	Corporate Medical Department		
	Protocol Template		
Identification Number	**Version Number**	**State**	**Effective date**
FORM-000050125	2.0, CURRENT	Effective	08 Jan, 2021

Sponsor: **Menarini International Operations Luxembourg SA** **Protocol Version_1** ***of 27/09/2021***

Study Code: **MEIN/21/AmNe-Hyp/001**

PROTOCOL TITLE
CLINICAL STUDY PROTOCOL

*Open-la**B**el, multicenter, multinati**O**nal, in**T**erventional clinical **T**rial to assess eff**I**cacy and safety of the extemporaneous **C**ombination of n**E**bivo**L**ol and am**L**odipine in grade 1-2 hypertensive pat**I**ents versus each monotherapy – **BOTTICELLI Study***	
Protocol Code	*MEIN/21/AmNe-Hyp/001*
EudraCT - Number ClinicalTrials.gov - Number	*2021-005077-10* *NCT05513937*
Protocol Phase (if applicable)	*Phase IV*
Study type and design	*Interventional, multi-center, open-label study*
Protocol Version Number	*Version 1*
Protocol Version Date	*27 September 2021*
Sponsor and address	*Menarini International Operations Luxembourg SA* *Registered Offices: 1, Avenue de la Gare L-1611 Luxembourg* *Operative Offices: 5D, Rue Eugene Ruppert L-2453 Luxembourg* *Phone:(+352) 2649761* *Fax: (+352) 26497649*

Sponsor: **Menarini International Operations Luxembourg SA** **Protocol Version_1** ***of 27/09/2021***

Study Code: **MEIN/21/AmNe-Hyp/001**

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Sponsor: **Menarini International Operations Luxembourg SA** **Protocol Version_1** ***of 27/09/2021***

Study Code: **MEIN/21/AmNe-Hyp/001**

SUMMARY OF CHANGES FROM PREVIOUS VERSION

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

	Corporate Medical Department		
	Protocol Template		
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
ADR	Adverse drug reaction
AE	Adverse event
AEOSI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AML	Amlodipine
ATC	Anatomical Therapeutic Chemical
BBs	Beta-Blockers
BP	Blood Pressure
CCBs	Calcium Channel Blockers
COVID-19	Coronavirus Disease 2019
CRO	Clinical Research Organization
CVD	Cardiovascular disease
DBP	Diastolic Blood Pressure
DPO	Data Protection Officer
EC	Ethics Committee
ECG	Electrocardiogram
EOT	End of Treatment
eCRF	Electronic Case Report Form
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FPI	First Patient In
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practice
GLM	General linear model
HA	Health Authorities
HRT	Hormonal replacement therapy
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ICSR	Individual Case Safety Report
IMP	Investigational medicinal product
IP	Investigational product
IT	Information technology

IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
LPO	Last Patient Out
mITT	Modified Intent-to-treat
NEB	Nebivolol
NO	nitric oxide
PI	Principal Investigator
PP	Protocol Population
RCT	Randomized controlled trial
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard deviation
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
WOCBP	Woman of Childbearing Potential

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2 PROTOCOL SYNOPSIS

Title Acronym Sponsor Study Code	Open-la**B**el, multicenter, multinati**O**nal, in**T**erventional clinical **T**rial to assess eff**I**cacy and safety of the extemporaneous **C**ombination of n**E**bivo**L**ol and am**L**odipine in grade 1-2 hypertensive pat**I**ents versus each monotherapy BOTTICELLI Study MEIN/21/AmNe-Hyp/001
Study product, Dosage and Regimen: - Investigational Product - Reference Therapy (comparator)	Extemporaneous combination of nebivolol (NEB) 5 mg tablets (Anatomical Therapeutic Chemical [ATC] code: C07AB12) with amlodipine (AML) 5 mg (ATC code: C08CA01) tablets or amlodipine 10 mg (ATC code: C08CA01) tablets Each monotherapy: NEB 5 mg and amlodipine (as besylate) 5 mg tablets
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 8 weeks). <u>Screening Visit 1 (Week -4)</u>: Patients with Grade 1 - 2 hypertension with systolic blood pressure (SBP) ranging from ≥140 to ≤179 mmHg and diastolic blood pressure (DBP) ranging from ≥90 to ≤109 mmHg on treatment with any beta-blockers (BBs) or calcium channel blockers (CCBs)[c] including NEB 5 mg or AML 5 mg for at least one month prior to Visit 1 will be screened for eligibility. <u>Run-in period from Visit 1 (Week -4) to Visit 2 (Week 0)</u>: On the same day of the Screening visit, eligible patients will enter into a run-in period after screening, during which: • Patients receiving NEB 5 mg or AML 5 mg will continue the same therapy for 4 weeks. • Patients on any other BBs or CCBs[c] will be switched to NEB 5 mg or AML 5 mg.

