X		
Demography (age, sex, race)	X		
Concurrent diseases and medical conditions	X	X	X
Antihypertensive treatment with NEB or ZOF monotherapy[c]	X		
Study drug dispensing[d]		X	
Study drug return and accountability (Compliance assessment)		X[e]	X[f]
Concomitant medications	X	X	X
Urine pregnancy test	X	X	X
Physical examination	X	X	X
Vital signs	X	X	X
Laboratory test[g]	X		X
Blood pressure	X	X	X
ECG	X	X	X
AE/SAE assessment	X	X	X[h]

ACE-i: Angiotensin converting enzyme-inhibitors; AE: Adverse event; BB: Beta blockers; ECG: electrocardiogram; EOT: End of treatment; NEB: nebivolol; SAE: serious adverse event; ZOF: zofenopril calcium

a: For Visit 2, a window of ±2 days will be allowed at Week 0; and for Visit 3, a window of ±3 days will be allowed at Week 8

b: Patients meeting the eligibility criteria at Screening, will enter the run-in period on the same day

c: Patients on ZOF 30 mg or NEB 5 mg at Screening will continue the same therapy. Patients on any other ACE-i or BBs at Screening will be assigned to monotherapy with ZOF 30 mg or NEB 5 mg, respectively

d: Patients will be provided with the extemporaneous combination of NEB 5 mg with ZOF 30 mg

e: Adherence to monotherapies will be checked at the beginning of Visit 2

f: Adherence to the extemporaneous combination of NEB 5 mg with ZOF 30 mg will be checked at the end of Visit 3

g: 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

h: Patients having any ongoing AE/SAE at the end of the treatment, will be followed for further 2 weeks via a phone call to check about the status of the AE/SAE

5. STUDY RATIONALE AND BACKGROUND INFORMATION

Based on office blood pressure (BP), 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% to 45%.1 Elevated 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

The 2 well-established strategies to lower BP are lifestyle interventions and drug treatment.3

The drug treatment of hypertension is found on very solid evidence, supported by the largest number of outcome-based randomized clinical trials (RCTs) in clinical medicine. Meta-analyses of RCTs including several hundred thousand patients have shown that a 10 mmHg reduction in systolic blood pressure (SBP) or a 5 mmHg reduction in diastolic blood pressure (DBP) is associated with significant reductions in all major cardiovascular (CV) events by approximately 20%, all-cause mortality by 10% to 15%, stroke by approximately 35%, coronary events by approximately 20%, and heart failure by approximately 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 guidelines, the emphasis was on initial use of different monotherapies, increasing their dose, or substituting for another monotherapy. However, increasing the dose of monotherapy produces little additional BP-lowering and may increase the risk of adverse effects. For these reasons, more recent 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 based on the new evidence. As the 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) provided that the treatment is well tolerated, it will make the achievement of BP control even more challenging.3 Patients with hypertension are generally treated with multiple pharmaceutical products, fixed-dose combinations (FDCs) have generated increasing interest and have been recommended in treatment guidelines due to advantages in dosing and compliance, leading to improved treatment outcomes.

One of the main reasons why the current treatment strategy has failed to achieve better BP control rates is the insufficient use of combination treatment.

Blood pressure is a multiregulated 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 in most patients. Indeed, almost all patients in RCTs have required combinations of drugs to control their BP.6

Nebivolol (NEB, a beta blocker [BB]) and zofenopril calcium ([ZOF], an angiotensin converting enzyme [ACE]-inhibitor [ACE-i]) are antihypertensive drugs widely prescribed as monotherapies in the real world. Both drugs have specific benefit-risk profiles with different mechanisms of action. Beyond its beta receptor-blocking effects, nebivolol has a vasodilatory action,

presumably mediated by its ability to increase availability of vascular endothelial nitric oxide. Nebivolol shows a distinct hemodynamic profile including reduced peripheral vascular resistance and a neutral impact on cardiac output, metabolic profile, and overall tolerability. Because this mechanism of action appears to be independent of its renin inhibitory effects, an additional BP-lowering effect could be anticipated when nebivolol is combined with a blocker of the renin-angiotensin system.7

Zofenopril calcium 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 anti-hypertensive drugs currently recommended for the treatment of hypertension. Overall, clinical studies in patients with mild to moderate essential hypertension found that treatment with zofenopril calcium 30 to 60 mg/day was at least as effective and well tolerated as usual therapeutic dose regimens of other most widely used anti-hypertensive drugs.8

Despite data showing an added effect in providing NEB or ZOF to other anti-hypertensive treatment,9 there is scarce evidence at the moment on the anti-hypertensive effect of NEB/ZOF combination versus each monotherapy.

This study aims to assess the efficacy of NEB/ZOF, provided as an extemporaneous combination, in reducing systolic and diastolic BP in Grade 1 to 2 hypertensive patients versus each monotherapy.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

5.1 Assessment of Potential Risks and Benefits

Extemporaneous combination of ACE-i and BBs are often prescribed to control BP without major reported risks. 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. Patients with comorbidities may benefit from the effects of different antihypertensive medications classes. Approximately, 70% of patients with hypertension require 2 or more agents to achieve their target BP.7 In a meta-analysis published in 2010, FDCs of

antihypertensive agents not only improved compliance by 21%, but also allowed for a 50% increase in persistence with therapy.[10] 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.[11]

Using combination therapy could also drive a potential economic advantage, including reduced need to switch medications and long-term improvement in control of BP.7

6. TRIAL OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
PRIMARY		
To assess the antihypertensive effect of the extemporaneous combination of NEB 5 mg and ZOF 30 mg in lowering sitting DBP after 8 weeks of treatment, in patients with uncontrolled BP who were previously treated with NEB or ZOF monotherapies for at least 4 weeks	Change in mean sitting DBP between Week 0 (Visit 2) and Week 8 (Visit 3)	The association between elevated DBP and increased mortality risk has been reported several times in literature.[12]
SECONDARY		
• To assess the antihypertensive effect of the extemporaneous combination of NEB 5 mg and ZOF 30 mg in lowering sitting SBP after 8 weeks of treatment in patients with uncontrolled BP after at least 4 weeks of treatment with NEB or ZOF monotherapies	• Change in mean sitting SBP between Week 0 (Visit 2) and Week 8 (Visit 3)	Change in SBP after 8 weeks of treatment will show the added efficacy of the extemporaneous combination
• To evaluate the total number and percentage of patients who	• Total number and proportion	The proportion of patients at target is a very

