	Global Medical Department		
	Protocol Template		
Identification Number	**Version Number**	**State**	**Effective date**
FORM-000050125	3.0, CURRENT	Effective	13 May, 2022
Enclosure to: □ **Guideline**	□ **Policy**	x **Procedure 50066**	□ **Working Instruction**

Sponsor: **Menarini International Operations Luxembourg SA** **Protocol Version_3.0** ***of 13/07/2023***
Study Code: **MEIN/22/NeRam-Hyp/001**

PROTOCOL TITLE
CLINICAL STUDY PROTOCOL

Open-label, multicenter, multinAtionaL, inteRventional clinical Trial to assess Efficacy and safety of the exteMporaneous combInation of Nebivolol and Ramipril in hypertenSIve pAtients - ARTEMISIA study	
Protocol Code	MEIN/22/NeRam-Hyp/001
EudraCT (or National Clinical Trial Identified Number)	2022-003060-25 NCT06104423
Protocol Phase (if applicable)	Phase IV
Study type and design	Interventional, multicenter, open-label study
Protocol Version Number	Version 3.0
Protocol Version Date	13 July 2023
Sponsor and address	Menarini International Operations Luxembourg SA Registered Office: 1, Avenue de la Gare L-1611 Luxembourg [redacted]
Coordinating Investigator	Professor Giovambattista Desideri [redacted]
CRO	IQVIA

STATEMENT OF CONFIDENTIALITY

SUMMARY OF CHANGES FROM PREVIOUS VERSIONS

The following tables summarize the changes implemented in the current version of the Protocol (v3.0 of 13/07/2023) compared to the previously approved version of the Protocol (v1.0 of 12/10/2022). The changes are divided according to the Protocol version in which they were implemented.

Summary of changes implemented in the Protocol v2.0 (14 June 2023)

Note: For the sake of greater clarity, some rationales have been rephrased compared to the Protocol v2.0, without any change to the meaning itself.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 1: Responsibilities Section 20: Protocol approval page	Statistician details are updated as below: Name: Chaitanya Trivedi [redacted] Study medical expert & Global Clinical Operations Manager details are updated as below: Name: Simone Baldini [redacted]	Biostatistician and Study medical expert & Global Clinical Operations Manager details are updated.
Section 2: Protocol synopsis (objectives) Section 4: Trial objectives and end points Section 12.4: Analysis variables Section 12.5: Statistical analysis (primary efficacy analysis and secondary efficacy analysis)	Diastolic blood pressure (DBP) in the primary objective and primary end point has been updated to Systolic blood pressure (SBP). Systolic blood pressure in the secondary objective #1 and secondary end point #1 has been updated to Diastolic blood pressure.	The Sponsor has decided to widen the target population including also older patients. Consistently with the expected increase in median age of the study population, the primary endpoint has been changed to SBP which is deemed more relevant in elderly patients from a clinical perspective. Diastolic blood pressure has been changed to key secondary endpoint. **Note#1**: the entire Protocol has been harmonized according to this change, where needed.

Section 2: Protocol synopsis (Study population: Patient's characteristics) Section 6.2.1: Inclusion criteria	The age limitation of up to 65 years was updated to ≥ 18 years. Added the following verbiage at the end of the inclusion criteria #2 "and, as per Investigator's judgement, is deemed appropriate for a combination treatment with beta blockers (BB) and ACE-i."	The study population has been widened by including elderly subjects in order to better reflect the real use of the intended association in the hypertensive patient population. This will allow to provide comprehensive data in all age groups. Moreover, in addition to the eligibility criteria already included in the study, a specification in inclusion criterion # 2 is added to reiterate the importance of patient's selection.
Section 2: Protocol synopsis (Clinical sites, number of centers) Section 5: Study design	The number of investigational clinical sites updated to 26.	Number of clinical sites is updated after feasibility analysis.
Section 2: Protocol synopsis (Study duration [specify different study phases])	Updated the dates as below: First Patient In: estimated by September 2023 Last Patient Out: estimated by April 2024	To update estimated study start and end dates.
Section 2: Protocol synopsis (Statistical assumptions) Section 12.2: Determination of sample size	The following text has been modified based on the new sample size determination "A sample size of 215 achieves 90% power to detect a Systolic BP difference of -2.4 mmHg between the null hypothesis mean of 3.0 mmHg and the alternative hypothesis mean of 5.4 mmHg with a known standard deviation of 12.0 mmHg and with a significance level (alpha) of 0.05 using a one-sided one-sample t-test".	Sample size has been calculated according to the change in primary endpoint. To note, despite the change in primary endpoint, the sample size remains unchanged in respect of the earlier protocol version.
Section 5: Study design (Assessment period from Visit 2 [Week 0] to Visit 5 [Week 12]) Section 8.1: Assessment of efficacy	The following sentence has been added: "Three BP measurements will be performed for each arm"	For consistency with the rest of the Protocol.
	The following sentence has been updated: "using the same calibrated automated device, provided by the Sponsor, at each visit.	For consistency with the rest of the Protocol.
	The following sentence has been updated: "study medication should be taken at the study center after all assessments mentioned"	To harmonize the timeframe of investigational medicinal product (IMP) intake among visits and to ensure intake of the IMP after BP assessment.

Section 5.1: Procedures and study visits	The order of procedures/assessments planned for each following visit has been updated. The following sentence has been added as the last step for the following visits "Intake of the first dose of the dispensed study medication at the site at the end of all other procedures/assessments" • Screening and start of Run-in period (Visit 1, Week −4) • Assessment period (Visit 2, Week 0) • Assessment period (Visit 3, Week 4) • Assessment period (Visit 4, Week 8)	Improved description to facilitate correct understanding of the order of the listed procedures.
Section 8.1: Assessment of efficacy	Updated the following sentence with values rather than grading: "in patients with hypertension with mean sitting SBP ≥ 140 mmHg and ≤ 179 mmHg and/or mean sitting DBP ≥ 90 mmHg and ≤ 109 mmHg."	For consistency with the rest of the Protocol.
Section 12.2: Determination of sample size	The following sentence has been added "Such a difference in SBP is highly clinically significant in a population-wide perspective since, as clearly demonstrated by Hardy et al, if applied nationwide, a hypothetical 1 mmHg shift in SBP among African American and white US populations aged 45 to 64 years was estimated to prevent ≈9338 incident heart failure events, 6210 incident coronary heart disease events, and 3761 incident stroke events annually, while the hypothetical intervention achieving the larger SBP reduction of 2 mmHg was associated with larger reductions in the incidence of coronary heart disease, stroke, and heart failure for both racial groups."	Determination of sample size has been updated and clinical rationale has been provided to reflect the change in the primary objective and endpoint.
Section 12.5: Statistical analysis	The null and alternate hypothesis has been updated as below: H0: There is no change in the sitting SBP post combination therapy.	Statistical analysis has been updated according to the update in primary objective of the study.

	H1: There is a difference in the sitting SBP post combination therapy. The following text regarding hypothesis testing has been updated as below: "Change from baseline in sitting SBP from prior and post combination therapy will be tested using paired t-test. The p-value obtained from the paired t-test will be presented."	
Section 19: References	The following reference has been added: "Hardy et al. Reducing the Blood Pressure–Related Burden of Cardiovascular Disease: Impact of Achievable Improvements in Blood Pressure Prevention and Control. J Am Heart Assoc. 2015 Oct; 4(10): e002276.	New reference has been added as per the addition of new text in section determination of sample size.
Throughout	Minor editorial and document formatting revisions.	Administrative revisions implemented for clarity and consistency. Minor changes, therefore, have not been summarized.

Summary of changes implemented in the Protocol v3.0 (13 July 2023)

Affected Section(s)	Summary of Revisions Made	Rationale
Section 2: Protocol synopsis (objectives, endpoints, Study duration) Section 2.1: Study scheme Section 4: Trial objectives and end points Section 5: Study design Section 7: Study treatment Section 12.4: Analysis variables Section 12.5: Statistical analysis	For the purpose of this study, uncontrolled BP is amended as follows: sitting SBP/DBP: ≥ 130/80 mmHg in patients < 65 years old. sitting SBP/DBP: ≥ 140/80 mmHg in patients ≥ 65 years old The optimal BP goal is modified accordingly, as follows: sitting BP < 130/80 mmHg in patients < 65 years old sitting BP < 140/80 mmHg in patients ≥ 65 years old	Thresholds and target BP goals have been amended by age groups according to 2018 ESC/ESH guidelines. **Note**: the entire Protocol has been harmonized according to this change, where needed.

Throughout	Minor editorial and document formatting revisions. E.g.: 1) In the following sentence "and" has been replaced by "and/or" for further clarification: "Hypertensive patients with Systolic blood pressure (SBP) ranging from ≥ 140 to ≤ 179 mmHg and/or Diastolic blood pressure (DBP) ranging from ≥ 90 to ≤ 109 mmHg on treatment." 2) The following sentence has been updated as below for following visits by removing the word first dose: "Intake of the dispensed study medication at the site at the end of all other procedures/assessments" • Screening and start of Run-in period (Visit 1, Week −4) • Assessment period (Visit 2, Week 0) • Assessment period (Visit 3, Week 4) • Assessment period (Visit 4, Week 8)	Administrative revisions implemented for clarity and consistency. Minor changes, therefore, have not been summarized.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
ACE-i	Angiotensin converting enzyme inhibitor
ADR	Adverse drug reaction
AE	Adverse event
RAM	Ramipril
ATC	Anatomical Therapeutic Chemical
BBs	Beta Blockers
BP	Blood Pressure
CHD	Coronary Heart Disease
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DPO	Data Protection Officer
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoS	End of Study
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practice
HA	Health Authorities
HRT	Hormonal replacement therapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
IMP	Investigational medicinal product
ISO	International Organization for Standardization
IT	Information technology
mITT	Modified Intent-to-treat
MoA	Mechanism of action
NEB	Nebivolol
NO	Nitric Oxide
PI	Principal Investigator
PP	Per-Protocol Population
Q1	First quartile

Q3	Third quartile
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SOP	Standard Operative Procedures
SUSAR	Serious Unexpected Adverse Drug Reaction
TMF	Trial Master File
UPT	Urine pregnancy test
ULN	Upper Limit of Normal

1 RESPONSIBILITIES

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2 PROTOCOL SYNOPSIS

Title Acronym Sponsor Study Code	Open-label, multicenter, multinAtionaL, inteRventional clinical Trial to assess EffIcacy and safety of the exteMporaneous combInation of Nebivolol and Ramipril in hypertenSIve pAtients. ARTEMISIA Study MEIN/22/NeRam-Hyp/001
Investigational medicinal products, Dosage and Regimen:	• Monotherapy Nebivolol (NEB) 5 mg (Anatomical Therapeutic Chemical [ATC] code C09DX05) and Monotherapy Ramipril (RAM) 5 mg (ATC code C09AA05). • Extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg. **Note**: Investigational medicinal product (IMP) or study treatment refers to both, monotherapy (NEB 5 mg or RAM 5 mg) and extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg.
Study Type and Design.	This is a Phase IV, interventional, open-label, multicenter, multinational study with 2 study periods: a Run-in period of 4 weeks and an Assessment period of 12 weeks.
Phase	Phase IV
Objectives	**Note**: For the purpose of this study, uncontrolled BP is defined as sitting SBP/DBP: • ≥ 130/80 mmHg in patients < 65 years old • ≥ 140/80 mmHg in patients ≥ 65 years old **Primary Objective** • To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg in lowering sitting Systolic blood pressure (SBP) between Visit 2 (Week 0) and Visit 5 (Week 12) in patients with uncontrolled blood pressure (BP) previously treated with NEB 5 mg or RAM 5 mg monotherapies for at least 30 days. **Secondary Objectives** • To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg in lowering sitting Diastolic BP (DBP) between Visit 2 (Week 0) and Visit 5 (Week 12) in patients with uncontrolled BP previously treated with NEB 5 mg or RAM 5 mg monotherapies for at least 30 days.

- To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg, in lowering sitting DBP and SBP between:
  - Visit 2 (Week 0) and Visit 3 (Week 4)
  - Visit 2 (Week 0) and Visit 4 (Week 8)
- To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the standard BP goal (sitting BP < 140/90 mmHg) at Visit 5 (Week 12).
- To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 5 (Week 12).
- To assess the adherence to the study treatment at Visit 2 (Week 0), at Visit 3 (Week 4), at Visit 4 (Week 8) and at Visit 5 (Week 12).
- To evaluate the safety and tolerability of the monotherapies (NEB 5 mg and RAM 5 mg) and of the extemporaneous combinations (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg, NEB/RAM 5/10 mg).