Patients entering this phase in therapy with NEB 5 mg or AML 5 mg should be in a 1:1 ratio.

Assessment period from Visit 2 (Week 0) to Visit 4 (Week 8): After 4 weeks (±2 days) of run-in period of monotherapy, BP will be further assessed at Visit 2. Patients with uncontrolled BP levels (sitting SBP/DBP ≥130/80 mmHg) at Visit 2, with the treatment adherence (ranging between 80% to 120%) who did tolerate the treatment will enter into the assessment period and will be assigned to the extemporaneous combination of NEB 5 mg and AML 5 mg. Patients with controlled BP levels (sitting SBP/DBP <130/80 mmHg) and/or who do not tolerate the treatment or have an adherence range below 80% or above 120%, will be withdrawn from the study.

After 4 weeks ±2 days in the assessment period, patients BP will be further evaluated at Visit 3: patients with controlled BP levels (sitting SBP/DBP <130/80 mmHg) will continue the same extemporaneous combination, while patients with uncontrolled BP levels will be uptitrated from extemporaneous combination NEB/AML 5/5 mg to extemporaneous combination of NEB/AML 5/10 mg for further 4 weeks.

At the end of the assessment period (8 weeks ±4 days), Visit 4 will take place. To correctly evaluate the additional effect of the combination therapy, the number of patients with uncontrolled BP on NEB or AML monotherapy needs to be balanced at Visit 2. In order to maintain a 1:1 ratio during the assessment period, a cap of 110 patients for each treatment arm (ie. NEB and AML) will be included at Visit 2 in order to maintain a balanced number of uncontrolled patients entering the assessment period for each drug. The evaluation will be done every 50 patients. If the rate of entrance in the assessment period for one of the 2 tested drugs will deviate more than 5%, a corrective measure will be initiated: according to the enrolment site statistics, one or more sites will be informed to enroll a greater number of patients being treated with the least represented drug in the assessment period.

	A total number of 290 patients will be screened considering 25% of drop-out rate, to obtain approximately 216 completed patients at the end of the study (Visit 4).
Phase	IV
Objectives	Primary objective: • To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg in lowering the sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP, previously treated with NEB 5 mg or AML 5 mg monotherapies for at least 4 weeks. Secondary objectives: • To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg in lowering sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with NEB 5 mg or AML 5 mg monotherapies for at least 4 weeks. • To assess the antihypertensive efficacy of the extemporaneous combination of NEB/AML 5/10 mg versus extemporaneous combination of NEB/AML 5/5 mg, in lowering sitting DBP and SBP between Visit 3 (Week 4) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with NEB 5 mg or AML 5 mg monotherapies for at least 4 weeks. • To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg by evaluating the patients who achieve BP goal (sitting BP <130/80 mmHg) at Visit 2 (Week 0), at Visit 3 (Week 4), and at Visit 4 (Week 8). • To assess the compliance to the treatment (percentage of actual doses taken versus doses to be taken) at Visit 2 (Week 0), at Visit 3 (Week 4), and at Visit 4 (Week 8). • To evaluate the safety and tolerability of the monotherapies (NEB 5 mg and AML 5 mg) and of the extemporaneous

combinations (NEB 5 mg and AML 5mg or AML 10 mg) after 8 weeks of treatment.

Exploratory objectives:

- To assess change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8):
  - In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1.
- To assess the change in mean sitting DBP and SBP between Visit 2 (Week 0) and Visit 3 (Week 4) for uncontrolled patients at Visit 3 (Week 4).
- To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg by evaluating the number of patients achieving the BP goal (sitting BP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8):
  - In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1 (Week -4).
- To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg by evaluating the number of patients divided into subgroups according to the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting BP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8):
  - In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1.
Endpoints	<u>Primary endpoint:</u> • Change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8). <u>Secondary endpoints:</u> • Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8). • Change in mean sitting DBP and SBP between Visit 3 (Week 4) and Visit 4 (Week 8) in patients receiving extemporaneous combination of NEB/AML 5/5 mg versus patients uptitrated to the extemporaneous combination of NEB/AML 5/10 mg. • Number and proportion of patients achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8). • Adherence to the treatments (% of doses taken/doses to be taken) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8). • Safety and tolerability of the monotherapies (NEB 5 mg and AML 5 mg) and of the extemporaneous combinations (NEB 5 mg and AML 5mg or AML 10 mg) will be 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, Adverse events of special interest, clinically significant abnormal change in vital signs, electrocardiogram (only at Visit 1 and Visit 4), laboratory parameters (if applicable) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8). <u>Exploratory Endpoints</u>: • Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8): ○ In the group of patients who were on NEB 5 mg and