achieved the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3	of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Week 0 (Visit 2) and Week 8 (Visit 3)	important clinical indicator of therapeutic success
• To assess compliance to the monotherapy and extemporaneous combination (actual doses taken versus doses to be taken)	• Adherence to treatment will be measured through treatment compliance which is 100 × (actual doses taken versus planned doses to be taken) from Visit 1 to Visit 2 for the monotherapies, and from Visit 2 to Visit 3 for the extemporaneous combination	Monitoring compliance is extremely important to better understand the efficacy of the extemporaneous combination
• To evaluate the safety and tolerability of the ZOF and NEB monotherapies, and the extemporaneous combination of NEB 5 mg and ZOF 30 mg after 8 weeks of treatment	• Safety and tolerability of the NEB and ZOF monotherapies, as well as extemporaneous combination between NEB 5 mg and ZOF 30 mg will be measured by AEs, SAEs, AEOSI, vital signs, physical examination, ECG, and concomitant medications at Week 0 (Visit 2) and Week 8 (Visit 3)	Incidence of ADRs, AEs, SAEs, vital signs, physical examination, ECG, and concomitant medications needs to be studied to address safety and tolerability of the extemporaneous combination
EXPLORATORY		
• To assess the antihypertensive efficacy at different time points in patients who (1) received NEB or ZOF monotherapies before the run-in period,	• Change in mean sitting SBP and DBP between Visit 1 and Visit 2: (a) in the group of patients who were ZOF 30 mg and NEB 5 mg at Visit 1 and continued on the	Evaluation of the antihypertensive efficacy of monotherapies and combination therapy in patients with different CV risk

(2) received any other ACE-i or BB monotherapies before the run-in period.	same treatment until Visit 2 and (b) in the group of patients who switched to ZOF 30 mg or NEB 5 mg from any other ACE-i or BB at Visit 1 until Visit 2 • Change in mean sitting SBP and DBP between Visit 1 and Visit 3: (a) in the group of patients who were on ZOF 30 mg and NEB 5 mg at Visit 1 and continued the same and (b) in the group of patients who switched to ZOF 30 mg or NEB 5 mg from any other ACE-i or BB at Visit 1 until Visit 2 • Number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3 evaluated in patients: (a) who were on ZOF 30 mg and NEB 5 mg at Visit 1 or (b) who switched to ZOF 30 mg or NEB 5 mg from any other ACE-i and BB at Visit 1	factors
• To assess the antihypertensive effect on patients, based on their hypertension grade, presence or absence of hypercholesterolemia, presence or absence of diabetes at Visit 2 and Visit 3	• Number and proportion of patients, divided in subgroups based on the hypertension grade, the presence or absence of diabetes, the presence or absence of hypercholesterolemia achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and	

	Visit 3	

ACE-i: Angiotensin converting enzyme-inhibitor; ADR: adverse drug reaction; AE: Adverse event; AEOSI: Adverse event of special interest; BB: beta blocker; BP: blood pressure; CV: Cardiovascular; DBP: diastolic blood pressure; ECG: Electrocardiogram; NEB: Nebivolol; SAE: serious adverse event; SBP: systolic blood pressure; ZOF: Zofenopril calcium

7. STUDY DESIGN

This is a phase IV, open-label, multicenter, multinational, interventional study to assess the effectiveness and safety of the extemporaneous combination of NEB and ZOF in grade 1 to 2 hypertensive patients versus each monotherapy (NEB or ZOF).

The study will be conducted in approximately 15 sites in the European Union countries. The total study duration is 12 weeks including a run-in period of 4 weeks and an assessment period of 8 weeks.

At Visit 1, after providing informed consent, the eligible grade 1-2 hypertensive patients (with blood pressure [BP] ranging from ≥140/90 mmHg to ≤179/109 mmHg), who were on treatment since at least 1 month, with any ACE-i or BB including ZOF 30 mg and NEB 5 mg will be screened for the eligibility criteria including BP. On the same day, the eligible patients will enter the run-in period of 4 weeks (Week -4 to Week 0). Efforts will be made to achieve 1:1 ratio in the enrolment of patients receiving any ACE-i or BB. The eligibility for grade 1-2 hypertension will be based upon the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines 2018, and the BP criteria is defined as mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥90 mmHg and ≤109 mmHg.

During the run-in period of 4 weeks (Week -4 to Week 0):

- Patients on ZOF 30 mg or NEB 5 mg will continue the same therapy. Patients on any other ACE-i will be assigned to monotherapy with ZOF 30 mg and the patients on any other BB will be assigned to monotherapy with NEB 5 mg, respectively.

Patients with controlled BP (sitting SBP/DBP ≤130/80 mmHg), at Week 0 (Visit 2), patients with uncontrolled BP (sitting SBP/DBP >130/80 mmHg) whose adherence to the treatment is not included from 80% to 120% or patients who cannot tolerate one of the monotherapies will not proceed further into the study.

After the run-in period, the patients will be treated with the extemporaneous combination of NEB 5 mg and ZOF 30 mg for 8 weeks (assessment period), ie, from Week 0 (Visit 2) till Week 8 (Visit 3).

To correctly evaluate the additional effect of the combination therapy, the number of patients with uncontrolled BP on NEB 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 (ie, NEB 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. 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. A total number of 290 patients will be screened considering 25% of drop-out rate, to obtain approximately 216 completed patients at the end of the study.

Blood pressure and heart rate will be measured at all visits using a calibrated, fully automated machine with a cuff that is appropriate to the size of the upper arm. If a fully automated machine is not available, BP may be measured manually. The same method (either automated or manual) and the same arm (right or left) must be used throughout the study. The patient should be in a seated position with feet touching the floor. Patients should be seated quietly for several minutes in a chair with their backs supported, their feet flat on the ground, and their arms bared and supported at heart level. At each clinic visit, 3 BP measurements will be collected 24 hours (±3 hours) after the last study drug intake and the mean values will be recorded. Each BP measure must be recorded within ±2 mmHg. Patients will be instructed to take study medication at the same time each day except on the days of study visits when study medication will be taken after all visit evaluations have been performed.

The patients will attend an End of Treatment at Visit 3 (Week 8) at the end of assessment period. Safety (AEs, SAEs) will be measured at all visits. In case of any abnormality of clinically relevant safety finding at any of the visits according to the Investigator, the patient will be

contacted over phone within 24 hours ensuring their safety measures. Any patient having an ongoing AE or SAE at the End of Treatment (Visit 3), will be followed for further 2 weeks over phone.

Patients included in the study should follow the diet and lifestyle counselling.

At the End of Treatment Visit patients will be advised to maintain the recommended diet and physical activity/exercise pattern as per local standards of care.