Exploratory Objectives

- To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the standard BP goal (sitting BP < 140/90 mmHg) at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8).
- To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), at Visit 3 (Week 4), and at Visit 4 (Week 8).
- To assess the antihypertensive efficacy in terms of sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population.
- To evaluate sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies or who switched

	to NEB 5 mg or RAM 5 mg from any other beta blocker (BB) or angiotensin-converting enzyme inhibitors (ACE-is) at Visit 1. • To evaluate sitting DBP and SBP at Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in patients with uncontrolled hypertension. • To assess the change in sitting DBP and SBP from Visit 2 (Week 0) to Visit 3 (Week 4), from Visit 3 (Week 4) to Visit 4 (Week 8), and from Visit 4 (Week 8) to Visit 5 (Week 12) in patients with uncontrolled hypertension. • To evaluate the total number and percentage of patients who achieved the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) in the group of patients: ○ who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies. ○ who switched to mg or RAM 5 mg from any other BBs or ACE-i at Visit 1 (Week -4). • To assess the antihypertensive effect in terms of achieving standard BP goal (sitting SBP/DBP < 140/90 mmHg) and optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) in patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies or who switched to NEB 5 mg or RAM 5 mg from any other BB or ACE-i at Visit 1 categorized by their hypertension grade at diagnosis, Coronary Heart Disease (CHD), presence of diabetes, presence of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, Visit 5.
Endpoints	**Primary Endpoint** • Change in mean sitting SBP between Visit 2 (Week 0) and Visit 5 (Week 12). **Secondary Endpoints** • Change in mean sitting DBP between Visit 2 (Week 0) and Visit 5 (Week 12). • Change in mean sitting DBP and SBP between: ○ Visit 2 (Week 0) and Visit 3 (Week 4) ○ Visit 2 (Week 0) and Visit 4 (Week 8) • Number and proportion of patients achieving the standard BP goal (sitting BP < 140/90 mmHg) at Visit 5 (Week 12). • Number and proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting

BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 5 (Week 12).

- Adherence to treatment estimated as % of doses taken/doses to be taken at Visit 2 (Week 0), at Visit 3 (Week 4), at Visit 4 (Week 8) and at Visit 5 (Week 12).
- Safety and tolerability of the monotherapies (NEB 5 mg and RAM 5 mg) and of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg, NEB/RAM 5/10 mg) measured by incidence, intensity (severity), seriousness of adverse events during the study period, (Screening, Run-in period and Assessment period), relationship to the study treatments, clinically significant abnormal change in vital signs, electrocardiogram (ECG), laboratory parameters, and use of concomitant medications at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12).

Exploratory Endpoints

- Number and proportion of patients achieving the standard BP goal (sitting BP < 140/90 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8).
- Number and proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8).
- Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population.
- Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the following subgroups:
  - in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies;
  - in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BB or ACE-i at Visit 1.
- Mean sitting DBP and SBP for uncontrolled patients at Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12).
- Change in mean sitting DBP and SBP for patients with uncontrolled hypertension from Visit 2 (Week 0) to Visit 3 (Week 4); from Visit 3 (Week 4) to Visit 4 (Week 8); and from Visit 4 (Week 8) to Visit 5 (Week 12).
- Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years

	old / sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12): ○ in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies. ○ in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACE-i at Visit 1 (Week -4). • Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old / sitting BP < 140/80 mmHg in patients ≥ 65 years old) who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies, categorized by their hypertension grade at diagnosis, CHD, presence of diabetes, and/or of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, and Visit 5. • Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) who switched to NEB 5 mg or RAM 5 mg from any other BB or ACE-i at Visit 1, categorized by their hypertension grade at diagnosis, CHD, presence of diabetes, and/or of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, and Visit 5.
Study Population: Patients' characteristics Number of Patients	Two hundred and seventy (270) male or female patients aged ≥ 18 years with uncontrolled hypertension, who are on treatment with any BBs or ACE-is, including NEB (only 5 mg dosage allowed) or RAM (only 5 mg dosage allowed) for at least 30 days prior to Visit 1, will be screened for eligibility. A total number of 270 patients will be screened considering a screen failure/drop-out rate of 20%, to obtain at least 215 completed patients at the end of the study (Visit 5) (patients who complete all visits including End of Study (EoS) Visit [Visit 5]). **Inclusion criteria:** Patient will be considered eligible to be enrolled in the study only if he/she meets all the following inclusion criteria: 1. Willing to comply with all study activities and procedures for the duration of the study and provided signed, written informed consent prior to any study procedures at Screening Visit (Visit 1). 2. Male or female patients aged ≥ 18 years with hypertension with mean sitting SBP ≥ 140 mmHg and ≤ 179 mmHg and/or mean

	sitting DBP ≥ 90 mmHg and ≤ 109 mmHg at Visit 1 (screening), while on monotherapy treatment either with BBs (NEB 5 mg or any dose if other BB) or ACE-i (RAM 5 mg or any dose if other ACE-i) for at least 30 days before Visit 1 (screening) and, as per Investigator's judgement, is deemed appropriate for a combination treatment with BB and ACE-i. 3. Ability to take oral medication and willing to adhere to the drug regimen. 4. 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 highly effective contraception (e.g., method of birth control throughout the study period and for 4 weeks after study completion defined as a method which results in a failure rate of less than 1% per year) and also must refrain from donating or storing eggs during this time. Highly effective contraception methods can be: • Combined hormonal contraception (estrogen- and progestogen-containing) associated with inhibition of ovulation (oral, intravaginal, and transdermal). • Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable). • Intrauterine device. • Intrauterine hormone-releasing system. • Bilateral tubal occlusion. • Vasectomized partner (procedure conducted at least 2 months before the screening), (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). 5. A male patient with female sexual partners 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 sperm during this period. **Exclusion criteria:** Any patient who meets any of the following criteria will not qualify for entry into the study: 1. Patients with documented history of hypersensitivity to NEB, RAM, other BBs or other ACE-is, or any related products, excipients of the formulations, as outlined in the relevant

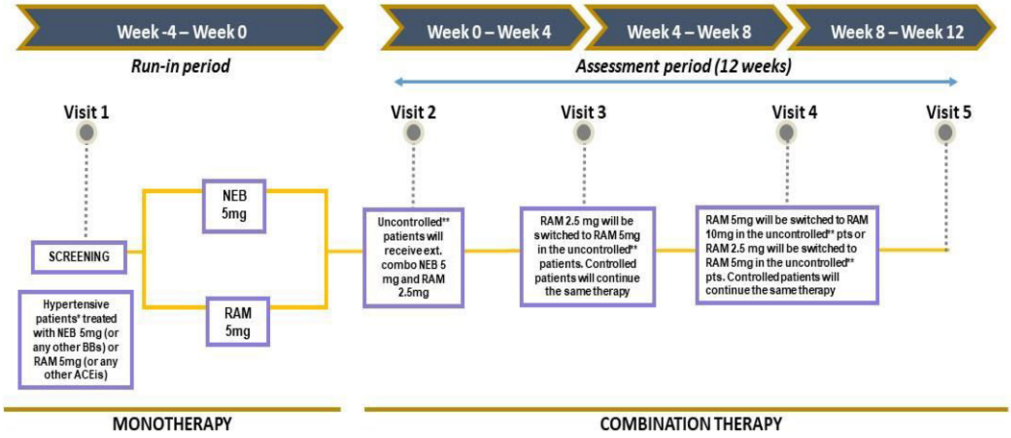
	Investigator's Brochure, summary of product characteristics or local package inserts for Nebivolol and Ramipril. 2. Patients with serious disorders (in the opinion of the Investigator) which may limit the ability to evaluate the efficacy or safety of the tested medications, including cerebrovascular, 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 conditions within the last 6 months: myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, bypass surgery, heart failure, hypertensive encephalopathy, valve replacement (transcatheter aortic valve implantation, mitraclip), cerebrovascular accident (stroke), or transient ischemic attack. 4. Patients with condition of hypotension with SBP < 90 mmHg and/or DBP < 60 mmHg. 5. Acute heart failure (12 months before enrolment), cardiogenic shock, or episodes of heart failure decompensation requiring intravenous inotropic therapy. 6. Patients with secondary hypertension of any etiology including renal diseases, Cushing's syndrome, hyperaldosteronism, renovascular disease and thyroid disorders. 7. 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), obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis) or symptomatic coronary disease. 8. Patients with clinical evidence of renal disease (including significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney), severe renal impairment or renal transplant. 9. Patients with clinically relevant hepatic impairment. 10. Patients with a history of angioneurotic edema. 11. Patients with sick sinus syndrome, including sino-atrial block. 12. Patient with second- and third-degree heart block (without a pacemaker). 13. History of bronchospasm and bronchial asthma. 14. Untreated phaeochromocytoma. 15. Patients with bradycardia (heart rate < 60 bpm; < 50 bpm in patients already on BBs treatment).

	16. Patient with history of metabolic acidosis. 17. Patients with severe peripheral circulatory disturbances. 18. Participation in another interventional study within the last 30 days before Screening Visit (Visit 1). 19. Patients with diseases that, in the opinion of the Investigator, prevent a careful adherence to the protocol. 20. Patients using and not suitable for withdrawing the prohibited medications prior to the administration of study treatment. 21. Pregnant and breastfeeding women. NOTE: a pregnancy test will be performed on all women of childbearing potential at each study visit. 22. Patients with medical history of cirrhosis (Child Pugh class B or higher). 23. History of unexplained syncope within the prior 2 years, or a known syncopal disorder. 24. Patients who received renal denervation in the last 3 years or other device-based non-pharmacological treatment of hypertension. 25. Any other contraindication to either NEB or RAM as per respective SmPC.
Clinical Sites Number of Centers	Approximately 26 clinical sites
List of Countries	Bulgaria, Poland, and Hungary
Study Duration (specify different study phases):	This study will last up to 16 weeks. **Screening Visit 1 (Week -4):** Hypertensive patients with SBP ranging from ≥ 140 to ≤ 179 mmHg and/or DBP ranging from ≥ 90 to ≤ 109 mmHg on treatment, for at least 30 days prior to screening, with NEB 5 mg or any other BB, or RAM 5 mg or any other ACE-i will be screened for eligibility (Visit 1). Patients that did not meet eligibility criteria will be considered as screening failures and will not be re-screened. **Run-in period from Visit 1 (Week -4) to Visit 2 (Week 0):** On the same day of the Screening Visit, eligible patients will enter a Run-in period, during which: • Patients receiving NEB 5 mg or RAM 5 mg will continue the same therapy for 4 weeks. • Patients on any other BB will be assigned to monotherapy with NEB 5 mg while patients on any other ACE-i will be assigned to monotherapy with RAM 5 mg for 4 weeks. The study is designed in order to ensure that 1:1 ratio between patients in the NEB and RAM arms will be achieved. For details see *Section 5*. **Assessment period from Visit 2 (Week 0) to Visit 5 (Week 12):** After 4 weeks (± 2 days) of the run-in period of monotherapy (Week 0), BP will be further assessed at Visit 2.

	Patients with uncontrolled BP levels (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old) at Visit 2, with adequate treatment adherence (ranging between 80% to 120%) and who did tolerate the treatment, will enter into the Assessment period and will be assigned to the extemporaneous combination of NEB/RAM 5/2.5 mg. Patients with controlled BP levels (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) and/or who do not tolerate the treatment or have an adherence range below 80% or above 120%, will be withdrawn from the study (drop-out patients). After 4 weeks ± 2 days in the Assessment period (Week 4), patients BP will be further evaluated at Visit 3: patients with controlled BP levels (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) will continue the same extemporaneous combination, while patients with uncontrolled BP levels (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old) will be up-titrated from NEB/RAM 5/2.5 mg to NEB/RAM 5/5 mg for further 4 weeks ± 2 days. After further 4 weeks ± 2 days (Week 8) the BP will be assessed again (Visit 4): controlled patients will continue the same extemporaneous combination, while uncontrolled patients: • if on NEB/RAM 5/2.5 mg, will be up-titrated to NEB/RAM 5/5 mg for further 4 weeks ± 2 days (Visit 5, Week 12); • if on NEB/RAM 5/5 mg, will be up-titrated to NEB/RAM 5/10 mg for further 4 weeks ± 2 days (Visit 5, Week 12). At the end of the Assessment period (12 weeks ± 2 days) at Visit 5, the antihypertensive effect of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg or NEB/RAM 5/10 mg) will be evaluated. First Patient In: estimated by September 2023 Last Patient Out: estimated by April 2024
Patient Study Phases Duration	For patients completing the study, participation will last up to 16 weeks: • 4 weeks of Run-in period (monotherapy) • 12 weeks of Assessment period (extemporaneous combination)
Statistical Assumptions	The primary endpoint will be assessed before and after Assessment period at Week 12, by a paired t-test using the Modified Intent-to-Treat population and the Per-Protocol population. A sample size of 215 achieves 90% power to detect a Systolic BP difference of -2.4 mmHg between the null hypothesis mean of 3.0 mmHg and the alternative hypothesis mean of 5.4 mmHg with a known standard deviation of 12.0 mmHg and with a significance level (alpha) of 0.05 using a one-sided

	one-sample t-test. Assuming an approximate 20% screen failure/drop-out rate, two-hundred and seventy (270) patients with uncontrolled hypertension are planned to be screened to obtain at least 215 completed patients at the end of the study (Visit 5) (patients who complete all visits including EoS Visit [Visit 5]). Hypothesis about the direction of the treatment effect: one-sided test has more statistical power to detect an effect in one direction because it is expected that combination therapy increases treatment efficacy in patients with uncontrolled hypertension previously treated with NEB or RAM monotherapies for at least 30 days. In this scenario, it is possible to exclude the hypothesis of testing the possibility that the combination therapy is less effective than the monotherapy, for this reason a one-sided test is more appropriate.

2.1 Study Scheme



Abbreviations: NEB = Nebivolol; BBs = Beta blockers; RAM = Ramipril; ACE-is = Angiotensin-converting enzyme inhibitors; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; pts = patients.