	AML 5 mg at Visit 1 and continued to be on the same therapies. o In the group of patients who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1. • Change in mean sitting DBP and SBP for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4). • Number and proportion of patients achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8): o In the group of patients who were on NEB 5 mg and AML 5 mg at Visit 1 (Week -4) and continued to be on the same therapies. o In the group of patients who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1 (Week- 4). • Number and proportion of patients divided into subgroups according to the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8): o In the group of patients who were on NEB 5 mg and AML 5 mg at Visit 1 (Week -4) and continued to be on the same therapies. o In the group of patients, who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1 (Week -4).
Study Population: Patients characteristics Number of Patients	Approximately 290 male or female uncontrolled hypertensive patients between ≥18 and <65 years of age, who are on treatment with any BBs or CCBs, including NEB (only 5 mg dosage allowed) or AML (only 5 mg dosage allowed) for at least one month prior to Visit 1, will be screened for eligibility. A total number of 290 patients will be screened considering a screen failure/drop-out rate of 25%, to obtain approximately 216 completed patients at the end of the study (Visit 4).

Inclusion criteria:

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

1. Male or female patients with Grade 1 - 2 hypertension with mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥90 mmHg and ≤109 mmHg at screening (in accordance with the 2018 European Society of Cardiology / European Society of Hypertension guidelines definition), ≥18 and <65 years of age, on monotherapy treatment either with BBs or CCBs for at least 4 weeks before Visit 1 (screening).
2. Patients are able to understand and have freely given written informed consent at Screening Visit.
3. Patients who are able to comply with all study procedures and who are available for the duration of the study.
4. Ability to take oral medication and willing to adhere to the drug regimen.
5. Female patients are eligible to participate if not pregnant, or not breastfeeding and if they refrain from donating or storing eggs. For females of reproductive potential: use of highly effective contraception (eg. method of birth control throughout the study period and for 4 weeks after study completion defined as a method which results in a failure rate of <1% per year) such as:
    - 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 the

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

6. A male patient must agree to use contraception during the whole study period and for at least 1 week after the last dose of study treatment and refrain from donating sperms during this period.

Exclusion criteria:

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

1. Patients with significant history of hypersensitivity to nebivolol, amlodipine, other BBs or other dihydropyridines, or any related products (including excipients of the formulations) as outlined in the relevant Investigators Brochures, summary of product characteristics[12,13] or local package inserts for NEB and AML.
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 <60mmHg.
5. Acute heart failure, cardiogenic shock, or episodes of heart failure decompensation requiring intravenous inotropic