7.1 Procedures and Study Visits

Patients will attend a total of 3 visits during the study. The description of the activities, procedures and tests to be performed at each visit is detailed below:

1. Screening and Start of Run-in period (Visit 1, Week -4):

The following procedures/assessments must be completed during the Screening on the same day prior to the run-in period (Visit 1):

- Obtaining informed consent
- Checking inclusion and exclusion criteria
- Recording of medical history
- Recording of prior and concomitant medications
- Collection of demographic data
- Recording concurrent diseases and medical conditions
- Antihypertensive treatment with NEB or ZOF monotherapy
- Physical and vital signs examination
- BP measurement
- Electrocardiogram (ECG)
- Laboratory tests (see Section 10.2) (A follow-up phone call will be made within 24 hours in case of any abnormality and clinically relevant results from the laboratory tests according to the Investigator)
- Urine pregnancy test
- AEs and serious adverse events (SAEs) assessment

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

- Patients who are already on therapy with ZOF 30 mg or NEB 5 mg will be provided with the same medication
- Patients taking any other BBs will be provided with NEB 5 mg, and patients taking any other ACE-i will be provided with ZOF 30 mg

2. Start of the assessment period (Visit 2, Week 0):

At the end of the run-in period (treatment with monotherapies for 4 weeks ±2 days), only 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.
The starting of extemporaneous combination ZOF 30 mg /NEB 5mg dosing is noted as Week 0.
The following procedures/assessments must be completed:

- Recording of concurrent diseases and medical conditions
- Study drug dispensing (Patients will be provided with the extemporaneous combination ZOF 30 mg/NEB 5 mg)
- Recording of concomitant medications
- Physical examination and vital signs
- BP measurement
- ECG
- Urine pregnancy test (UPT)
- Compliance assessment by return of ZOF and NEB tablets (also empty blisters) and accountability
- AEs and serious adverse events (SAEs) assessment

3. End of the Assessment Period (Visit 3, Week 8):

The end of assessment period will be considered as end of 8 week ±3 days treatment with the extemporaneous combination ZOF 30 mg/NEB 5mg.

The following procedures/assessments must be completed:

- Recording of concurrent diseases and medical conditions
- Recording of concomitant medications
- Physical examination and vital signs
- BP measurement
- ECG
- Laboratory test (A follow-up phone call after will be performed within 24 hours from results in case of any abnormality and clinically relevant results from the laboratory tests according to the Investigator)
- Urine pregnancy test (UPT)
- Compliance assessment by study drug (extemporaneous combination of ZOF 30 mg and NEB 5 mg) return (also empty blisters) and accountability
- AE and SAE 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

Note: Patients will be counselled to follow a heart healthy diet as per local or regional guidelines and should be encouraged (as able) to participate in a regular exercise programme throughout the study.

8. SELECTION OF PATIENTS

Informed Consent Process

Prior to the patient's enrolment into the study and before performing any study related procedures, the Investigator or his/her authorized delegate, shall obtain the patient's written, dated, and signed informed consent to participate into the study and to the confidential disclosure, processing and transferring of necessary documentation of the patient's health and personal data to the contract research organization (CRO), Sponsor, and its Affiliates, the competent health authorities (HA), 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 informed consent form [ICF] refer to Section 19).

The institution and Investigator undertake to duly inform patients 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 patient has to freely date and sign the ICF before being enrolled into the study and before undergoing any study procedure. The Investigator must store the original of the signed ICF in the Investigator's File, and the patient will be provided with a copy of it. If a protocol amendment affects the terms of the ICF, it will be revised to reflect the protocol change and submitted to Ethics Committee (EC) and the HA for approval. The Investigator will ensure that this new consent form is signed by all patients subsequently entered in the study and those currently in the study, if affected by the amendment.

8.1 Inclusion and Exclusion Criteria

A patient will be considered eligible to be enrolled in the study only if he/she meets all of the inclusion criteria and none of the exclusion criteria.

8.1.1. Inclusion Criteria

1. Male or female Caucasian uncontrolled hypertensive patients ≥18 and <65 years of age (see definition in criterion 3), in monotherapy either with ACE-i or BBs since at least 1 month, at Screening
2. Patients are able to understand and have freely given written informed consent at Screening
3. Patients with mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥ 90 mmHg and ≤109 mmHg at Screening
4. Patients who are able to comply with all study procedures and who are available for the duration of the study
5. Ability to take oral medication and willing to adhere to the drug regimen
6. A female patient of childbearing potential is eligible to participate if she is not pregnant, or not breastfeeding. A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Women of childbearing potential

must agree to use of highly effective contraception (eg, 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) and also must refrain from donating or storing eggs during this time. Highly effective contraception methods can be:

- 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 (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success)

7. A male patient with female partner 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.

8.1.2 Exclusion Criteria

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

1. Known contraindications, allergies, or hypersensitivities to any of the study medications or excipient as outlined in the investigators brochures IBs, summary of product characteristics (SmPCs) or local package inserts for NEB and ZOF[13,14]
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, hematological, 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, heart

failure, hypertensive encephalopathy, cerebrovascular accident (stroke), or transient ischemic attack

4. Patients with secondary hypertension of any etiology such as renal diseases, pheochromocytoma, or Cushing's syndrome
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. History of angioneurotic edema
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. History of bronchospasm and bronchial asthma
12. Patients with bradycardia (heart rate <60 bpm)
13. Patient with metabolic acidosis
14. Patients with severe peripheral circulatory disturbances
15. Participation in another study within the last 4 weeks
16. Patients with diseases that, in the opinion of the Investigator, prevent a careful adherence to the protocol
17. Pregnant and breastfeeding women. NOTE: a pregnancy test will be performed on all women of childbearing potential at each study visit

8.1.3 Screening Failures

Screening failures are defined as patients who consented to participate in the clinical trial, but do not meet one or more criteria required for participation in the trial during the screening procedures (Visit 1). There will be no rescreening of screening failure patients in this study.

9. STUDY TREATMENT

The treatments administered during the run-in period of the study are NEB 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 NEB 5 mg and ZOF 30 mg. Details on the study design is provided in Section 7.

Further details on study treatment is provided below in Table 9.1.

Table 9.1 Study Treatment Details

Study Treatment Name:	Nebivolol **Marketing Authorisation Holder**: A. Menarini Industrie Farmaceutiche Riunite srl, Via Sette Santi n. 3, 50131 Florence	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
Dosage Formulation:	Tablet	Film-coated tablet
Unit Dose Strength(s)/Dosage Level(s):	5 mg once daily	30 mg once daily
Route of Administration:	Oral	Oral
Dosing Instructions*:	1 tablet of study medication will be administered with a glass of water once daily	1 tablet of study medication will be administered with a glass of water once daily
Packaging and Labelling:	Study medication will be provided in a PVC//Aluminium blister	Study medication will be provided in a PVC/PVDC//Aluminium blister
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 precautions 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 precautions are needed.

*The patients will take the monotherapy tablets or the extemporaneous combination of NEB and ZOF in the morning between 6 am to 10 am except on the visit days. On the visit days, the patients will take the monotherapy tablets or the extemporaneous combination of NEB and ZOF after the study assessments. It is important to keep the medication intake on the same time every day throughout the study period. NO restriction will be there concerning food intake and both the monotherapies, or the extemporaneous combination can be given with or without meals.