Note:

For the purpose of this study, uncontrolled BP is defined as sitting SBP/DBP:

- ≥ 130/80 mmHg in patients < 65 years old
- ≥ 140/80 mmHg in patients ≥ 65 years old

There is no randomization procedure.

Patients treated with Ramipril or Nebivolol in dosages higher than 5 mg/daily will not be eligible.

* Systolic blood pressure ranging from ≥ 140 to ≤ 179 mmHg and/or Diastolic blood pressure ranging from ≥ 90 to ≤ 109 mmHg.

** Sitting SBP/DBP:

- ≥ 130/80 mmHg in patients < 65 years old
- ≥ 140/80 mmHg in patients ≥ 65 years old

2.2 Schedule of Assessments

	Week -4 Visit 1	**Week 0 Visit 2 (± 2 days)**	**Week 4 Visit 3 (± 2 days)**	**Week 8 Visit 4 (± 2 days)**	**Week 12/EOT Visit 5 (± 2 days)**
	Screening + Start of Run-in Period	**End of Run-in period and Start of Assessment Period**	**Assessment Period**	**Assessment Period**	**End of Assessment Period**
Informed consent form[a]	X				
Inclusion/exclusion criteria	X				
Medical history	X				
Prior medications	X				
Demographic Information[b]	X				
Concurrent diseases and medical conditions	X	X	X	X	X
Monotherapy of NEB 5 mg or RAM 5 mg dispensing[c]	X				
Extemporaneous combination of NEB/RAM 5/2.5 mg dispensing[d]		X	X	X	
Extemporaneous combination of NEB/RAM 5/5 mg dispensing[e, f]			X	X	
Extemporaneous combination of NEB/RAM 5/10 mg dispensing[f]				X	
Study treatment return/accounting (Adherence assessment)		X	X	X	X
Concomitant medications[g]	X	X	X	X	X
Urine Pregnancy test[h]	X	X	X	X	X

	Week -4 Visit 1	**Week 0 Visit 2 (± 2 days)**	**Week 4 Visit 3 (± 2 days)**	**Week 8 Visit 4 (± 2 days)**	**Week 12/EOT Visit 5 (± 2 days)**
	Screening + Start of Run-in Period	**End of Run-in period and Start of Assessment Period**	**Assessment Period**	**Assessment Period**	**End of Assessment Period**
Physical examination	X	X	X	X	X
Vital signs[i]	X	X	X	X	X
Laboratory tests[j]	X				X
Blood pressure measurement	X	X	X	X	X
Electrocardiogram	X				X
AE/SAE assessment[k]	X	X	X	X	X
Written instructions for self blood pressure measurement and patient diary provided to patient[l]	X	X	X		
Written instructions for self-blood pressure measurement and patient diary returned to site[l]		X	X	X	X
BP device provided to patient[l]	X				
BP device returned to site[l]					X

Abbreviations: AE = adverse event; RAM = Ramipril; BBs = beta blockers; BP = blood pressure; ACE-is = Angiotensin-converting enzyme inhibitors; COVID-19 = Coronavirus Disease 2019, ECG = electrocardiogram; EOT = end of treatment; NEB = nebivolol, and SAE = serious adverse event.

Notes:

a. Informed consent must be signed prior to any study-related procedure.
b. Screening patient information will be obtained in accordance with local regulation, including age, sex (with childbearing status of females and menopausal status), height, weight, race, and ethnicity.
c. Patients on NEB 5 mg or RAM 5 mg will continue the same therapy for 4 weeks (Run-in period), while patients on any other BBs will be assigned to monotherapy with NEB 5 mg and patients on other ACE-is will be assigned to monotherapy with RAM 5 mg.

d. Only patients with uncontrolled BP at Visit 2 will receive NEB/RAM 5/2.5 mg for next 4 weeks, while patients with controlled BP levels will be withdrawn from the study.
e. Only patients with uncontrolled BP at Visit 3 will be up-titrated from NEB/RAM 5/2.5 mg to NEB/RAM 5/5 mg for next 4 weeks, while patients with controlled BP levels will continue the same extemporaneous combination.
f. Only patients with uncontrolled BP at Visit 4 will be up-titrated if on NEB/RAM 5/2.5 mg to NEB/RAM 5/5 mg and if on NEB/RAM 5/5 mg to NEB/RAM 5/10 mg for next 4 weeks, while patients with controlled BP levels will continue the same extemporaneous combination as Visit 3.
g. All concomitant medications ongoing at the time of the consent and any surgery/procedures should be reported.
h. Pregnancy test (urine) is only for female patients of childbearing potential.
i. Vital signs will include body temperature, respiratory rate, sitting BP, and pulse rate.
j. To ensure patient safety, the patients will be contacted over a phone call within 24 hours, in case of any abnormality and clinically relevant laboratory test according to the Investigator's judgment at any visit.
k. 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.
l. These procedures are referred to the COVID-19 Appendix (Appendix 2).

3 STUDY BACKGROUND AND RATIONALE

The overall prevalence of hypertension in adults is around 30% to 45%.[1] Elevated blood pressure (BP) is the leading contributor to premature death and disability worldwide.[2]
Although several effective antihypertensive drugs are available, most hypertensive patients have a suboptimal blood pressure control. The use of combined treatment, including 2 or more drugs with different mechanisms of action (MoAs), is an effective therapeutic strategy to optimize BP control instead of using monotherapy.[3,4]
Combination therapy based on beta blockers (BBs) and angiotensin-converting enzyme inhibitors (ACE-is) has been widely adopted and is currently recommended by guidelines[4,5,6].
Indeed, their different MoAs, by antagonizing the sympatho-adrenergic system and the renin-angiotensin system are complementary and synergistic, especially in lowering BP and protecting towards cardiac remodeling and hypertrophy.[7,8]
Nebivolol (BB) and Ramipril (ACE-i) are antihypertensive drugs widely used as monotherapies or in combination with other antihypertensives in the clinical practice.[8,9,10]
Both drugs have proven efficacy in reducing blood pressure and in the prevention of cardiac events as well as a good safety profile.[5]
Nebivolol is a third generation long-acting and highly selective β1-adrenergic receptor antagonist. The pharmacologic profile of NEB differs from those of other BB agents, since, in addition to cardioselectivity mediated via β1 receptor blockade, it also promotes nitric oxide-mediated vasodilation by stimulating endothelial nitric oxide synthase via β3 agonism.[11]
Nebivolol shows a particular hemodynamic profile including reduced peripheral vascular resistance and a neutral impact on cardiac output. In addition, it is well-tolerated. Studies on nebivolol have shown that it has more favorable effects on central BP, aortic stiffness, endothelial dysfunction, etc. It has no adverse effect on the risk of new-onset diabetes and a more favorable side effect profile than classical beta-blockers, including less adverse effects on sexual function. Because NEB mechanism of action appears to be independent of its renin inhibitory effects, an additional BP-lowering effect could be anticipated when NEB is combined with a blocker of the renin-angiotensin system.[12]
Ramipril is a second-generation ACE-i. It is a prodrug and is hydrolyzed in vivo to release the active metabolite, Ramiprilat, which has a long elimination half-life, permitting once-daily administration.[9]
Ramipril, administered at different doses, has been widely investigated for the treatment of patients with hypertension and its BP-lowering effect has been compared with either placebo

or with different classes of antihypertensive drugs currently recommended for the treatment of hypertension.[9,10]
To date, there is scarce evidence on the antihypertensive effect of NEB used in extemporaneous combination with an ACE-i and more specifically with RAM in the treatment of hypertensive patients.
The ARTEMISIA trial will be conducted to evaluate whether a 12-week treatment with the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg is effective in patients with uncontrolled BP previously treated with NEB 5 mg or RAM 5 mg monotherapies for at least 30 days.

3.1 Assessment of Potential Risks and Benefits

The combination of a beta-adrenergic blocker with an ACE-i is used when monotherapy is not fully effective in controlling BP or when more BP reduction is needed. Recent clinical guidelines for the management of hypertension emphasize the clinical benefits of the combined use of different antihypertensive agents. Approximately, 70% of patients with hypertension require 2 or more agents to achieve their target BP. Combination therapy improves rates of BP control and requires less time to achieve target BP as compared to monotherapy.[3] Fixed-Dose Combination (FDC) therapy containing 2 antihypertensive agents in a single tablet offers various advantages over monotherapy, including increased efficacy, less incidence of adverse events, and significant improvement in patient's adherence to treatment.[4] In a meta-analysis published in 2010, Fixed-Dose Combinations of antihypertensive agents not only improved patient's adherence to treatment, but also showed improvement in BP control with less adverse events.[14] In a randomized controlled trial, over 70% of participants achieved a blood pressure target of < 140/90 mmHg using FDC therapy.[15]
In addition, it should be remarked that Nebivolol and Ramipril are medications characterized by a well-established use in clinical practice due to their efficacy and favorable safety profiles.

4 TRIAL OBJECTIVES AND ENDPOINTS

Note: For the purpose of this study, uncontrolled BP is defined as sitting SBP/DBP:

- ≥ 130/80 mmHg in patients < 65 years old
- ≥ 140/80 mmHg in patients ≥ 65 years old

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5 mg, RAM 5 mg or RAM 10 mg in lowering sitting Systolic blood pressure (SBP) between Visit 2 (Week 0) and Visit 5 (Week 12) in patients with uncontrolled blood pressure (BP) previously treated with NEB 5 mg or RAM 5 mg monotherapies for at least 30 days.	• Change in mean sitting SBP between Visit 2 (Week 0) and Visit 5 (Week 12).	• The association between elevated SBP and increased mortality risk has been reported in literature in individuals over age 50.[16]
Secondary		
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5 mg, RAM 5 mg or RAM 10 mg in lowering sitting Diastolic BP (DBP) between Visit 2 (Week 0) and Visit 5 (Week 12) in patients with uncontrolled BP previously treated with NEB 5 mg or RAM 5 mg monotherapies for at least 30 days.	• Change in mean sitting DBP between Visit 2 (Week 0) and Visit 5 (Week 12).	• The association between elevated DBP and increased mortality rate has been reported in literature especially in younger patients.[16]

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg in lowering sitting DBP and SBP between: • Visit 2 (Week 0) and Visit 3 (Week 4) • Visit 2 (Week 0) and Visit 4 (Week 8)	• Change in mean sitting DBP and SBP between: • Visit 2 (Week 0) and Visit 3 (Week 4) • Visit 2 (Week 0) and Visit 4 (Week 8)	• For individuals over 50, the mortality rate began to significantly increase at a SBP ≥ 140 independent of DBP. In individuals ≤ 50 years of age, DBP was the more important predictor of mortality.[16]
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the standard BP goal (sitting BP < 140/90 mmHg) at Visit 5 (Week 12).	• Number and proportion of patients achieving the standard BP goal (sitting BP < 140/90 mmHg) at Visit 5 (Week 12).	• The proportion of patients achieving the target is a very important clinical indicator of therapeutic success.[19]
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 5 (Week 12).	• Number and proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 5 (Week 12).	• The proportion of patients achieving the target is a very important clinical indicator of therapeutic success. [19]
• To assess the adherence to the study treatment at Visit 2 (Week 0), at Visit 3 (Week 4), at Visit 4 (Week 8), and at Visit 5 (Week 12).	• Adherence to treatment estimated as % of doses taken/doses to be taken at Visit 2 (Week 0), at Visit 3 (Week 4), at Visit 4 (Week 8), and at Visit 5 (Week 12).	• Monitoring adherence is extremely important to better evaluate the efficacy and tolerability of the extemporaneous combination.

OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
• To evaluate the safety and tolerability of the monotherapies (NEB 5 mg and RAM 5 mg) and of the extemporaneous combinations (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg, NEB/RAM 5/10 mg).	• Safety and tolerability of the monotherapies (NEB 5 mg and RAM 5 mg) and of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg, NEB/RAM 5/10 mg) measured by incidence, intensity (severity), seriousness of Adverse Events (AEs) during the study period, (screening, Run-in period and Assessment period), relationship to the study treatments, clinically significant abnormal change in vital signs, electrocardiogram (ECG), laboratory parameters and use of concomitant medications at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12).	• Incidence of adverse drug reactions (ADRs), AEs, serious adverse events (SAEs), needs to be studied to address safety and tolerability of the extemporaneous combination.
Exploratory		
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the standard BP goal (sitting BP < 140/90 mmHg) at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8).	• Number and proportion of patients achieving the standard BP goal (sitting BP < 140/90 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).	• The proportion of patients achieving the target is a very important clinical indicator of therapeutic success. [19]
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years	• Number and proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8).	• The proportion of patients achieving the target is a very important clinical indicator of therapeutic success. [19]

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), at Visit 3 (Week 4), and at Visit 4 (Week 8).		
• To assess the antihypertensive efficacy in terms of sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population.	• Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population.	• To gain specific knowledge on the antihypertensive effect of the extemporaneous combination in patients uncontrolled after 30 days of combined therapy.
• To evaluate sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) in patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies or who switched to NEB 5 mg or RAM 5 mg from any other beta blocker (BB) or angiotensin-converting enzyme inhibitors (ACE-is) at Visit 1.	• Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the following subgroups: • in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies. • in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BB or ACE-i at Visit 1.	• Evaluation of the antihypertensive efficacy of combination therapy in the subgroup of patients who were on nebivolol or on ramipril at the inclusion in the study or who switched from a different BB or ACE-i will provide useful information on the impact (if any) that previous monotherapies have on the antihypertensive effect of the extemporaneous combination.
• To evaluate sitting DBP and SBP at Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in patients with uncontrolled hypertension.	• Mean sitting DBP and SBP for uncontrolled patients at Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12).	• To gain specific knowledge on the antihypertensive effect of the extemporaneous combination in patients uncontrolled after 30 days of combined therapy.

OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
• To assess the change in sitting DBP and SBP from Visit 2 (Week 0) to Visit 3 (Week 4), from Visit 3 (Week 4) to Visit 4 (Week 8), and from Visit 4 (Week 8) to Visit 5 (Week 12) in patients with uncontrolled hypertension.	• Change in mean sitting DBP and SBP for uncontrolled patients from Visit 2 (Week 0) to Visit 3 (Week 4); from Visit 3 (Week 4) to Visit 4 (Week 8); and from Visit 4 (Week 8) to Visit 5 (Week 12).	• To gain knowledge on the antihypertensive effect of the extemporaneous combination in patients divided by subgroups and who continued the same therapies or who switched to NEB or RAM.

• To evaluate the total number and percentage of patients who achieved the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) in the group of patients:
  ◦ who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.
  ◦ who switched to mg or RAM 5 mg from any other BBs or ACE-i at Visit 1 (Week -4).
	• Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12):
	  ◦ in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.
	  ◦ in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACE-i at Visit 1 (Week -4).
		• The proportion of patients achieving the target is a very important clinical indicator of therapeutic success. [19]

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
• To assess the antihypertensive effect in terms of achieving target BP goals in patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies or who switched to NEB 5 mg or RAM 5 mg from any other BB or ACE-i at Visit 1 categorized by their hypertension grade at diagnosis, Coronary Heart Disease (CHD), presence of diabetes, presence of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, and Visit 5.	• Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goals (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies, categorized by their hypertension grade at diagnosis, CHD, presence of diabetes, and/or of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, and Visit 5. • Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goals (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) who switched to NEB 5 mg or RAM 5 mg from any other BB or ACE-i at Visit 1, categorized by their hypertension grade at diagnosis, CHD, presence of diabetes, and/or of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, and Visit 5.	• To gain knowledge on the efficacy of the extemporaneous combination in patients divided by subgroups categorized by their hypertension grade at diagnosis, CHD, presence of diabetes, and/or of hypercholesterolemia and who continued same therapies or who switched to NEB or RAM.

5 STUDY DESIGN

This is a Phase IV, interventional, multicenter, open-label, multinational study with 2 study periods (a Run-in period of 4 weeks and an Assessment period of 12 weeks) to assess the efficacy and safety of the extemporaneous combination of NEB and RAM in reducing SBP and DBP in hypertensive patients uncontrolled by monotherapy.
The trial will be conducted in approximately 26 investigational clinical sites in Bulgaria, Poland, and Hungary. The total study duration is 16 weeks including a Run-in period of 4 weeks and an Assessment period of 12 weeks.
Note: For the purpose of this study, uncontrolled BP is defined as sitting SBP/DBP:

- ≥ 130/80 mmHg in patients < 65 years old
- ≥ 140/80 mmHg in patients ≥ 65 years old

Screening Visit 1 (Week -4):
Hypertensive patients with SBP ranging from ≥ 140 to ≤ 179 mmHg and/or DBP ranging from ≥ 90 to ≤ 109 mmHg on treatment, for at least 30 days prior to screening, with NEB 5 mg or any other BB, or RAM 5 mg or any other ACE-i will be screened for eligibility (Visit 1). Patients that did not meet eligibility criteria will be considered as screening failures and will not be re-screened.
Run-in period from Visit 1 (Week -4) to Visit 2 (Week 0):
On the same day of the Screening Visit, eligible patients will enter a Run-in period, during which:

- Patients receiving NEB 5 mg or RAM 5 mg will continue the same therapy for 4 weeks.
- Patients on any other BB will be assigned to monotherapy with NEB 5 mg while patients on any other ACE-i will be assigned to monotherapy with RAM 5 mg for 4 weeks.

The study is designed in order to ensure that 1:1 ratio between patients in the NEB and RAM arms will be achieved. For details see *Section 5*.
Assessment period from Visit 2 (Week 0) to Visit 5 (Week 12):
After 4 weeks (± 2 days) of the Run-in period of monotherapy (Week 0), BP will be further assessed at Visit 2.
Patients with uncontrolled BP levels (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old) at Visit 2, with adequate treatment adherence (ranging between 80% to 120%) and who did tolerate the treatment, will enter into the Assessment period and will be assigned to the extemporaneous combination of NEB/RAM 5/2.5 mg. Patients with controlled BP levels (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) and/or who do not tolerate the treatment or have an adherence range below 80% or above 120%, will be withdrawn from the study (drop-out patients).

After 4 weeks ± 2 days in the Assessment period (Week 4), patients BP will be further evaluated at Visit 3: patients with controlled BP levels (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) will continue the same extemporaneous combination, while patients with uncontrolled BP levels (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old) will be up-titrated from NEB/RAM 5/2.5 mg to NEB/RAM 5/5 mg for further 4 weeks ± 2 days.
After further 4 weeks ± 2 days (Week 8) the BP will be assessed again (Visit 4): controlled patients will continue the same extemporaneous combination, while uncontrolled patients:

- if on NEB/RAM 5/2.5 mg, will be up-titrated to NEB/RAM 5/5 mg for further 4 weeks ± 2 days (Visit 5, Week 12);
- if on NEB/RAM 5/5 mg, will be up-titrated to NEB/RAM 5/10 mg for further 4 weeks ± 2 days (Visit 5, Week 12).

At the end of the Assessment period (12 weeks ± 2 days), at Visit 5, the antihypertensive effect of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg or NEB/RAM 5/10 mg) will be evaluated.
To correctly evaluate the additional effect of the combination therapy, the number of patients with uncontrolled BP on NEB or RAM monotherapy needs to be balanced at Visit 2. To maintain a 1:1 ratio during the Assessment period, a cap of 110 patients for each treatment arm (i.e., NEB and RAM) will be included at Visit 2 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 entrance in the Assessment period for 1 of the 2 tested drugs will deviate more than 5%, a corrective measure will be initiated: according to the enrolment site statistics, 1 or more sites will be informed to enroll a greater number of patients being treated with the least represented drug in the Assessment period.
A total number of 270 patients will be screened considering a screen failure/drop-out rate of 20%, to obtain at least 215 completed patients at the end of the study (Visit 5) (patients who complete all visits including EoS Visit [Visit 5]).
Sitting BP will be measured at all visits before blood sampling. Blood Pressure will be measured in both arms at the Screening Visit (Visit 1) to detect possible between-arm differences. Three BP measurements will be performed for each arm. The arm with the higher mean DBP will be identified at screening and will be used in all subsequent visits for BP assessment. Blood pressure measurements should be performed as nearly as possible within the same time frame of the day (7:00 a.m. to 12:00 p.m.), on the same arm, possibly by the same trained member of the site staff/personnel and using the same calibrated automated device, provided by the Sponsor, at each visit.
Patients should be seated comfortably in a quiet environment for 5 minutes before beginning BP measurements. Three BP measurements will be recorded, 1 to 2 minutes apart, and

additional measurements only if the first 2 readings differ by > 10 mmHg. The mean of the 3 recordings in sitting position will be used as the BP value for that visit. All BP measurements during the treatment phase will be performed as through readings (i.e., 24 + 2 hours after the last drug intake). Study medication should be taken on the same time every day during the study; except the days of site visits, when study medication should be taken at the study center after all assessments mentioned as per study flow chart (*Section 2.2*). At Visit 1 (Week -4) and Visit 5 (Week 12), a 12-lead ECG will be performed.
Safety (AEs, SAEs) will be measured at all visits. Any patient having an ongoing AE or SAE at the last visit, will be followed-up for further 2 weeks through a phone call to check about the status of the AE/SAE.
At any visit, in case of a clinically relevant laboratory test abnormality according to the Investigator's judgment, the patient will be contacted through a phone call within 24 hours.

5.1 Procedures and Study Visits

Patients will attend a total of 5 visits during the study. However, due to social restriction measures, the patients may not be able to visit the study site. In such cases, the screening visit is a mandatory in-clinic visit and therefore must be performed at the study site. The Principal Investigator (PI) remains responsible for reviewing all study-related assessments.
The patients may not be able to visit the site to perform BP measurement for primary and secondary analysis, clinical laboratory tests, vital sign and physical examination, ECG, or other assessments required by the study flow chart. In such cases, these assessments will be performed by the health care professionals (study staff or qualified designee) at patient's home, if allowed by the country regulations.
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:

- Obtaining signed 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.
- Physical examination and vital signs measurements.
- BP measurement.

- ECG.
- Laboratory tests (see *Section 8.2*) (a follow-up phone call will be made within 24 hours in case of any clinically significant abnormality from the laboratory tests according to the Investigator).
- Urine pregnancy test (UPT) (only for female patients).
- Dispensing of BP device.
- Dispensing of written instruction for self BP measurement and patient diary.
- Assessment of AEs and SAEs.
- Dispensing of antihypertensive treatment with NEB 5 mg or RAM 5 mg monotherapy during the visit and for the next 4 weeks (Run-in period) to eligible patients.
- Intake of the dispensed study medication at the site at the end of all other procedures/assessments.

The patients meeting all inclusion criteria and none of the exclusion criteria will enter the Run-in period on the same day for 4 weeks ± 2 days and will receive monotherapy of NEB 5 mg or RAM 5 mg:

- Patients who are already on therapy with NEB 5 mg or RAM 5 mg will be provided with the same medication, i.e., NEB 5 mg or RAM 5 mg, respectively.
- Patients taking any other BBs or ACE-is will be switched to NEB 5 mg or RAM 5 mg, respectively.

2. 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 (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old), who tolerated the treatment and whose adherence to the therapy ranges from 80% to 120%, will enter the 12-week Assessment period.

The starting of extemporaneous combination NEB/RAM 5/2.5 mg dosing is noted as Week 0.

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.
- UPT (only for female patients).
- Adherence assessment by return of NEB and RAM tablets (also empty blisters) and accountability.
- Assessment of AES and SAEs.
- Dispensing of written instruction for self BP measurement and patient diary.

- Return of written instruction for self BP measurement and patient diary dispensed at Visit 1 to site.
- Study drug dispensing (patients will be provided with the extemporaneous combination of NEB/RAM 5/2.5 mg) during the visit and for the next 4 weeks to eligible patients.
- Intake of the dispensed study medication at the site at the end of all other procedures/assessments.

3. Assessment Period (Visit 3, Week 4):

During the Assessment period, patients with controlled BP (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 3 (Week 4) will continue to receive same extemporaneous combination of NEB/RAM 5/2.5 mg for next 4 weeks ± 2 days till Visit 4 (Week 8). For patients with uncontrolled BP (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old), the RAM dose will be up-titrated from 2.5 mg to 5 mg and the patients will receive the extemporaneous combination NEB/RAM 5/5 mg for next 4 weeks ± 2 days till Visit 4 (Week 8).

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.
- UPT (only for female patients).
- Adherence assessment by return of NEB and RAM tablets (also empty blisters) and accountability.
- Assessment of AES and SAEs.
- Dispensing of written instruction for self BP measurement and patient diary.
- Return of written instruction for self BP measurement and patient diary dispensed at Visit 2 to site.
- Study drug dispensing (patients with controlled BP will be provided with the extemporaneous combination of NEB/RAM 5/2.5 mg and patients with uncontrolled BP will be provided with NEB/RAM 5/5 mg) during the visit and for the next 4 weeks to eligible patients.
- Intake of the dispensed study medication at the site at the end of all other procedures/assessments.

4. Assessment Period (Visit 4, Week 8):

During the Assessment period, patients with controlled BP (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 4 will continue to receive the same extemporaneous combination as Visit 3 for next 4 weeks ± 2 days till Visit 5 (Week 12).

For patients with uncontrolled BP (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old):

- Patients on NEB/RAM 5/2.5 mg will be up-titrated to NEB/RAM 5/5 mg for next 4 weeks ± 2 days till Visit 5 (Week 12).
- Patients on NEB/RAM 5/5 mg will be up-titrated to NEB/RAM 5/10 mg for next 4 weeks ± 2 days till Visit 5 (Week 12).

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.
- UPT (only for female patients).
- Adherence assessment by return of NEB and RAM tablets (also empty blisters) and accountability.
- Assessment of AES and SAEs.
- Dispensing of written instruction for self BP measurement and patient diary.
- Return of written instruction for self BP measurement and patient diary dispensed at Visit 3 to site.
- Study drug dispensing (patients with controlled BP will be provided with the extemporaneous combination NEB/RAM 5/2.5 mg or NEB/RAM 5/5 mg, based on previous schedule; patients with uncontrolled BP will be provided with the extemporaneous combination NEB/RAM 5/5 mg or NEB/RAM 5/10 mg) during the visit and for the next 4 weeks to eligible patients.
- Intake of the dispensed study medication at the site at the end of all other procedures/assessments.