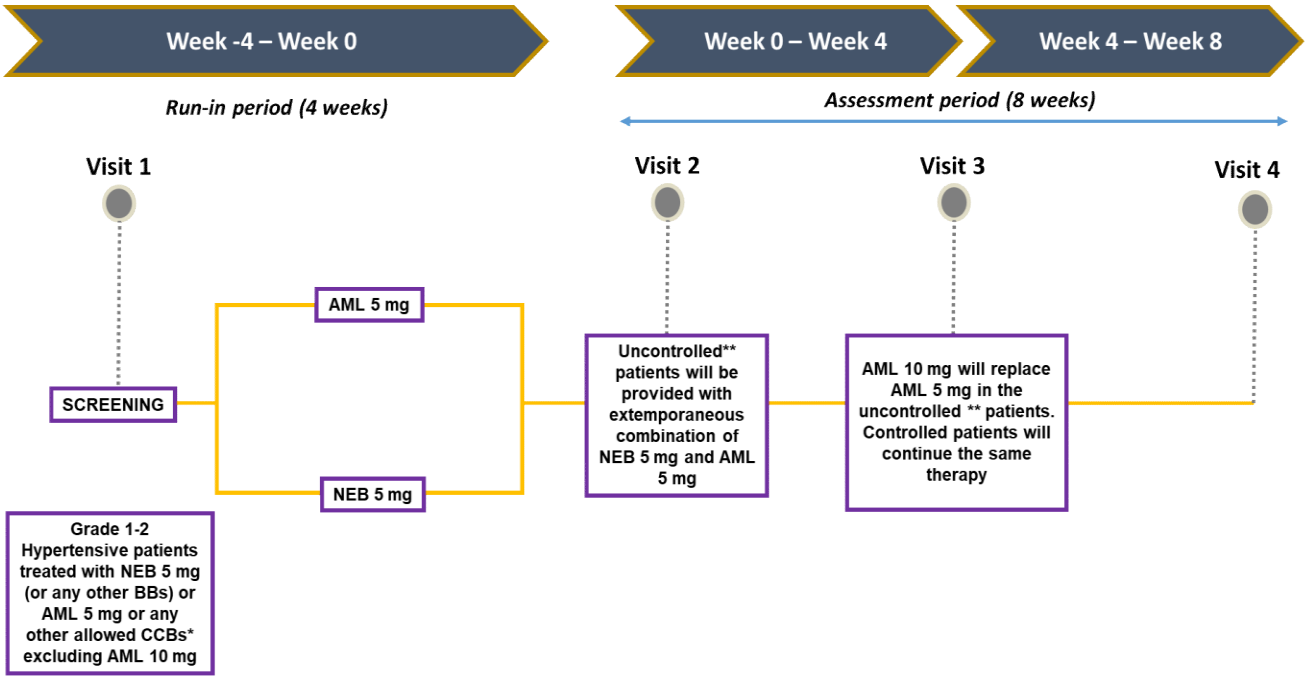
	therapy. 6. Patients with secondary hypertension of any etiology including renal diseases, pheochromocytoma, Cushing's syndrome, hyperaldosteronism, renovascular disease, and thyroid disorders. 7. Patients with a narrowing of the aortic or bicuspid valve, an obstruction of cardiac outflow (obstructive, hypertrophic cardiomyopathy), obstruction of the outflow tract of the left ventricle (eg. high grade aortic stenosis) or symptomatic coronary disease. 8. Patients with severe renal impairment or renal transplant. 9. Patients with clinically relevant hepatic impairment. 10. Patients with sick sinus syndrome, including sino-atrial block. 11. Patients with second- or third-degree heart block (without a pacemaker). 12. Patients with history of bronchospasm and bronchial asthma. 13. Patients with untreated pheochromocytoma. 14. Patients with bradycardia (heart rate <60 bpm; <50 bpm in patients already on BBs treatment). 15. Patient with metabolic acidosis. 16. Patients with severe peripheral circulatory disturbances. 17. Participation in another interventional study within the last 4 weeks before Screening Visit (Visit 1). 18. Patients with diseases that, in the opinion of the Investigator, prevent a careful adherence to the protocol. 19. Patients using and not suitable for withdrawing the prohibited medications prior to the administration of study treatment.
Clinical Sites Number of Centers	Approximately 25 investigational clinical sites
List of Countries	Bulgaria, Poland, and Ukraine.
Study Duration (specify different study phases):	This study will last 12 weeks. <u>Screening Visit (Visit 1, Week -4):</u>

	Grade 1 - 2 hypertensive patients (BP ranging from ≥140 to ≤179mmHg for SBP and from ≥90 to ≤109 mmHg for DBP) on treatment with any BBs or CCBs[c], including NEB (only 5 mg dosage allowed) or AML (only 5 mg dosage allowed) for at least one month prior to Visit 1 will be screened for eligibility. <u>Run-in period (4 weeks) from Visit 1 (Week -4) to Visit 2 (Week 0):</u> Eligible patients will enter a 4-week run-in period on the same day of the Screening visit. Patients receiving NEB 5 mg or AML 5 mg will continue the same therapy, while patients on any other BBs or CCBs[c] will be switched to NEB 5 mg or AML 5 mg, respectively. Patients entering this phase of therapy with NEB 5 mg or AML 5 mg should be in a 1:1 ratio. <u>Assessment period (8 weeks) from Visit 2 (Week 0) to Visit 4 (Week 8):</u> • Patients having uncontrolled BP (sitting SBP/DBP ≥130/80 mmHg) at Visit 2 will be assigned to the extemporaneous combination of NEB 5 mg and AML 5 mg. • After 4 weeks ±2 days at Visit 3 the BP will be assessed again: o In case of controlled BP levels (sitting SBP/DBP <130/80 mmHg), patients will continue to be on the same extemporaneous combination for next 4 weeks ±2 days (Visit 4, Week 8). o In case of uncontrolled BP levels (sitting SBP/DBP ≥130/80 mmHg), the AML dose will be uptitrated from 5 mg to 10 mg and the patients will receive the extemporaneous combination of NEB/AML 5/10 mg for next 4 weeks ±2 days (Visit 4, Week 8).
First Patient In (FPI) Last Patient Out (LPO)	End of March 2022 Beginning of December 2022.
Patient Study Phases Duration	For patients completing the study, participation will last up to 12 weeks:

	• 4 weeks of run-in period (monotherapy) • 8 weeks of assessment period (extemporaneous combination)
Statistical Assumptions	The primary endpoint will be assessed before and after assessment period at Week 8 by a paired t-test using the modified Intent-to-treat population and the Per-Protocol population. Only those patients for whom we have DBP assessment results available at both Week 4 and Week 8 will be considered. No imputation will be performed for missing DBP. To test the covariate effects and the effects of interactions between covariates on the primary efficacy endpoint (change in mean sitting DBP) as well as the first secondary efficacy endpoint (change in mean sitting SBP), a repeated measures general linear model (GLM) will be proposed. The GLM repeated measures procedure provides analysis of variance when the same measurement is made several times on each patient. Age, gender, body mass index, and baseline DBP will be included in the GLM model as covariates. The GLM model will be explained in detail in the Statistical Analysis Plan, approved before database lock. All the other continuous secondary/exploratory endpoints will be assessed across different study visits using a paired t-test or independent t-test, as applicable. All secondary/exploratory endpoints related to proportion of patients achieving the BP goal at Week 4 and Week 8 will be analyzed descriptively along with the relative 95% CI to assess if there is a significant difference from Week 0 where all patients were uncontrolled. **Sample size**: A total sample size of 216 patients is required to achieve 90% power at a 5% significance level assuming a difference in mean DBP from baseline (Visit 2) to 8 weeks (Visit 4) of 4 mmHg and a standard deviation for this difference of 10 mmHg. The mean change in DBP for the null hypothesis is set equal to 2 mmHg.

	A total number of 290 patients will be screened considering 25% of drop-out rate, to obtain approximately 216 completed patients at the end of the study (Visit 4).

2.1 Study Scheme



Abbreviations: AML = amlodipine; BBs = beta-blocker; CCBs = calcium channel blockers; DBP = diastolic blood pressure; NEB = nebivolol, and SBP = systolic blood pressure.

Note:

There is no randomization procedure.

*Allowed CCBs at screening includes Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine.

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

Grade 1 - 2 hypertensive patients: Patients with SBP/DBP ranging from ≥140/90 mmHg to ≤179/109 mmHg.

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

Controlled patients: Patients with sitting SBP/DBP <130/80 mmHg.

2.2 Study Flow Chart

	Week -4 Visit 1	**Week 0 Visit 2**	**Week 4 Visit 3**	**Week 8/EOT Visit 4**
	Screening + Start of Run-in Period	**End of Run-in period and Start of 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
Monotherapy of NEB 5 mg or AML 5 mg dispensing[c]	X			
Extemporaneous combination of NEB/AML 5/5 mg dispensing		X	X[d]	
Extemporaneous combination of NEB/AML 5/10 mg dispensing			X[e]	
Study treatment return/accounting (Compliance assessment)		X	X	X
Concomitant medications[f]	X	X	X	X
Urine Pregnancy test[g]	X	X	X	X
Physical examination	X	X	X	X
Vital signs[h]	X	X	X	X
Laboratory tests[i]	X			X
Blood pressure measurement	X	X	X	X
ECG	X			X
AE/SAE assessment[j]	X	X	X	X

Sponsor: **Menarini International Operations Luxembourg SA** **Protocol Version_1** ***of 27/09/2021***

Study Code**: MEIN/21/AmNe-Hyp/001**

	Week -4 Visit 1	**Week 0 Visit 2**	**Week 4 Visit 3**	**Week 8/EOT Visit 4**
	Screening + Start of Run-in Period	**End of Run-in period and Start of Assessment Period**	**Assessment Period**	**End of Assessment Period**
Written instructions for self-blood pressure measurement and patient diary provided to patient[k]	X	X	X	
Written instructions for self-blood pressure measurement and patient diary returned to site[k]		X	X	X
BP device provided to patient[k]	X			
BP device returned to site[k]				X