9.1 Study Treatment Formulation, Appearance, Packaging, and Labelling

Study treatment dosage form, strength, formulation

Nebivolol 5 mg: NEB 5 mg is white, round, cross-scored tablet with one-sided dividing cross score

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

Study treatment manufacturing

The NEB 5 mg 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 are reported in relative SmPC.[13,14]

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 NEB 5 mg will be provided in dedicated treatment boxes/kits to be dispensed at Visit 1 (beginning of the run-in period) and at Visit 2 (start of the assessment period).

- **Visit 1 (run-in period)**
    - ZOF 30 mg: each trial participant is provided with one labelled box (blue label) containing 42 film-coated tablets (3 blisters of 14 tablets each) of zofenopril calcium 30 mg.

- NEB 30 mg: each trial participant is provided with one labelled box (yellow label) containing 42 tablets (3 blisters of 14 tablets each) of nebivolol 5 mg.

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

- **Visit 2 (assessment period)**

Each trial participant is provided with one treatment kit made up by

- ZOF 30 mg: one labelled box (blue label) containing 70 film-coated tablets (5 blisters with 14 film-coated tablets each) of zofenopril calcium 30 mg
- NEB 5 mg: one labelled box (yellow label) containing 70 tablets (5 blisters with 14 tablets each) of nebivolol 5 mg.

The two labelled boxes are then sealed together into a transparent plastic film in order 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 NEB 5 mg (nebivolol 5 mg) as one round tablet, according to Study Protocol.

9.2 Study Treatment Distribution and Return/Destruction

The Principal Investigator (PI) will be responsible for the management of all study medications to be used for the clinical trial. An inventory will be maintained by the PI (or designee) to include a signed account of all medications received, dispensed to, and returned by each patient at the planned visits. An explanation will be given for any discrepancies. At the conclusion of the study, the Drug Accountability Form will be completed after a final medication supply inventory.

All supplied (used or unused) study treatment must be accounted for and provided with relative return documentation duly filled in, signed, and dated as appropriate. Any discrepancy (if any) must be investigated and satisfactorily explained. Destruction of study medications will be carried out by Manufacturer after written authorization of the Sponsor.

9.3 Product Storage and Stability

No special storage conditions are required.

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.

9.4 Study Product Compliance

Compliance with study treatment will be assessed at Visit 2 for monotherapy and Visit 3 for the combination therapy. The PI must instruct patients to return the medications at each visit. The amount of study medication taken by the patient will be derived by counting the number of tablets in the blister returned and will be recorded in the source document and in the electronic case report form (eCRF).

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.

9.5 Concomitant Therapies

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. Patients should remain on the same concomitant medication at a stable dose throughout the study.

9.6 Non-Permitted Medications

The patients will not be permitted to use any of the following medications from Screening till the end of treatment. Blood pressure modifying drugs including alpha receptor blockers and agonists, beta receptor blockers and agonists, calcium antagonists, ACE-i, diuretics, centrally acting antihypertensives (eg, clonidine, methyldopa, guanfacine), reserpine, moxonidine, chronic nitrate treatment (eg, isosorbide dinitrate or isosorbide mononitrate) and angiotensin II antagonists are not permitted, even if used for other indications.

9.7 Rescue Medication

Not applicable.

10. STUDY ASSESSMENT AND PROCEDURES

10.1 Assessment of Efficacy

The efficacy variable is to assess the antihypertensive effect of the extemporaneous combination of NEB/ZOF (5 mg/30 mg) in grade 1 to 2 hypertensive patients versus each monotherapy after 8 weeks of treatment. Data for this variable will be collected from BP measurements.

BP measurements:

Blood pressure will be measured at all visits. The arm with the higher mean DBP will be identified at Screening and will be used in all subsequent visits for BP monitoring. Blood pressure measurements should be performed as nearly as possible at the same time of the day (between 7:00 AM to 12:00 noon), on the same arm, by the same personnel, and using the same calibrated equipment at each visit.

All BP measurements will be performed after at least 10 minutes of rest; in sitting position in triplicate (spaced by at least 1 minute), and once in standing position using a calibrated and validated automated sphygmomanometer. The mean of the 3 recordings in the 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 period will be performed as through readings (ie, 24+3 hours after the last study treatment intake). 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.

10.2 Assessment of Safety

Safety will be assessed through collection of treatment-emergent AEs, serious AEs (SAE), AEs of special interest (AEOSI), that started after the first dose of study treatments (incidence, severity, seriousness, treatment causality), and physical examination (body weight, height, vital signs, BP, and heart rate). Safety assessments will be performed at time points as described in Section 4.1.

10.2.1 Physical Examination:

Physical examination will be performed according to the local practice. Physical examination will consist of the following body systems: eyes, ears, nose, throat, cardiovascular system, respiratory system, gastrointestinal system, dermatologic system, extremities, musculoskeletal system, nervous system, and lymph nodes. Height and weight will also be recorded at Screening. Any new finding, or worsening of a previous finding, should be reported as a new AE.

10.2.2 Vital Signs

Vital signs will include body temperature (tympanic measurement), respiratory rate, sitting BP (see Section 10.1), and pulse (bpm). All BP measurements will be performed after at least 10 minutes of rest; in sitting position in triplicate (spaced by at least 1 minute), and once in standing position. The mean of the 3 BP readings in sitting position will be recorded on the eCRF. Blood pressure and pulse measurements will be assessed with a completely automated device.

10.2.3 Clinical Laboratory Tests

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood is approximately 40 mL, which will be the total blood collected during the study.

A follow-up phone call after each visit will be performed within 24 hours from results only in case of abnormality and clinically relevant laboratory test according to the Investigator judgement.

The local laboratory will perform laboratory tests for hematology and serum chemistry as listed below. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results.

Hematology	Serum Chemistry
Red blood cell	ALT
White blood cell	Albumin
Hemoglobin	Alkaline phosphatase
Hematocrit	AST
Platelets	Total protein
Neutrophils	Direct bilirubin
Lymphocytes	Total bilirubin
Monocytes	Creatinine
Eosinophils	Blood urea nitrogen
Basophils	Creatine kinase
Neutrophils absolute, Lymphocytes absolute, Monocytes absolute, Eosinophils absolute, Basophils absolute	GGT
	Triglycerides
	Cholesterol
	High- and low-density lipoprotein
	Chloride
	Blood glucose
	Serum potassium

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

10.2.4 Electrocardiograms

A single 12-lead resting ECG will be recorded after the patient has been supine for at least 5 minutes to calculate the heart rate and measure PR, QRS, QT, and QTc intervals. The results will be recorded in the eCRF. A trained clinical site physician will perform the clinical assessment of each 12-lead ECG. Additional 12-lead ECGs will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required.

11. SAFETY DATA MANAGEMENT

11.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

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

11.2 Drug Relationship

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

1. **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
2. **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
3. **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
4. **Unassessable:** The relationship cannot be judged, because the information is insufficient or contradictory and cannot be supplemented or verified

5. **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
6. **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.