5. End of the Assessment Period (Visit 5, Week 12):

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 tests (a follow-up phone call will be made within 24 hours in case of any clinically significant abnormality from the laboratory tests according to the Investigator).
- UPT (only for female patients).
- Adherence assessment by return of NEB and RAM tablets (also empty blisters) and accountability.
- Assessment of AES and SAEs (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).
- Return of written instruction for self BP measurement and patient diary dispensed at Visit 4 to the site.
- Return of BP device (dispensed at Visit 1) to the site.

6 SELECTION OF SUBJECTS

6.1 Informed Consent Process

Prior to the patient's enrolment into the study and before performing any study-related procedures, the Investigator - or its 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 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 17*).
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 freely has to date and sign the ICF before being enrolled into the study and before undergoing any study procedure. The Investigator must store the 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 would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to Ethics Committee (EC) 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.

6.2 Inclusion and Exclusion Criteria

6.2.1 Inclusion Criteria

Patient will be considered eligible to be enrolled in the study only if he/she meets all the following inclusion criteria:

1. Willing to comply with all study activities and procedures for the duration of the study and provided signed, written informed consent prior to any study procedures at Screening Visit.
2. Male or female patients aged ≥ 18 years with hypertension with mean sitting SBP ≥ 140 mmHg and ≤ 179 mmHg and/or mean sitting DBP ≥ 90 mmHg and ≤ 109 mmHg at Visit 1 (screening), while on monotherapy treatment either with BBs (NEB 5 mg or any dose if other BB) or ACE-is (RAM 5 mg or any dose if other ACE-i) for at least 30 days before Visit 1 (screening) and, as per Investigator's judgement, is deemed appropriate for a combination treatment with BB and ACE-i.
3. Ability to take oral medication and willing to adhere to the drug regimen.

4. 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 (e.g., method of birth control throughout the study period and for 4 weeks after study completion defined as a method which results in a failure rate of less than 1% per year) and also must refrain from donating or storing eggs during this time. Highly effective contraception methods can be:
   - Combined hormonal contraception (estrogen- and progestogen-containing) associated with inhibition of ovulation (oral, intravaginal, and transdermal).
   - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable).
   - Intrauterine device.
   - Intrauterine hormone-releasing system.
   - Bilateral tubal occlusion.
   - Vasectomized partner (procedure conducted at least 2 months before the screening), (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).
5. A male patient must agree to use contraception during the whole study period and for at least 1 week after the last dose of study treatment and refrain from donating sperm during this period.

6.2.2 Exclusion Criteria

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

1. Patients with documented history of hypersensitivity to NEB, RAM, other BBs or other ACE-is, or any related products, excipients of the formulations, as outlined in the relevant Investigator's Brochure (IB), summary of product characteristics (SmPC) or local package inserts for Nebivolol and Ramipril.
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 conditions within the last 6 months: myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, bypass surgery, heart failure, hypertensive encephalopathy, valve replacement

(transcatheter aortic valve implantation, mitraclip), cerebrovascular accident (stroke), or transient ischemic attack.

4. Patients with condition of hypotension with SBP < 90 mmHg and/or DBP < 60 mmHg.
5. Acute heart failure (12 months before enrolment), cardiogenic shock, or episodes of heart failure decompensation requiring intravenous inotropic therapy.
6. Patients with secondary hypertension of any etiology including renal diseases, Cushing's syndrome, hyperaldosteronism, renovascular disease and thyroid disorders.
7. 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), obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis) or symptomatic coronary disease.
8. Patients with clinical evidence of renal disease (including significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney), severe renal impairment or renal transplant.
9. Patients with clinically relevant hepatic impairment.
10. Patients with a history of angioneurotic edema.
11. Patients with sick sinus syndrome, including sino-atrial block.
12. Patient with second- and third-degree heart block (without a pacemaker).
13. History of bronchospasm and bronchial asthma.
14. Untreated phaeochromocytoma.
15. Patients with bradycardia (heart rate < 60 bpm; < 50 bpm in patients already on BBs treatment).
16. Patient with history of metabolic acidosis.
17. Patients with severe peripheral circulatory disturbances.
18. Participation in another interventional study within the last 30 days before Screening Visit (Visit 1).
19. Patients with diseases that, in the opinion of the Investigator, prevent a careful adherence to the protocol.
20. Patients using and not suitable for withdrawing the prohibited medications prior to the administration of study treatment.
21. Pregnant and breastfeeding women. NOTE: a pregnancy test will be performed on all women of childbearing potential at each study visit.
22. Patients with medical history of cirrhosis (Child Pugh class B or higher).
23. History of unexplained syncope within the prior 2 years, or a known syncopal disorder.
24. Patients who received renal denervation in the last 3 years or other device-based non-pharmacological treatment of hypertension.
25. Any other contraindication to either NEB or RAM as per respective SmPC.

6.2.3 Screening Failures

Patients who consented to participate in the clinical trial by signing the ICF, but do not meet one or more eligibility criteria required for participation in the trial during the screening procedures (Visit 1), and subsequently are not assigned to the study treatment (monotherapy) or entered in the study are considered screening failures. There will be no rescreening of screening failure patients in this study.
Adverse events will be collected and recorded on the eCRF.

7 STUDY TREATMENT

Note: Investigational medicinal product (IMP) or study treatment refers to both monotherapy (NEB 5 mg, RAM 5 mg) and extemporaneous combination of NEB 5 mg with RAM 2.5 mg, 5 mg, or 10 mg.
The study treatment administered during the trial:

- Run-in period (Visit 1 to Visit 2): Patients receiving NEB 5 mg or RAM 5 mg will continue to receive the same, while patients on any other BBs or ACE-is, will receive NEB 5 mg or RAM 5 mg respectively prior to enrolment into the study.
- Assessment period (Visit 2 to Visit 3): Extemporaneous combination of NEB 5 mg and RAM 2.5 mg in patients with uncontrolled BP levels (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old) at Visit 2.
- Assessment period (Visit 3 to Visit 4): Extemporaneous combination of NEB 5 mg and RAM 2.5 mg in patients with controlled BP levels (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 3 and extemporaneous combination of NEB 5 mg and RAM 5 mg in patients with uncontrolled BP levels (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old) at Visit 3.
- Assessment period (Visit 4 to Visit 5): Patients with controlled BP levels (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 4 will continue to receive same extemporaneous combination as Visit 3, while patients with uncontrolled BP levels (sitting BP ≥ 130/80 mmHg in patients < 65 years old/sitting BP ≥ 140/80 mmHg in patients ≥ 65 years old) at Visit 4 if on NEB/RAM 5/2.5 mg will receive NEB/RAM 5/5 mg and if on NEB/RAM 5/5 mg will receive NEB/RAM 5/10 mg.

Details on the study design are provided in *Section 5*.

Further details on study treatment are provided below in Table 1.

Table 1 Study Treatment Details

Study Treatment Name:	Nebivolol **Marketing Authorization Holder**: A. Menarini Industrie Farmaceutiche Riunite srl, Via Sette Santi n. 3, 50131 Florence (Italy)	Ramipril **Marketing Authorization Holder**: Zentiva Italia S.r.l., Viale L.Bodio, 37/B - 20158 Milan (Italy)
Dosage Formulation:	Tablet	Tablet
Unit Dose Strength(s)/Dosage Level(s):	5 mg, once daily	2.5 mg/5 mg/10 mg, once daily
Route of Administration:	Oral	Oral
Dosing Instructions:	1 tablet of study medication to be administered according to instructions of Investigator	1 tablet of study medication to be administered according to instructions of Investigator
Primary Packaging:	Study medication will be provided in its original marketed PVC/Aluminum blisters	Study medication will be provided in its original marketed PVC/Aluminum blisters
Storage Conditions:	Study treatment must be stored in its original packaging and kept in a secure area (in accordance with the label's instructions) with access limited to the Investigator and authorized site staff. No other special precautions are required.	Study treatments must be stored in its original packaging and kept in a secure area (in accordance with the label's instructions) with access limited to the Investigator and authorized site staff. No other special precautions are required.

Abbreviations: PVC = Polyvinyl chloride

*The patients will take the monotherapy tablets or the extemporaneous combination of NEB and RAM in the morning between 6 am and 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 RAM 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.

7.1 Study Treatment Formulation, Appearance, Packaging, and Labeling

Study treatment dosage form, strength, formulation:
Nebivolol 5 mg: white, round, cross-scored tablet.
Ramipril 2.5 mg: yellowish oblong tablet with score line.
Ramipril 5 mg: light red oblong tablet with score line.
Ramipril 10 mg: white oblong tablet with score line.

Study treatment manufacturing:
The NEB 5 mg tablets and RAM 2.5/5/10 mg tablets will be sourced as authorized European Union (EU) marketed products from a commercial supplier in the European market. Marketing authorization holders and relative Manufacturers are reported in relative SmPC.[17,18]

Study treatment packaging and labeling:
For clinical trial, the study treatment re-packaging, and labeling operations are performed by Manufacturer: A. Menarini Manufacturing Logistics and Services S.R.L. (Menarini Group), Via Sette Santi, 3-50131 Florence (Italy).
For clinical trial, the study treatment re-packaging, and labeling 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 wordings 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 NEB 5 mg and RAM 2.5/5/10 mg will be provided in dedicated treatment boxes (Patient Kits). Patient Kits must be dispensed at Visit 1 (beginning of the Run-in period), Visit 2 (start of the Assessment period), Visit 3, and Visit 4.
The Patient Kits are packaged with labels of different colors, in order to facilitate the recognition and distribution of study treatments.

Visit 1 (Run-in Period):

- NEB 5 mg: each trial participant is provided with 1 treatment Patient Kit with nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- RAM 5 mg: each trial participant is provided with 1 treatment Patient Kit with ramipril 5 mg 42 tablets (3 blisters with 14 tablets).

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

Visit 2 (Beginning of Assessment Period):
Each trial participant is provided with 1 treatment Patient Kit made up by:

- NEB 5 mg: 1 box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- RAM 2.5 mg: 1 box containing ramipril 2.5 mg 42 tablets (3 blisters with 14 tablets).

The 2 boxes are then sealed together into a transparent plastic film to realize the treatment patient kit.
Trial participant must be carefully instructed by Investigator or designee to take simultaneously (at the same time): NEB 5 mg as one white round tablet and RAM 2.5 mg as one yellowish oblong tablet, according to Study Protocol.

Visit 3 (Assessment Period):
Participants **with controlled BP** are provided with 1 treatment Patient Kit made up by:
- NEB 5 mg: 1 box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- RAM 2.5 mg: 1 box containing ramipril 2.5 mg 42 tablets (3 blisters with 14 tablets).

The 2 boxes are then sealed together into a transparent plastic film to realize the treatment Patient Kit.
Trial participant must be carefully instructed by Investigator or designee to take simultaneously (at the same time): NEB 5 mg as one white round tablet and RAM 2.5 mg as one yellowish oblong tablet, according to Study Protocol.
Participants **with uncontrolled BP** are provided with 1 treatment patient kit made up by:
- NEB 5 mg: 1 box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- RAM 5 mg: 1 box containing ramipril 5 mg 42 tablets (3 blisters with 14 tablets).

The 2 boxes are then sealed together into a transparent plastic film to realize the treatment patient kit.
Trial participant must be carefully instructed by Investigator or designee to take simultaneously (at the same time): NEB 5 mg as one white round tablet and RAM 5 mg as one light red oblong tablet, according to Study Protocol.
Visit 4 (Assessment Period):
Participants **with controlled BP who were on NEB/RAM 5/2.5 mg** are provided with 1 treatment Patient Kit made up of:
- NEB 5 mg: 1 box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- RAM 2.5 mg: 1 box containing ramipril 2.5 mg 42 tablets (3 blisters with 14 tablets).

The 2 boxes are then sealed together into a transparent plastic film to realize the treatment patient kit.
Trial patient must be carefully instructed by Investigator or designee to take simultaneously (at the same time): NEB 5 mg as one white round tablet and RAM 2.5 mg as one yellowish oblong tablet, according to Study Protocol.
Participants **with controlled BP who were on NEB/RAM 5/5 mg** are provided with 1 treatment Patient Kit made up by:
- NEB 5 mg: 1 box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- RAM 5 mg: 1 box containing ramipril 5 mg 42 tablets (3 blisters with 14 tablets).

The 2 boxes are then sealed together into a transparent plastic film to realize the treatment Patient Kit.
Trial participant must be carefully instructed by Investigator or designee to take simultaneously (at the same time): NEB 5 mg as one white round tablet and RAM 5 mg as one light red oblong tablet, according to Study Protocol.

Participants **with uncontrolled BP who were on NEB/RAM 5/2.5 mg** are provided with 1 treatment Patient Kit made up of:

- NEB 5 mg: 1 box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- RAM 5 mg: 1 box containing ramipril 5 mg 42 tablets (3 blisters with 14 tablets).

The 2 boxes are then sealed together into a transparent plastic film to realize the treatment Patient Kit.
Trial patient must be carefully instructed by Investigator or designee to take simultaneously (at the same time): NEB 5 mg as one white round tablet and RAM 5 mg as one light red oblong tablet, according to Study Protocol.
Participants **with uncontrolled BP who were on NEB/RAM 5/5 mg** are provided with 1 treatment Patient Kit made up by:

- NEB 5 mg: 1 box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- RAM 10 mg: 1 box containing ramipril 10 mg 42 tablets (3 blisters with 14 tablets).

The 2 boxes are then sealed together into a transparent plastic film to realize the treatment Patient Kit.
Trial patient must be carefully instructed by Investigator or designee to take simultaneously (at the same time): NEB 5 mg as one white round tablet and RAM 10 mg as one white oblong tablet, according to Study Protocol.

7.2 Study Treatment Distribution and Return / Destruction

The 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.
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 treatments 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 after written authorization from the Sponsor.
The following paragraph is applicable for all study visits (Visits 2, 3, 4, and 5) except Visit 1 (screening).
Due to social restriction measures, the patient may not be able to reach the study site. In such cases, the study treatment will not be dispensed to the patients at the site. Instead, the study treatment may be distributed to the patients' home at the times defined in the study flow chart by the designated site staff or by a distributor independent from and acting on behalf of the

Sponsor in line with national law or temporary national emergency measures. Patients will be informed and trained on the new dispensing procedures. Patients will be instructed to keep unused/partially used study treatment, which will be collected by the designated site staff at the earliest possible time or agreed with the patient to return to site via courier.

7.3 Product Storage and Stability

Nebivolol 5 mg tablets do not require any special storage conditions, according to relative SmPC.
Ramipril 2.5/5/10 mg tablets do not require any special storage conditions, according to relative SmPC.
Nevertheless, the medicinal products must be stored in its original packaging and kept in a protected area, according to information reported in the relative packaging labels.

7.4 Study Product Adherence

Adherence with study treatment will be assessed at Visit 2 for monotherapy and Visit 3, Visit 4, and Visit 5 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 estimated by using the below formula:
(number of doses taken during the study)/(number of doses to be taken during the study)×100
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 adherent.

7.5 Concomitant Therapy(ies)

Any medication that the patient was receiving at the time of enrolment and any other regular or occasional use of any concomitant medication during the study will be recorded in the source documents and in the eCRF. Whenever possible, without jeopardizing the patients care, study patients should remain on the same concomitant medication at a stable dose throughout the study. In order to facilitate recording of medication history, patients will be asked to bring their medication, preferably in their original packaging.

7.6 Not Permitted Medications

The following drugs modifying BP, even if used for other indications, are considered not permitted medications and the patients will not be permitted to use these medications from screening until the end of treatment.
Blood pressure modifying drugs including:

- Alpha receptor blockers and agonists
- Beta receptor blockers apart from the study drug and agonists
- Calcium antagonists
- Angiotensin converting enzyme inhibitors apart from the study drug
- Diuretics
- Centrally acting antihypertensive (e.g., clonidine, methyldopa, guanfacine)
- Reserpine
- Moxonidine
- Chronic nitrate treatment (e.g., isosorbide dinitrate or isosorbide mononitrate)
- Phosphodiesterase inhibitors and angiotensin II receptor blockers

Moreover, special attention should be paid to contraindicated/not-recommended drugs as per Nebivolol and Ramipril SmPCs, in particular the CYP3A4 inductors and inhibitors.

7.7 Rescue Medicine

Not applicable.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Assessment of Efficacy

The efficacy variable is to assess the antihypertensive effect of the extemporaneous combination of NEB (5 mg)/RAM (5 mg/2.5, 5, 10 mg) in patients with hypertension with mean sitting SBP ≥ 140 mmHg and ≤ 179 mmHg and/or mean sitting DBP ≥ 90 mmHg and ≤ 109 mmHg versus each monotherapy after 12 weeks of treatment. Data for this variable will be collected from BP measurements.
BP measurements:
Sitting BP will be measured at all visits before blood sampling. Blood pressure will be measured in both arms at the screening visit (Visit 1) to detect possible between-arm differences. Three BP measurements will be performed for each arm. 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 a.m. to 12:00 p.m.), on the same arm, possibly by the same trained member of the site staff/personnel, and using the same calibrated automated device, provided by the Sponsor, at each visit.
Patients should be seated comfortably in a quiet environment for 5 minutes before beginning BP measurements. Three BP measurements will be recorded, 1 to 2 minutes apart, and additional measurements only if the first 2 readings differ by > 10 mmHg. The mean of the 3 recordings in sitting position will be used as the BP value for that visit. All BP measurements during the treatment phase will be performed as through readings (i.e., 24 + 2 hours after the last study medication intake) using the same calibrated automated device, provided by the Sponsor. Study medication should be taken on the same time every day during the study; except the days of site visits, when study medication should be taken at the study center after all assessments mentioned as per study flow chart (*Section 2.2*).

8.2 Assessment of Safety

Safety will be assessed through collection of treatment-emergent AEs, SAEs, that start after the first dose of study treatment (analyzed in terms of incidence, severity, seriousness, and treatment causality), and physical examination (body weight and height), vital signs, BP, and heart rate. Safety assessments will be performed at time points as described in *Section 2.2*. Unscheduled visits/assessments for AEs management and/or follow up are permitted at any time to ensure patient's safety.

Physical Examination

A detailed physical examination will be performed according to the local practice. This examination includes assessments of the general appearance, skin and mucosa, superficial lymph nodes, head and neck, chest, abdomen, musculoskeletal, and neurological systems. 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.

Vital Signs

Vital signs will include body temperature (tympanic measurement), respiratory rate (breaths per minute), sitting BP (see *Section 8.1*), and pulse rate (beats per minute). All BP measurements will be performed after 5 minutes of rest in sitting position in triplicate (spaced by 1 to 2 minutes), and additional measurements only if the first 2 readings differ by > 10 mmHg. The mean of the 3 BP readings in sitting position will be used as the BP value for that visit and will be recorded on the source documents and in the eCRF. Blood pressure and pulse measurements will be assessed with the same calibrated automated device, provided by the Sponsor, at each visit.

Clinical Laboratory Tests

Safety and tolerability will be assessed by monitoring laboratory measurements.
All samples will be collected in accordance with standard laboratory procedures (ISO). The maximum volume of blood is approximately 40 mL, which will be the total blood collected during the study (Visit 1 and Visit 5).
A follow-up phone call after Visit 1 and Visit 5 will be made within 24 hours in case of any clinically significant abnormality laboratory tests according to the Investigator's judgment.
The local laboratory will perform laboratory tests for hematology and serum chemistry. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results.
Any clinically significant laboratory test results observed after Informed Consent signature and prior to first IMP administration must not be considered as an AE. The following hematology and serum chemistry laboratory tests will be performed at Visit 1 (Week -4) and Visit 5 (Week 12).

Table 2 Clinical Laboratory Tests

Hematology	**Serum Chemistry**
Red blood cell	Alanine aminotransferase (ALT)
White blood cell	Aspartate aminotransferase (AST)
Hemoglobin	Albumin
Hematocrit	Alkaline phosphatase
Mean corpuscular volume (MCV)	Direct bilirubin
Mean corpuscular hemoglobin (MCH)	Total bilirubin
Mean corpuscular hemoglobin concentration (MCHC)	Total protein
Platelets	Creatinine
Neutrophils	estimated Glomerular Filtration Rate (eGFR)
Lymphocytes	Blood urea nitrogen
Monocytes	Creatine kinase
Eosinophils	Gamma-glutamyl transferase
Basophils	Triglycerides
Neutrophils absolute	Cholesterol
Lymphocytes absolute	High- and low-density lipoprotein
Monocytes absolute	Chloride
Eosinophils absolute	Blood glucose
Basophils absolute	Potassium
	Lactate dehydrogenase (LDH)
	Uric acid
	Coagulation parameters
	Prothrombin Time (PT)
	Partial Thromboplastin Time (PTT)
	International Normalized Ratio (INR)

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

Electrocardiograms
A single 12-lead resting ECG will be recorded after the patient has been in supine position for at least 5 minutes to calculate the heart rate and measure PR, QRS, QT, and QTc intervals at Visit 1 (Week -4) and Visit 5 (Week 12). 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 if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required.
Urine Pregnancy tests
Urine pregnancy tests (only for female of child-bearing potential) will be performed at each Visit 1, 2, 3, 4, and 5, by determination of the urine β human chorionic gonadotropin, using locally available commercial dipsticks. Unscheduled re-tests can be performed as required according to the Investigator's judgment.

9 SAFETY DATA MANAGEMENT

9.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigational patient administered a medicinal product, 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.

9.2 Drug Relationship

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

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

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

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

9.3 Adverse Drug Reaction (ADR)

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

1. Certain
2. Probable
3. Possible
4. Unassessable

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

1. Unlikely
2. Not related

9.4 Seriousness

An AE / ADR is considered serious when:

1. Results in death.
2. Is life-threatening.

Note: Life-threatening is considered as any AE in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalization or prolongation of existing hospitalization.
- results in persistent or significant disability / incapacity.
- is a congenital anomaly / birth defect.
- is another 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 non-serious when it does not fulfill the conditions for the definition of Serious AE/ADR.

9.5 Adverse Event/Adverse Drug Reaction Intensity

Investigators must assess the severity/intensity of a Serious or a Non-serious AE or ADR and attributed according to the following definitions:

- **Mild:** does not interfere with routine activities; in case of laboratory tests when there is a mild abnormality.
- **Moderate**: interferes with the routine activities; in case of laboratory tests when there is a moderate abnormality.
- **Severe**: makes it impossible to perform routine activities; in case of laboratory tests when there is a significant abnormality.

9.6 Adverse Event/Adverse Drug Reaction Expectedness

An AE/ADR is considered Unexpected when the nature, severity, or outcome of the AE/ADR is not consistent with the information provided in the Reference Safety Document (to be specified: SmPC).

9.7 Serious Unexpected Adverse Drug Reaction (SUSAR)

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

9.8 Individual Case Safety Report (ICSR)

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

9.9 Collection, Recording and Reporting of AEs

At each visit, the Investigator will collect and assess any subjective or objective AE occurred to each patient after his/her signature of the informed consent.
Any AE (or adverse experience) occurring prior to first IMP administration should be considered as medical history or pre-existing conditions and should be recorded on the Medical History/Pre-existing eCRF page and not on the AE page.
Any clinically significant laboratory test results observed after informed consent signature and prior to first IMP administration, should be recorded in Lab Test page of the eCRF, and must not be considered as an AE.
The Investigator should manage as AE any laboratory test abnormality (newly occurring after the IMP administration or worsening of previously known abnormalities) considered as clinically relevant: i.e., values significantly above or under normal range or which require an intervention or diagnostic tests or may result in the IMP discontinuation.
Any AE communicated by the patient or by the patient's relatives or delegates through phone calls, letters or e-mails will also be collected and assessed.
The Investigator shall record on the respective eCRF AE pages, any recognized AE identifying an ICSR, occurred after IMP administration, both serious and non-serious, whether or not thought to be drug-related, observed in or reported by the patient (or relatives/delegates), specifying the judgment on the causal relationship with the study treatment (monotherapy or extemporaneous combination).
Any available information and diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall be recorded in and/or attached to the concerned CRF pages/sections.
The Investigator is expected to also record any AE which was ongoing at the last treatment dose and a follow-up phone call should be made after 2 weeks from the last study visit. The Investigator is expected to follow up any AE occurred during the study, including the follow-up period, until the outcome of the AE has been determined.
The Investigator must report all the collected information on any ICSR with Serious and Non-Serious AE (whether or not thought to be related to the investigational drug), providing the concerned eCRF AE pages by alert e-mail, after the first knowledge of the occurrence of the case, to:

CRO Pharmacovigilance Officer: Will be reported through CRO's Pharmacovigilance (PHV_HAB48701_SO@iqvia.com) group for which its details will be provided via study guidelines.

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

9.10 Management of Serious AEs (SAEs) including laboratory abnormalities

9.10.1 Reporting Duties of the Investigator

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

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

9.10.2 Reporting Duties of the Sponsor

The Sponsor shall ensure that all relevant information about any SUSAR, is expeditiously reported to the competent HAs and EC 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.

When the study is blinded, the patient's code will be broken before the expedited reporting to the competent HAs and the EC.

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

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

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

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

9.11 Management of Non-serious AEs including laboratory abnormalities

9.11.1 Reporting Duties of the Investigator

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

9.12 Management of any laboratory abnormality

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

9.13 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 and follow-up periods, 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 CRF as a SAE and managed as above described.
Eligibility of a woman of childbearing potential (WOCBP) will be considered as described in *Section 6.2.1*. 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 site 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 hormone, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10 WITHDRAWAL CRITERIA

Patients may discontinue the study product, but remain in the study for follow-up, especially for safety and study endpoints (if applicable).

Withdrawal from the study treatment

Withdrawal from the study treatment (monotherapy or extemporaneous combination therapy) refers to any patient who does not receive the complete course, i.e., when no further planned dose is administered from the date of withdrawal. A patient withdrawn from the study treatment 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 treatment (monotherapy or extemporaneous combination therapy) may be discontinued for any of the reasons listed below:

- Any AE, which required treatment termination according to the Investigator's judgment.
- 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.

In addition to the scheduled visits, patients who have been withdrawn from study treatment (monotherapy or extemporaneous combination therapy) may also undergo additional medical follow-up at the discretion of the Investigator.

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 judgment.
- Abnormal renal function (creatinine clearance < 30 mL/min) or abnormal liver enzyme parameters (alanine aminotransferase or aspartate aminotransferase level of > 2.5 × upper limit of normal [ULN] or total bilirubin level > 1.5 × ULN) as described in Table 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 that in the opinion of the Investigator or Sponsor necessitates the patient being withdrawn.