11.3 Adverse Drug Reaction

An adverse drug reaction (ADR) is any untoward and unintended response to a study treatment related to any dose administered.

The definition implies a reasonable possibility of a causal relationship between the event and the study treatment. 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. Unassessable

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

1. Unlikely
2. Not related

11.4 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.

3. Requires inpatient hospitalization or prolongation of existing hospitalization;
4. Results in persistent or significant disability/incapacity;
5. Is a congenital anomaly/birth defect;
6. Is a medically important condition that may jeopardize 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 nonserious when it does not fulfil the conditions for the definition of a serious AE/ADR.

11.5 Adverse Event/Adverse Drug Reaction Intensity

The intensity level of a serious or a nonserious AE (NSAE) 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 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

11.6 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 ZOF and NEB).[13, 14]

11.7 Serious Unexpected Adverse Drug Reaction

Any SAE judged by the Investigator or the Sponsor as drug-related (see Section 11.3) and considered as unexpected qualifies as a serious unexpected adverse drug reaction (SUSAR).

Suspected unexpected serious adverse drug reactions are subjected to expedited reporting, as specified in Section 11.10, as having a "Reasonable Possibility" of relationship with the IMP.

11.8 Individual Case Safety Report

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

11.9 Collection, Recording, and Reporting of AEs

At each visit the Investigator will collect and assess any AEs that have occurred in each patient since he/she had signed the informed consent.

Any laboratory test abnormality (newly occurring after the study treatment administration or worsening of previously known abnormalities) that the Investigator considers as clinically relevant: ie, values significantly above or under normal range or which require an intervention or diagnostic tests or may result in the study treatment discontinuation will be reported as an AE.

Any AE communicated by the patient or by the patient's relatives or delegates through phone calls, letters, or emails will also be collected and assessed.

The Investigator shall record on the respective eCRF AE recording pages/AE form any recognised AE identifying an individual case safety report (ICSR), both serious and nonserious, whether or not thought to be drug-related, observed in or reported by the patient (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 record also 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.

The Investigator must report all the collected information on any ICSR including seriousness (whether or not thought to be related to the investigational drug), providing the concerned eCRF AE pages by alert e-mail, after the first knowledge of the occurrence of the case, to:

CRO Pharmacovigilance Officer: Will be reported through CRO's Pharmacovigilance group (ZoNe_SO@IQVIA.com) for which its details will be provided via study guidelines

When relevant, the eCRF pages concerning medical history, concomitant medication, and laboratory tests should also be sent to the Sponsor by e-mail.

11.10 Management of Serious AEs (SAEs) Including Laboratory Abnormalities

Reporting Duties of the Investigator

If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs **after the end of the clinical trial** in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor

The Investigator must report all the collected information on any serious ICSR (whether or not thought to be related to the investigational drug), as specified above, no later than 24 hours after the first knowledge of the occurrence of the case.

Any further information and supporting documentation that becomes available (copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall be provided no later than 24 hours after first knowledge, by the Investigator, to the CRO by alert e-mail, 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/EC.

Reporting Duties of the Sponsor

The Sponsor shall ensure that all relevant information about any SUSAR, is expeditiously reported to the competent authorities and ECs 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 patented 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 treatment.

When appropriate and applicable, the Sponsor will arrange for adequate information to be communicated to the Investigators.

For trials in high morbidity and/or mortality disease, where the efficacy endpoint could also be a serious unexpected ADR or when a fatal or other serious outcome is the primary efficacy endpoint, agreement with the competent authority will be reached to treat the SAE as disease-related and not subject to expedited reporting.

11.11 Management of Nonserious AEs Including Laboratory Abnormalities

Reporting Duties of the Investigator

The Investigator must report all the collected information on any NSAE ICSR (whether or not thought to be related to the investigational drug), as specified above, 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 Investigator first becomes aware, to the CRO by e-mail or fax, to be forwarded to the Sponsor.

11.12 Management of Any Laboratory Abnormality

Any laboratory test abnormality which is considered by the Investigator as an AE, is to be managed as detailed above (refer to Section 10.2). However, all "out of range" values should be collected and reviewed periodically (modality to be established) by the CRO and the Sponsor.

11.13 Management of Pregnancy Exposure Cases

The Investigator is expected to record in the provided form any case of pregnancy exposure occurring in a female patient or in a male patient's partner during the treatment, sending it within 5 days after being made aware of the pregnancy, to the CRO by e-mail or fax, 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 an SAE and managed as described above.

Eligibility of a woman of childbearing potential (WOCBP) will be considered as described in Section 8.1. 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:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.

Note: Documentation can come from the study center 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.

12. WITHDRAWAL CRITERIA

Withdrawal of monotherapies or the study drug

Withdrawal from the monotherapies or study drug refers to any patient who does not receive the complete course, ie, when no further planned dose is administered from the date of withdrawal. A patient withdrawn from the monotherapies or study drug may continue further study procedures (safety) planned in the study protocol, as deemed appropriate by the Investigator once the safety of the patient is recovered/reassured.

A patient's study drug or monotherapies may be discontinued for any of the reasons below. In addition to the scheduled visits, patient who have been withdrawn from study drug or monotherapies may also undergo additional medical follow-up at the discretion of the Investigator.

- Any AE, which required treatment termination according to the Investigator's judgement
- Clinically significant intercurrent illness or laboratory results which could compromise the safety of the patient or the scientific value of the study
- Investigator deems it to be in the best interest of the patient to discontinue
- Requirement to use prohibited medication that could compromise the safety of the patient or the scientific value of the study

Withdrawal of patient from the study

The patient may withdraw from the study at any time without explanation, without losing the right to future medical care. The participation of the patient may, at any moment, be terminated by the Investigator, if considered appropriate.

A patient can be withdrawn during the study for any of the following reasons:

- Any AE, which required treatment and study termination for the patient according to the Investigator's judgement
- Abnormal renal function or liver enzyme parameters as described in Section 10.2
- Patient becomes pregnant during the study
- Request of the patient (without giving any reason)
- Investigator deems it to be in the best interest of the patient to discontinue
- Failure to adequately comply with the dosing, evaluations, or other requirements of the study
- If the patient meets an exclusion criterion (newly developed or not previously recognized) that precludes further study participation
- Use of any prohibited medication (eg, concomitant use of aliskiren-containing products and ACE-i with sacubitril/valsartan or any other drug as specified per SmPCs of ZOF or NEB) that in the opinion of the Investigator or Sponsor necessitates the patient being withdrawn

The reason for the withdrawal of monotherapies or study drug, or withdrawal from the study must be well documented in the eCRF page and should capture the date and the specific underlying reason for discontinuation of study treatment or patient discontinuation/withdrawal.

Patients who discontinue from the study early will be asked, anyway, to complete all the assessments of Visit 3. Patients may discontinue the study product, but remain in the study for follow-up, especially for safety study endpoints (if applicable).