The reason for the withdrawal of study treatment, or withdrawal from the study must be well documented in the source documents and 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 5. Patients may discontinue the study treatment, 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 9.9*) and should be followed-up until the AE is resolved or the Investigator deems further observations or examinations as no longer medically indicated.

11 LOST TO FOLLOW UP

A patient will be considered lost to follow-up if he/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 and 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.

12 STATISTIC

12.1 Statistical Methods (Blinding and Randomization)

This is an open-label study. In this study all the patients will receive monotherapy in the Run-in period and combination therapy in the study Assessment period. No randomization will be required.

12.2 Determination of Sample Size

A sample size of 215 achieves 90% power to detect a Systolic BP difference of -2.4 mmHg between the null hypothesis mean of 3.0 mmHg and the alternative hypothesis mean of 5.4 mmHg with a known standard deviation of 12.0 mmHg and with a significance level (alpha) of 0.05 using a one-sided one-sample t-test. Such a difference in SBP is highly clinically significant in a population-wide perspective since, as clearly demonstrated by Hardy et al[20], if applied nationwide, a hypothetical 1 mmHg shift in SBP among African American and white US populations aged 45 to 64 years was estimated to prevent ≈9338 incident heart failure events, 6210 incident coronary heart disease events, and 3761 incident stroke events annually, while the hypothetical intervention achieving the larger SBP reduction of 2 mmHg was associated with larger reductions in the incidence of coronary heart disease, stroke, and heart failure for both racial groups.
A total number of 270 patients will be screened considering a screen failure/drop-out rate of 20%, to obtain at least 215 completed patients at the EoS (Visit 5) (patients who complete all visits including EoS Visit [Visit 5]).

12.3 Analysis Populations

In this study, 4 types of analysis population will be used.

- Enrolled population: Patients who are enrolled into the study (i.e., signed ICF and met the eligibility criteria) and may or may not receive the study treatment (monotherapy and/or combination therapy).
- Safety population: Patients who are in the Enrolled population and receive at least 1 dose of monotherapy (either followed by combination therapy or not).
- Modified Intent-to-Treat (mITT) population: Patients who are in the Enrolled population and receive at least 1 dose of combination therapy and have at least baseline (Week 0) and Week 12 assessments with primary efficacy data.
- Per-Protocol (PP) population: All patients included in the mITT population who do not have any major protocol deviations that could affect the primary efficacy analyses.

12.4 Analysis Variables

Analysis of Variables and Populations Used		
Efficacy		
	Analysis Variables	**Population Used**
Primary efficacy	Change in mean sitting SBP between Visit 2 (Week 0) and Visit 5 (Week 12).	mITT population, PP population
Secondary efficacy	• Change in mean sitting DBP between Visit 2 (Week 0) and Visit 5 (Week 12).	mITT population,
	• Change in mean sitting DBP and SBP between Visit 2 (Week 0) and Visit 3 (Week 4) and Visit 2 (Week 0) and Visit 4 (Week 8). • Number and proportion of patients achieving standard BP goal (sitting SBP/DBP < 140/90 mmHg) at Visit 5 (Week 12). • Number and proportion of patients achieving optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 5 (Week 12).	mITT population
	• Adherence to treatment estimated as % of doses taken/doses to be taken at Visit 2 (Week 0), at Visit 3 (Week 4), at Visit 4 (Week 8), and at Visit 5 (Week 12).	Safety population
	• Safety and tolerability of the monotherapies (NEB 5 mg and RAM 5 mg) and of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg, NEB/RAM 5/10 mg).	Safety population
Exploratory efficacy	• Number and proportion of patients achieving standard BP goal (sitting SBP/DBP < 140/90 mmHg). • Number and proportion of patients achieving optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8). • Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population. • Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the following subgroups: ○ in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies. ○ in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACE-is at Visit 1. • Mean sitting DBP and SBP for uncontrolled patients at Visit 3 (Week 4), at Visit 4 (Week 8), and at Visit 5 (Week 12).	Enrolled Population

Analysis of Variables and Populations Used		
Efficacy		
	Analysis Variables	**Population Used**
	• Change in mean sitting DBP and SBP for uncontrolled patients from Visit 2 (Week 0) to Visit 3 (Week 4); from Visit 3 (Week 4) to Visit 4 (Week 8); from Visit 4 (Week 8) to Visit 5 (Week 12). • Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12): ○ in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies. ○ in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACE-is at Visit 1 (Week -4). • Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies categorized by their hypertension grade at diagnosis, CHD, presence of diabetes, and/or of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, and Visit 5. • Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) who switched to NEB 5 mg or RAM 5 mg from any other BB or ACE-i at Visit 1 categorized by their hypertension grade at diagnosis, CHD, presence of diabetes, and/or of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, Visit 5.	
Safety	Incidence, intensity (severity), seriousness of AEs during the study period, (screening, Run-in period, and Assessment period), relationship to the study treatments, clinically significant abnormal change in vital signs, ECG, laboratory parameters, and use of concomitant medications at Visit 2 (Week 0), Visit 3 (Week 4) Visit 4 (Week 8), and Visit 5 (Week 12).	Safety population
Abbreviations: ACE-i = Angiotensin-converting enzyme inhibitor; AE = Adverse event; RAM = Ramipril; BB = Beta blocker; BP = Blood pressure; CHD = Coronary heart disease; DBP = Diastolic blood pressure;		

Analysis of Variables and Populations Used		
Efficacy		
	Analysis Variables	**Population Used**
ECG = Electrocardiogram; ITT = Intent-to-treat; mITT = Modified Intent-to-Treat; NEB = Nebivolol; PP = Per-protocol; and SBP = Systolic blood pressure		

12.5 Statistical Analysis

Descriptive statistics

Patient disposition, demographics and baseline characteristics will be summarized for monotherapy and combination therapy. Medical history will be summarized only for monotherapy. Prior and concomitant medications will be summarized for combination therapy (NEB + RAM).

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

Primary (efficacy) analysis

The primary efficacy analysis will be conducted on the mITT population. The results will be interpreted for the same population.

The primary endpoint is the change in mean sitting SBP between Visit 2 (Week 0) and Visit 5 (Week 12).

The statistical hypothesis will be defined as below:

H0: There is no change in the sitting SBP post combination therapy.

H1: There is a difference in the sitting SBP post combination therapy.

The above hypothesis will be tested as following:

- Change from baseline in sitting SBP from prior and post combination therapy will be tested using paired t-test. The p-value obtained from the paired t-test will be presented.
- Assumption of Normality will be investigated using Wilk-Shapiro test. If the data is found to be non-Normal, the paired t-test will be replaced by Wilcoxon signed rank test.
- The primary endpoint will be summarized descriptively using n, mean, median, SD, Q1 (first quartile), Q3 (third quartile), minimum, and maximum.

Sensitivity analysis

The sensitivity analyses will be conducted using the PP population.

The PP population will be used to assess the robustness of the results obtained using the mITT population.

Secondary (efficacy) analysis

Secondary efficacy variables will be summarized in a descriptive manner using the mITT population.

- Change in mean sitting DBP between Visit 2 (Week 0) and Visit 5 (Week 12).
- Change in mean sitting DBP and SBP between:
  - Visit 2 (Week 0) and Visit 3 (Week 4)
  - Visit 2 (Week 0) and Visit 4 (Week 8)
- Number and proportion of patients achieving the standard BP goal (sitting BP < 140/90 mmHg) at Visit 5 (Week 12).
- Number and proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 5 (Week 12).
- Adherence to treatment estimated as % of doses taken/doses to be taken at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12).
- Safety and tolerability of the monotherapies (NEB 5 mg and RAM 5 mg) and of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg, NEB/RAM 5/10 mg).

Change in sitting BP between visits will be compared using a two-sided paired t-test with 5% significance level. The p-value obtained from the paired t-test will be presented. Assumption of Normality will be investigated using Wilk-Shapiro test. If the data is found to be non-Normal, the paired t-test will be replaced by Wilcoxon signed rank test.

The continuous secondary endpoints will also be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, minimum, and maximum.

The number of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) will be summarized for Visit 5 (Week 12).

Adherence with study treatment will be assessed at Visit 2 for monotherapy and Visit 3, Visit 4, and Visit 5 for the combination therapy. The amount of study treatment 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 eCRF.

Adherence to treatment will be estimated by using the below formula:

(number of doses taken during the study)/(number of doses to be taken during the study) ×100

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.

Exploratory (efficacy) analysis

Exploratory efficacy variables will be summarized in a descriptive manner using enrolled population for Visits 1, 2, 3, 4 and 5.

- Number and proportion of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8).
- Change in mean sitting DBP and SBP from Visit 1 (Week -4) to Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population.
- Change in mean sitting DBP and SBP from Visit 1 (Week -4) to Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population:
  - in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies.
  - in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACE-is at Visit 1.
- Mean sitting DBP and SBP for uncontrolled patients at Visit 3 (Week 4), at Visit 4 (Week 8), and at Visit 5 (Week 12).
- Change in mean sitting DBP and SBP for uncontrolled patients from Visit 2 (Week 0) to Visit 3 (Week 4); from Visit 3 (Week 4) to Visit 4 (Week 8); from Visit 4 (Week 8) to Visit 5 (Week 12).
- Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12):
  - in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.
  - in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACE-is at Visit 1 (Week -4).
- Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies by their hypertension grade, CHD, presence of diabetes, and/or of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, and Visit 5.

- Number and percentage (proportion) of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) who switched to NEB 5 mg or RAM 5 mg from any other BB or ACE-i at Visit 1 by their hypertension grade, CHD, presence of diabetes, and/or of hypercholesterolemia, at Visit 2, Visit 3, Visit 4, and Visit 5.

The number of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) will be summarized for Visit 2, Visit 3, and Visit 4, along with percentage.

A p-value using McNemar's test will be presented to compare the proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) between Visit 2 and Visit 3, between Visit 2 and Visit 4, and between Visit 3 and Visit 4. Exact McNemar's test will be used to obtain the p-value when the number of patients achieving BP goal is zero at any visit.

Change in sitting DBP and SBP between visits will be using paired t-test. The p-value obtained from the paired t-test will be presented. Assumption of Normality will be investigated using Wilk-Shapiro test. If the data is found to be non-Normal, the paired t-test will be replaced by Wilcoxon signed rank test.

The continuous exploratory endpoints will also be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, minimum, and maximum.

Subgroup analysis

Not applicable

Safety analysis

Safety analysis will be based on the safety population.

Adverse events recorded during the study will be mapped to a system organ class and preferred term using the Medical Dictionary for Regulatory Activities. 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.

Summaries will be provided for treatment-emergent adverse event related AEs, SAEs, AEs based on their severity, deaths, and AEs leading to discontinuation from study.

Laboratory, ECG, Physical examination, and Vital signs data will be summarized by each visit for absolute values as well as change from baseline. The number of normal, abnormal not clinically significant and abnormal clinically significant values on each parameter will be summarized for ECG and Physical examination using shift tables.

Interim analysis and stopping rules

Not applicable

Data imputations
All analyses will be performed on observed data. Missing data will not be imputed for this study.

12.6 Protocol Deviations and Protocol Amendments

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

12.7 Statistical Analysis Plan

This study is an open-label study and statistical analysis plan (SAP) will be written prior to first patient in and before any statistical activities are performed. However, the SAP 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.

13 STUDY DISCONTINUATION AND CLOSURE

In case this study gets 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.
Possible reasons for early termination or temporary suspension of the study include, but is not limited to:

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

The Sponsor and the Investigator should take the following steps to follow up on patient safety and ensure data integrity:

- Notify the IEC.
- Contact all patients by phone and distribute written communication that the study has been stopped.
- Advise all patients to report for an early termination visit.
- Make plans to follow all patients for AEs for 2 months after the study has been stopped or for as long as it takes for any AE/SAEs to resolve, whichever is longer.
- Instruct study staff to enter all data in the case report form and ensure their completion.

The study patients will be contacted by the PI (or a designee), as applicable, and be informed of changes to study visit schedule.
Adequate measures will be taken to ensure the safety of the patients.

14 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.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study Monitoring/Data Quality Control

Site monitoring is conducted to ensure that the rights and well-being of trial patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in adherence with the currently approved protocol/amendment(s), with International Council for Harmonisation (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/source documents 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. In case remote monitoring activities are activated, appropriate measures to be agreed on a case-by-case basis with the Sponsor shall be implemented to ensure the protection of personal data of data subjects and the confidentiality of their identity, in compliance with the applicable laws and regulations.

15.2 Case Report Forms

Data collected during the study will be recorded in the eCRF. Data reported on the eCRF must 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.

15.3 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 Health Authority representatives at any time. Principal Investigators must agree to the audit/inspection of the study site, facilities, and of study-related records by the Health Authority representatives

and/or by the Sponsor, and/or its delegates, which must be performed in accordance with national laws concerning personal data protection.

16 ETHICS ASPECTS

This study will be carried out in compliance with the Study Protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, ICH-GCP Guidelines, EU-Directives and Regulations (EU REG) (where applicable) and national requirements of the participating countries.

16.1 Ethics Committees

Before starting the study in a study site, Study Protocol and relevant documentation (subject information leaflet, ICF, IB and other documents, according to National Regulations) must be submitted to and approved by the EC 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.

16.2 Subject's Insurance

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

17 PERSONAL DATA PROTECTION SECTION

17.1 General Principles on Personal Data Compliance

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the patients shall remain protected in accordance with the applicable law on personal data protection such as the EU General Data Protection Regulation (GDPR) 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 fulfillment of patients' privacy rights.

17.2 Acknowledgment

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 (i.e., the EU GDPR 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014) and local laws (i.e., 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 being the Sponsor a company incorporated under Luxembourg law, it has to mandatorily comply with Luxembourgish legal provisions on data protection: therefore the site, the PI, the local laboratory, the CRO shall cooperate with the Sponsor to allow the fulfillment 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.

17.3 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 the 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 the 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 (e.g., 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 Sponsor and Site are joint 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.

17.4 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 freedom, 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, Information Technology [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 subjects' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the subjects' 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 subjects' 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 uppercase and lowercase recognition, containing at least 3 "special" characters, such as uppercase letters [A-Z], lowercase letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her, such as name and year of birth (e.g., "johnbrown80") or easily predictable strings of characters (e.g., "qwerty", "12345", "admin", "user", etc.).
- Adequate cryptographic protection measures shall be put in place for data "at rest" and "in transit" (these include, for example, file system or database cryptography, or any

other equivalent IT measure which renders data unintelligible to those who are not authorized to access them).

- High level security measures shall be implemented also on the files or databases which contain the "key" to match the patients' personal data (i.e., name, surname, etc.) with their respective "Subject IDs" (as defined at point (iv) below).
- Backup processes and other measures that ensure rapid restoration of business-critical systems shall be implemented.
- Updated Antivirus and firewall programs shall be installed on the IT devices.

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

(ii) TRANSMISSION OF DATA

All the parties that transfer data through the 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. Remote monitoring/source data verification activities shall ensure the protection of the confidentiality of patients' data. Investigator, Sponsor and Site shall agree the appropriate measures to be implemented on a case-by-case basis.

(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 to ensure that access to a specific set of subjects' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study.
- appropriate measures to ensure that the authentication credentials are periodically updated (i.e., password change).

(iv) PSEUDONYMIZATION

All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudonymization" process). The PI shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to an alphanumerical code ["Patient ID"], whose format shall not make it possible to identify the patient directly or indirectly, to ensure that only anonymous data are transmitted to the Sponsor, the centralized laboratory and/or the CRO. The site/PI shall securely store a separate list (e.g., identification log) with the

identification code, together with all signed informed consents, in accordance with the security measures as defined above.

(v) SAMPLE STORAGE

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 (e.g., 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 (e.g., in case of centralized reading or local laboratory analysis).

(vi) 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 aforementioned measures shall be provided by the Sponsor, the site and/or the CRO to the competent HAs (including data protection authorities) and ECs 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 centralized laboratory undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

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

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

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

Any transfer of ownership of the content of the clinical TMF shall be documented. The new owner shall undertake the responsibilities set out in this protocol. The Sponsor appoints the Clinical Operations Director and the Clinical Operations Manager within the Sponsors' organization as responsible persons for archives. Access to archives shall be restricted to those individuals and delegates.

Once mandatory data retention time for the clinical TMF has elapsed, the study site/PI shall seek the authorization of the Sponsor to destroy the clinical TMF.

Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored, or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Site, Sponsor, CRO, 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.
Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (e.g., an unauthorized access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (e.g., cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability, alteration, theft, copy or dissemination of personal data.
Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the study, shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the Clinical Operations Director, the Sponsor's Data Protection Officer (DPO), the Site and the CRO (CRO responsible persons for Data Breach incidents management) and shall provide the following information:

1. Anomalous Event/Data Breach Type (e.g., data loss, unauthorized access, loss of company device, etc.).
2. Person or source that first reported the Anomalous Event/Data Breach.
3. Date and Time when the person who first reported the Anomalous Event/Data Breach became aware of it.
4. Anomalous Event/Data Breach Date and Time (actual or presumed).
5. Place (specify if actual or alleged) where the Anomalous Event/Data Breach occurred.
6. Anomalous Event/Data Breach Description.
7. Indicate the source of the Anomalous Event/Data Breach (e.g., Investigational Product source) - (if relevant).
8. Indicate the affected infrastructure/system/application/cloud/software/hardware/database and their location.
9. List or describe the processing/storage systems affected by the Anomalous Event/Data Breach (if relevant).
10. Number of data patients involved (if known).

11. Amount of allegedly breached data.
12. 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, 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.

17.6 Information notice on personal data protection and pseudonymization

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 patient about:

1. The applicable data protection legislation.
2. The kind of data shall be collected during the study listing them in detail or by category.
3. The purpose of data processing (e.g., performance of the study, pharmacovigilance) and the legal basis.
4. Whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study.
5. The use of data for future scientific research/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.

6. The pseudonymization procedure and scope.
7. Who can access patients' data and under what circumstances?
8. The period of data retention/storage as defined in *Section 17.4*, including the storage of the biological sample.
9. To which entities/countries outside the EU patients' data will be transmitted (if applicable), as per *Section 17.5*.
10. Patients' data protection rights as defined by the EU GDPR 679/2016.
11. Data Controllers/Data Processors and the relevant contact details.
12. Sponsor's DPO contacts.
13. In case of genetic data processing the possible findings, also about unexpected findings that might be disclosed on account of the processing of the genetic data.

17.7 Genetic Data

Genetic data will not be collected for this study.

17.8 Transfer of subjects' data outside the European Union

The study performance entails transferring patients' personal data (coded data) outside the EU. To this extent, the Sponsor, the site, the 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, and the exceptions under Article 49(1)(d) GDPR, where applicable (e.g., transfer of pseudonymized safety data to authorities of non-EU country where the product might be registered, to comply with safety reporting obligations and to fulfill a public interest in the field of health law recognized by EU and member state law).

17.9 Exercise of subjects' data privacy rights

Each study patient has the right to contact the Sponsor, the site, the PI, the centralized laboratory, the CRO to exercise the rights afforded to the patient by the law, including those afforded 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; 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 PI to destroy/delete his/her personal data, 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 centralized 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 centralized laboratory, and the CRO shall implement adequate organizational measures to reply to patients within the above-mentioned deadline.

17.10 Future research

With patients' optional and additional consent, the Sponsor and/or the site may use the data collected during the study for further medical and scientific research purposes. These may include, e.g., 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, subjects' data will be processed, pseudonymized and transferred abroad and may be shared with future research partners.

18 PUBLICATION POLICY AND RESULTS

By signing the Study Protocol, the Investigator (and his / her appointed staff) ensures that any information and all the study documents provided by the Sponsor will be maintained strictly confidential.
None of this material may be disclosed to any party not directly involved in the study without written permission from 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.

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20 PROTOCOL APPROVAL PAGE

Study Title: Open-label, multicenter, multinAtionaL, inteRventional clinical Trial to assess EffIcacy and safety of the exteMporaneous combInation of nebivolol and ramipril in hypertenSIve pAtients.

Code: MEIN/22/NeRam-Hyp/001

EUDRA-CT number: 2022-003060-25

The signers confirm that they have read and approved the protocol.

Study Medical Expert & Global Clinical Operations Manager: SIMONE BALDINI

Signature & Date: DocuSigned by: Simone Baldini 962DF96D244C489... 19-Jul-23 / /

Global Medical Director: LORENZO MELANI

Signature & Date: DocuSigned by: Lorenzo Melani 2C46ECDD80F8459... 19-lug-23 / /

Coordinating Investigator: PROFESSOR GIOVAMBATTISTA DESIDERI

Signature & Date: DocuSigned by: 274B2033F98E449... 19-lug-23 / /

Sponsor Statistician: GIORGIO REGGIARDO

Signature & Date: DocuSigned by: Giorgio Reggiardo 0CA310C9ED9B46D... 19-lug-23 / /

Statistician: CHAITANYA TRIVEDI

Signature & Date: DocuSigned by Chaitanya Trivedi Chaitanya Trivedi I approve this document July 17, 2023 | 7:44:09 AM PDT 4D4FD52653FE4F069A707DF1F92FA96E / /

21 INVESTIGATOR'S APPROVAL PAGE

I understand that all information concerning the product Menarini International Operations Luxembourg SA supplied, Nebivolol and Ramipril, in connection with this Study Protocol are confidential information. This information includes Study Protocol, eCRF and all other confidential documents provided to me during the course of the study.
I understand that any change in this Study Protocol must be approved in writing by Menarini International Operations Luxembourg SA and the Coordinating Investigator, submitted to the EC and HA.
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.
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: _____

22 APPENDICES

Appendix 1: Declaration of Helsinki.
Appendix 2: Management of clinical trial during Pandemic COVID-19.
Since December 2019, an outbreak of respiratory disease caused by a novel coronavirus, first detected in Wuhan City, Hubei Province, China, has been detected in nearly all countries of the world. The virus has been named "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On 08 March 2020, the World Health Organization declared the COVID-19 outbreak a global pandemic.
The COVID-19 public health emergency may impact the conduct of clinical trials of medical products. In response to the pandemic, various HA have issued guidelines to maintain the integrity of ongoing clinical studies.

Summary of changes in study-related procedures as a result of the COVID-19 pandemic	To assure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity, if necessary, the method of assessments may be changed at the discretion of the Sponsor. In addition, site visits may be replaced with home visits, telephone, or internet-based video-conferencing applications. For this study, except in an urgent situation, changes in study conduct need to be approved by the Sponsor before being initiated. The specific changes to be implemented will be based on the current conditions in the country/region and will be reassessed on an ongoing basis. Not all countries or all sites in a country may be impacted. Normal procedures, as described in this synopsis, will be resumed as soon as possible thereafter. This appendix describes the COVID-19 mitigation plans for ARTEMISIA study. The following mitigation measures will be implemented in study-related procedures because of the COVID-19 pandemic. Clinical Investigators should document in site files and in source documents as appropriate how restrictions related to COVID-19 originated changes to the study conduct, duration of changes, and which participants were affected by such changes. Communications with Sponsor in regard to the implementation of the herein described mitigation measures should be documented in the source documents.
Informed consent	This paragraph is applicable only in case a subject need to re-consent in study participation. Initial informed consent signature must be provided at site during Visit 1 (screening). Each participant must be provided with new information that might impact their willingness to participate in the study in a timely manner. Should the participant need to re-consent if permitted by investigative site procedures and local regulations, the informed consent form can be mailed to the participant.

	The participant can sign the consent form at home and mail it to the study site. Alternatively, the PI or designee can visit the participant at home to present the changes to the study and obtain the informed consent form signature at the participant's home. If the participant has any questions about the changes to the study prior to providing their signature, they will be provided with an opportunity to discuss these questions with the PI or designee. After having obtained the consent, a copy of the signed consent must be sent to or stay with the participant.
Study Treatment Distribution and Return	This paragraph is not applicable for Visit 1 (screening) but only for the subsequent visits. Due to social restriction measures, the participant may not be able to reach the study site. In such cases, the study treatment will not be dispensed to the participants at the site. Instead, the study treatment may be distributed to the participants' home at the times defined in the study flow chart by the designated site staff or by a distributor independent from and acting on behalf of the Sponsor in line with national law or temporary national emergency measures. Participants will be informed and trained on the new dispensing procedures. Participants will be instructed to keep unused study treatment, which will be collected by the designated site staff on the earliest possible time or agreed with the participant to return to site via courier.
Study assessment and procedures	The Screening Visit is a mandatory in-clinic visit and therefore should be performed at the site. The Principal Investigator continues to be responsible for reviewing all study-related assessments. The participant may not be able to reach the site to perform blood pressure (BP) measurement for primary and secondary analysis, clinical laboratory tests, vital sign and physical examination, electrocardiogram, or other assessments required by the study flow chart. In such cases, these assessments will be performed by the health care professionals (study staff or qualified designee) at participant's home, if allowed per country regulations. If home visits are restricted, the assessments can be performed by phone or video (telemedicine facilities). The participants will be provided with blood pressure measurement device for measuring BP and the BP will be measured by the participant with guidance from Investigator via telemedicine. For clinical laboratory tests and ECG (except Screening Visit) authorized/certified (as legally required nationally) local facilities can also be used. In such cases, the End of Assessment/Early Withdrawal visits should be prioritized, and attempts should be made to complete the assessments. At a minimum, the blood pressure monitoring (either by site staff or participant, as applicable), study medication accountability, assessment of AEs and concomitant medications should be performed.
Remote Monitoring Visit	Study monitors may consider ongoing remote data review and remote data verification, where applicable and if site agreed with this approach, and if

	allowed per local regulations, to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and wherever possible verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. The procedures for remote data review must be detailed in the monitoring plan.
Data Quality Assurance	During the period of travel restrictions or social distancing, the Sponsor may implement remote monitoring in place of on-site visits where available and if allowed per local regulations, to assure the accuracy and completeness of the data captured. Any such monitoring will be performed as per standard CRO procedures and must be documented in the monitoring plan.

Abbreviations: AE = adverse event; COVID-19 = Coronavirus Disease 2019; CRO = Contract Research Organization; eCRF = electronic case report form; GCP = Good Clinical Practice; ICH = International Council for Harmonisation; PI = Principal Investigator.