If a patient has been discontinued/withdrawn due to an AE, the Investigator must immediately notify the relevant pharmacovigilance contact (see Section 11.9) and should be followed-up until

the AE is resolved or the Investigator deems further observations or examinations as no longer medically indicated.

13. LOST TO FOLLOW-UP

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

The site will attempt to contact the patient and reschedule the missed visit. The site will also 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 to regain contact with the patient. These contact attempts should be documented in the patient's medical record or study file.

14. STATISTICS

14.1 Statistical Methods (Blinding and Randomization)

This is an open-label study. In this study all the patients are receiving monotherapy in the run-in period and combination therapy at the study treatment phase and no randomization is required.

14.2 Determination of Sample Size

Considering a screen failure and a drop-out rate of 25% from Visit 1 and Visit 3, the number of patients to be screened is 290. Two-hundred and sixteen with uncontrolled hypertension, are planned to be included at Screening in the assessment period lasting for 8 weeks. A total sample size of 216 patients is required to achieve 90% power at 5% significance level assuming a difference in mean DBP from baseline to 8 weeks of 4 mmHg and a standard deviation (SD) for this difference of 10 mmHg. The mean change in DBP for null hypothesis is set at 2 mmHg.

14.3 Analysis Populations

In this study, 3 types of analysis population will be used.

- Enrolled population: Patients who are enrolled into the study and may or may not receive the study drug (extemporaneous combination)
- Intent-to-Treat population: Patients who are in the Enrolled population and receive at least 1 dose of study drug (combination therapy) and have at least 1 post baseline safety assessment
- Safety population: Patients who are in the Enrolled population and receive at least 1 dose of study drug (combination therapy)
- Per protocol population: All patients included in the safety population who do not have any major protocol deviations will be included in this population

14.4 Analysis Variables

Analysis of Variables and Populations Used		
Efficacy		
	Analysis Variables	**Population Used**
Primary efficacy	Change in mean sitting DBP between Week 0 (Visit 2) and Week 8 (Visit 3)	ITT population, PP population
Secondary efficacy	Change in mean sitting SBP between Week 0 (Visit 2) and Week 8 (Visit 3)	ITT population, PP Population
	Number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Week 0 (Visit 2) and Week 8 (Visit 3)	ITT population
	Adherence to treatment will be measured through treatment compliance which is 100 × (actual doses taken/ planned doses)	Enrolled population, Safety population
Exploratory efficacy	• Change in mean sitting SBP and DBP between Visit 1 and Visit 2 in the group of patients on ZOF 30 and NEB 5 mg and in the group of patients switched to ZOF 30 mg or NEB 5 mg from any other ACE-I and BB • Change in mean sitting SBP and DBP between Visit 1 and Visit 3 in the group of patients on ZOF 30 mg and NEB 5 mg or in the group of patients switched to ZOF 30 mg or NEB 5 mg from any other ACE-i and BB • Number and proportion of patients in the group of patients on	Enrolled Population

	ZOF 30 and NEB 5 mg and in the group of patients switched to ZOF 30 mg or NEB 5 mg from any other ACE-I and BB achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3 suggested in Section 6	
Safety	Safety and tolerability of the extemporaneous combination between NEB 5 mg and ZOF 30 mg measured by AEs, SAEs, AEOSI, vital signs, physical examination, ECG, and concomitant medications at Week 0 (Visit 2) and Week 8 (Visit 3)	Safety population

AE: adverse event; AEOSI: adverse event of special interest; BP: blood pressure; DBP: diastolic blood pressure; ECG: electrocardiogram; ITT: Intent-to-treat; SAE: serious adverse event; NEB: nebivolol; SBP: systolic blood pressure; ZOF: zofenopril calcium

14.5 STATISTICAL ANALYSIS

14.5.1 Descriptive Statistics

Patient disposition, demographics and baseline characteristics, medical history, and prior and concomitant medication will be summarized by treatment group as well as overall.

Continuous variables will be summarized with the number of non-missing observations, mean, SD, standard error of the mean, minimum, median, and maximum. Categorical variables will be presented with the number of non-missing observations and column percentages (n, %).

14.5.2 Primary (efficacy) Analysis

The primary efficacy analysis will be conducted on the intent-to-treat (ITT) population. The interpretation of results will be based on ITT population. The PP population will be used to assess the robustness of the results obtained using the ITT population.

The primary endpoint is the mean change from baseline in sitting DBP at Week 8 (Visit 3) for patients who are receiving combination therapy.

The statistical hypothesis will be defined as below:

H_0: There is no change in the sitting DBP prior or post combination therapy

H_1: There is a difference in the sitting DBP prior or post combination therapy

The above hypothesis will be tested as following-

- Change from baseline in sitting DBP from prior and post combination therapy will be compared using paired t-test. The p-value will be presented using paired t-test.
- The primary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum.
- Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.

14.5.3 Sensitivity Analysis

The primary analysis will be conducted using the PP population.

14.5.4 Secondary (efficacy) Analysis

Secondary efficacy variables will be summarized in a descriptive manner using both ITT and PP population.

- Change in mean sitting SBP between Week 0 (Visit 2) and Week 8 (Visit 3):
    - Change from baseline in sitting SBP from prior and post combination therapy will be compared using paired t-test. The p-value will be presented using a paired t-test comparing mean at baseline and mean at Week 8.
    - The secondary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum.

Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.

The number of patients achieving BP goal (sitting BP ≤130/80 mmHg) will be summarized for Visit 2 and Visit 3, along with percentage. A p-value using McNemar's test will be presented to compare the proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) between Visit 2 and Visit 3.

14.5.5 Exploratory (Efficacy) Analysis

Exploratory efficacy variables will be summarized in a descriptive manner using safety population for Visits 1, 2 and 3.

- Change in mean sitting SBP and sitting DBP between Visit 1 and Visit 3 will be analyze as following
    - Change from baseline in sitting SBP and DBP from prior (Visit 1) and post (Visit 3) combination therapy will be compared using paired t-test. The p-value will be presented using a paired t-test comparing mean at baseline and mean at Week 8.
    - The exploratory endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum.

  Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.

The number of patients achieving BP goal (sitting BP ≤130/80 mmHg) will be summarized for Visit 1 and Visit 3, along with percentage. A p-value using McNemar's test will be presented to compare the proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) between Visit 1 and Visit 3.

14.5.6 Subgroup Analysis

Subgroup analysis will be conducted using ITT and PP population based on the following parameters.

- Country/Site
- Age (<40 years and ≥40 years)
- Gender (Male, Female, Other)
- Presence of diabetes (patients with or without diabetes)
- Presence of hypercholesterolemia (patients with or without hypercholesterolemia)
- Screening therapy (ACE-i, Beta blocker)
- Run-in period therapy (Monotherapies of ZOF 30 mg or NEB 5 mg)

14.5.7 Safety Analysis

Adverse Events:

Adverse events recorded during the study will be mapped to a system organ class (SOC) and preferred term (PT) using the current Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as new AEs that occur on or after the date/time of the first administration of study medication or worsen if an AE started prior to the start of first administration of study medication.

All the AEs will be presented with the following:

- Number of cases
- Number of patients with AE
- Percentage of patients with AE

Laboratory:

Laboratory parameters will be summarized descriptively using the safety population by visit. All laboratory data will be listed.

ECG:

Electrocardiogram parameters will be summarized descriptively using the safety population by visit. All ECG data will be listed.

Physical Examination (PE):

Physical examination parameters will be summarized descriptively using the safety population by visit. All PE data will be listed.

14.5.8 Interim Analysis and Stopping Rules

Not applicable.

14.5.9 Data Imputations

As a part of missing data analysis Multiple Imputation (MI) simulation method for imputing missing data will be conducted on the primary efficacy endpoint using ITT population. This will help to assess the impact of missing data on the primary analysis.

The SAS procedure MI will be used, and the details of MI procedure will be stated in the dataset specification document. If the data is monotone missing, an imputation model with regression baseline parameters (age, gender, country/site, monotherapy and baseline values) will be applied, otherwise Markov Chain Monte Carlo (MCMC) will be applied. All variables included in the analysis model and values at Week 0 for the primary endpoint will be included in the imputation model. To reduce the sampling variability from the imputation process, 50 datasets will be generated.

In the estimation step, separate analysis will be performed using the paired t-test.

After the completion of the estimation step SAS procedure MIANALYZE will be used to pool the estimates.

14.6 Protocol Deviations and Protocol Amendments

No deviations from the protocol should be initiated without prior approval by the 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, ie, are likely to have an impact on the safety of the patients, 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 country authorities (CAs) in the participating countries have to approve these amendments before implementation, according to applicable regulatory requirements.

Changes which have no significant impact on the medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the EC, CAs (where applicable) will be notified of this protocol amendment.

Any substantial amendments of the protocol will be integrated in an updated study protocol. The PI must ensure full compliance with the updated study protocol.

14.7 Statistical Analysis Plan

This study is an open-label study and statistical analysis plan (SAP) will be finalized prior to first patient in. However, in case of any protocol amendment or any modification which may not affect the integrity of data or primary analysis but may lead to modification of SAP version, will be finalized prior to database lock. 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 to the original primary endpoint or of the original primary analyses occurs during the study, these changes will be the subject of a substantial protocol amendment.

All statistical analyses not prespecified and run after database lock will be considered additional/exploratory analyses.

15. STUDY DISCONTINUATION AND CLOSURE

In case this study is temporarily suspended or prematurely terminated, written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study patients, Investigators, ECs, Sponsor, and regulatory authorities with the reason(s) for the termination or suspension. The study patients will be contacted, as applicable, and be informed of changes to study visit schedule.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator must permit study related monitoring, audits, EC review, and regulatory authorities' inspections and provide direct access to source data/documents. The Investigator/institution should maintain adequate and accurate source documents and study

records that include all pertinent observations on each of the study site patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Source documents are filed at the Investigator's study site.

17. QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Study Monitoring/Data Quality Control

Site monitoring is conducted to ensure that the rights and well-being of trial patients 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 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.

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.

17.2 Case Report Forms

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.

On the eCRF, patients will be identified by the patient number/code, assigned at the Screening Visit. The patient number/code will be a number composed of numeric values.

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 Investigator will be responsible for entering study data into the eCRF in accordance with the eCRF user guidelines.

17.3 Quality Assurance

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

18. ETHICAL ASPECTS

The study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human patients of the Declaration of Helsinki, International Council for Harmonisation – Good Clinical Practices (ICH-GCP) guidelines, EU-Directives and Regulations and national requirements of the participating countries.

18.1 Ethics Committees

Before starting the study in a study site, the study protocol and relevant documentation (Patient information leaflet, ICF, the Investigator's Brochure, and other documents, according to National Regulations) must be submitted to and approved by the ECs and the HAs of the participating countries.

In addition, all local national legal requirements for the conduct of a clinical study must 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.

18.2 Patient's Insurance

For patients participating in the study, the 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 patients in the ICF and/or provided as a separate document, in accordance with national requirements. The 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 the Sponsor immediately upon notice of any claims or lawsuits.

19. DATA PROTECTION LAWS 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 and the EU Regulation on clinical trials on medicinal products for human use 536/2014. This section defines the appropriate technical and organizational measures that shall be implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfilment of patients' privacy rights.

19.1 Acknowledgement

The site, the PI, 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 and local laws (ie, the laws of the country where the study is conducted) as well as by the Sponsor's national legislation.

In particular, it is hereby acknowledged that the Sponsor being a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore the site, the PI, the local laboratory, and 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 PI, the local laboratory, and the CRO.

19.2 Data Controllers and Data Processors

The Sponsor, the site, the PI, and the CRO acknowledges that according to the applicable privacy laws, the Sponsor and site will act as independent data controllers while the CRO and the PI will act as data processors respectively of the Sponsor and of site. Before beginning of the study, the site will instruct in writing the PI as its data processor*. However, if specific local laws or regulations mandate a different definition of the privacy roles, the Sponsor, the site, the PI, and the CRO will implement the relevant legal instruments (eg, if pursuant to the local laws the site is a data processor of the Sponsor, a Data Processing Agreement will be finalized; if pursuant to the local laws the Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalized).

*For clinical trials where the PIs are the owners of the site, this provision may not apply. In such cases, the PI might be considered as a Data Controller

19.3 Duties of the Parties Involved in the Performance of the Study

Collection and use of patients' personal data including their biological samples, 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 PI, 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, shall implement the following safety measures (physical, logical, organizational, technical, electronic, IT, 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 PI shall adopt all the necessary measures to prevent or minimize the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorized 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 PI shall ensure that the actual measures they have implemented are fit-for purpose and law-compliant, and in particular: - in order to minimize 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 3 months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least 3 "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 (eg, "johnbrown80") or easily predictable strings of characters (eg, "qwerty", "12345", "admin", "user", etc.);

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

-high level security measures shall also be implemented on the files or databases which contain the "key" to match the patients' personal data (ie, 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 IT devices.

The site shall regularly test and update the measures listed above. The site shall, at the Sponsor's request 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 centralized database(s) used to process study 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 CENTRALIZED DATABASE. The centralized 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 (ie, 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-anonymization" process). The PI 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. The site/PI shall securely store a separate list (eg: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.

The patient code pairing list (ie, the list where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived by the PI.

As outlined below, samples shall only be stored for as long as strictly necessary for the study's performance and should be destroyed after the analysis. Biological samples and any other examination (eg, X-ray, ECG) shall bear Patient ID, and in no case will they bear other information that may lead to the direct or indirect identification of the patient, especially when, in accordance with this protocol, samples shall be forwarded and shared outside the clinical site (eg, in case of centralized reading or local laboratory analysis).

(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 site and/or the CRO to the competent authorities (including data protection authorities) and ECs 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 PI, the CRO and the local laboratory undertake to adopt all the necessary activities to overcome such remarks to assure full compliance with data protection laws.

19.4 Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure, 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, PI etc.; data loss is when the data may still exist, but the site, Sponsor, CRO, PI 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 site, Sponsor, CRO, PI etc. An 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 (eg, an unauthorized access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (eg, 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 Clinical Operations Director, the Sponsor's Data Protection Officer, the site and the CRO (CRO responsible persons for Data Breach incidents management) and shall provide the following information:

(i) Anomalous Event / Data Breach Type (eg, 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 (eg, 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 has 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 EU, the 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. Categorize 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 minimize 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

19.5 Information notice on personal data protection and pseudo-anonymization

Prior to patients' enrolment in the study, the PI 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 PI 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 (eg, performance of the study, pharmacovigilance) 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 pseudonymization procedure and scope
(vii) who can access patients' data and under what circumstances
(viii) the period of data retention/storage as defined in Paragraph 19, including the storage of the biological sample
(ix) to which entities/countries outside the EU patients' data will be transmitted (if applicable), as per Paragraph 18.7
(x) patients' data protection rights as defined by the EU General Data Protection Regulation 679/2016
(xi) Data Controllers / Data Processors and the relevant contact details
(xii) Sponsor's Data Protection Officer contacts (DPO)

(xiii) in case of genetic data processing the possible findings, also with regard to unexpected findings that might be disclosed on account of the processing of the genetic data

19.6 Genetic Data

Genetic data will not be collected for this study.

19.7 Transfer of patient's 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 PI, 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.

19.8 Exercise of patients' data privacy rights

Each study patient has the right to contact the Sponsor, the site, the PI, the local laboratory, the CRO to exercise the rights afforded to the patient by the law, including the afforded ones under articles 15 to 22 of Regulation (EU) 2016/679, 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- use the same protocol terminology/definitions]; 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 anonymized 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 DPO any use of his/her personal data. Each patient is free to withdraw at any time from the study. In such case, each study patient may ask the site staff and the Investigator to destroy/delete his/her personal data (IF APPLICABLE: including his/her biological samples, unless they have been permanently anonymized), 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

the site, the PI, the local laboratory, the CRO receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by e-mail 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 PI, the local laboratory, the CRO shall implement adequate organizational measures to reply to patients within the above-mentioned deadline.

19.9 Future research

With patients' optional and additional consent, the Sponsor and/or the site may use the data collected during the course of the study for further medical and scientific research purposes. These may include, eg, retrospective clinical studies; clinical studies pertaining to the patients' pathology/medical condition(s)or similar conditions; studies which compare the data of this study with those from other sources to identify the factors involved in a disease; registration of new drugs

In the context of these additional research activities, patients' data will be processed, pseudonymized and transferred abroad and may be shared with future research partners.

In the context of these additional research activities, patients' data will be processed, anonymized and transferred abroad, and may be shared with future research partners –in most cases this will prevent patient's identification; however, in the unlikely event patients full identity really needs to be disclosed, the same precautions and safeguards as those described in this protocol will be implemented.

20. DATA HANDLING AND RECORDS KEEPING

Unless other laws require archiving for a longer period, the site and the PI shall archive the content of the clinical trial 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 Investigator should keep all study related documents, as specified in ICH E6 (GCP) Section 8 and by the applicable regulatory requirement(s), in the Investigator's File.

The media used to archive the content of the clinical trial file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph. Any modification to the content of the clinical TMF shall be traceable

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.

21. 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 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 final 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.

22. REFERENCES

1. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al, PURE Study Investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013;310:959-68.
2. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. JAMA. 2017;317:165–82.
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953-2041.
4. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957–67.
5. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. Overview, meta-analyses, and meta-regression analyses of randomized trials. J Hypertens. 2014;32:2285–95.
6. Mensah GA, Bakris G. Treatment and control of high blood pressure in adults. Cardiol Clin. 2010;28:609–22.
7. Weber MA, Basile J, Stapff M, Khan B, Zhou D. Blood pressure effects of combined β-blocker and angiotensin converting enzyme inhibitor therapy compared with the individual agents: a placebo-controlled study with nebivolol and lisinopril. J Clin Hypertens (Greenwich) 2012;14(9):588-92.
8. Nilsson P. Antihypertensive efficacy of zofenopril compared with atenolol in patients with mild to moderate hypertension. Blood Press Suppl. 2007;2:25-30.
9. Cicero AFG, Kuwabara M, Borghi C. A Critical review of nebivolol and its fixed-dose combinations in the treatment of hypertension. Drugs. 2018;78(17):1783-1790.
10. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55(2):399-407.

11. Vogel Anderson KL. Combination therapy in hypertension management. US Pharm. 2012;37(6)(Generic suppl):46-50.
12. Taylor BC, Wilt TJ, Welch HG. Impact of Diastolic and Systolic Blood Pressure on Mortality: Implications for the Definition of “Normal”. J Gen Intern Med. 2011;26(7):685–90.
13. Summary of product characteristics, Zofenil.
14. Summary of product characteristics, Labelling and Package Leaflet, v 3.0, Apr 2013, Nebivolol.

23. Protocol Approval Page

Study Title: Open-label, multicenter, multinational, interventional clinical trial to assess effectiveness and safety of the extemporaneous combination of nebivolol and zofenopril calcium in grade 1 to 2 hypertensive patients versus each monotherapy

Code: MEIN/19/ZoNe-HYP/001

EUDRACT number: 2020-002340-23

The signers confirm that they have read and approved the protocol

Study Medical Expert: Dr Marco Salvatore

Signature & Date: Marco Salvatore 11 / 09 / 2020

Corporate Medical Director: Dr Lorenzo Melani

Signature & Date: 11 /09 / 2020

Coordinating Investigator: Professor Massimo Volpe

Signature & Date: 14 / 09 / 2020

Statistician: Susmita Sanyal

Signature & Date: Susmita Sanyal 21 / 09 / 2020

24. Investigator's Approval Page

I understand that all information concerning the product Menarini Pharmaceutical supplied ..... in connection with this study protocol are confidential information. This information includes: Protocol, Investigator's Brochure, Case Report Form, Other documents _____.

I understand that any change in this study protocol must be approved in writing by Menarini Pharmaceutical and the Coordinating 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 Pharmaceutical.

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 Center File is stolen or anyhow damaged, I will promptly inform the Sponsor and declare it to the Competent Authorities.

Principal Investigator: _____

Signature & Date: _____

25. APPENDICES

25.1 Appendix 1: Declaration of Helsinki