Abbreviations: AE = adverse event; AML = amlodipine; BBs = beta-blocker; BP = blood pressure; CCBs = calcium channel blockers; COVID-19 = Coronavirus Disease 2019, ECG = electrocardiogram; EOT = end of treatment; FSH = follicular stimulating hormone; IP = investigational product; 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 AML 5 mg will continue the same therapy for 4 weeks (run-in period). Patients on any other BBs will be assigned to monotherapy with NEB 5 mg and the patients on other CCBs (except AML 10 mg) will be assigned to monotherapy with AML 5 mg. The allowed CCBs are: felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine).
d. Only patients with controlled BP at Visit 3 will receive NEB/AML 5/5 mg for next 4 weeks.
e. Only patients with uncontrolled BP at Visit 3 will receive NEB/AML 5/10 mg for next 4 weeks.
f. All concomitant medications ongoing at the time of the consent and any surgery/procedures should be reported.
g. Pregnancy test (urine): only for females of childbearing potential.
h. Vital signs will include body temperature, respiratory rate, and pulse rate.
i. 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.

j. 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.
k. These procedures are referred to the COVID-19 Appendix (Appendix 2).

3 STUDY RATIONALE AND BACKGROUND INFORMATION

Cardiovascular disease (CVD) is a significant source of morbidity and mortality worldwide, with approximately 18.6 million deaths in 2019[1].

Hypertension is the primary risk factor for CVD. It is also a leading risk factor for all-cause mortality and is one of the largest contributors to global disability-adjusted life years. Hypertension is among the major contributors of cardiac complications, stroke, heart diseases, kidney failure, including premature death and disabilities[2]. Epidemiological research over the past half-century has confirmed that the risk from hypertension is strong, continuous, graded, and doubles for each increment of 20 mmHg systolic blood pressure (SBP) or 10 mmHg diastolic BP (DBP) in adults[3].

As per the estimation of World Health Organization, globally more than 1.13 billion of people are affected with hypertension among which less than 1 in each 5 is under control[2]. The overall prevalence of hypertension in adults is around 30 to 45%[4]. Elevated BP was the leading global contributor to premature death in 2015, accounting for almost 10 million deaths and over 200 million disability-adjusted life years[5].

There are two well-established strategies to lower BP: lifestyle interventions and drug treatment[6]. There is strong evidence from clinical trials that antihypertensive therapy reduces substantially premature morbidity and mortality.

A meta-analysis of 123 randomized controlled trials (RCTs) with 613,815 participants showed relative risk reductions proportional to the magnitude of the blood pressure reductions achieved. Every 10 mmHg reduction in SBP significantly reduced the risk of major CVD events (relative risk [RR] 0.80, 95% confidence interval [CI] 0.77-0.83), coronary heart disease (0.83, 0.78-0.88), stroke (0.73, 0.68-0.77), and heart failure (0.72, 0.67-0.78), which, in the populations studied, led to a significant 13% reduction in all-cause mortality (0.87, 0.84-0.91). Blood pressure lowering significantly reduces vascular risk across various baseline BP levels and comorbidities[7].

A total of 68 RCTs with 245,885 individuals were eligible, of which 47 (153,825 individuals) were 'intentional' RCTs. All outcomes were reduced ($p < 0.001$) by BP lowering, stroke (-36%

[-29, -42]), and heart failure (-43% [-28, -54]) to a greater extent, with smaller reductions for coronary events (coronary heart disease [CHD]: -16% [-10, -21]), cardiovascular (-18% [-11, -24]), and all-cause mortality (-11% [-5, -16]). Absolute risk reductions were 17 (14, 20) strokes, 28 (19, 35) cardiovascular events, and 8 (4, 12) deaths prevented every 1000 patients treated for 5 years. Logarithmic risk ratios were related to SBP, DBP, and PP reductions (p = 0.001-0.003) for stroke and composite cardiovascular events, but not for CHD[8].

However, for most patients, achieving BP targets is often not possible with a single agent. In fact, at least 75% of individuals with hypertension require treatment with at least 2 antihypertensive drugs in order to achieve BP control[9]. The most recent European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines recommend that, when BP-lowering drugs are used, the first objective should be to lower BP to <140/90 mmHg in all patients. Provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.

With the emphasis of a BP target in most patients of 130/80 mmHg or lower, majority of patients would require a combination therapy. The combination of medications targeting multiple mechanisms reduces the heterogeneity of the BP response to initial treatment and provides a steeper dose response than is observed with escalating doses of monotherapy. Two-drug combinations have shown to be safe and well tolerated[6]. Patients with hypertension are now generally treated with multiple pharmaceutical products, BP is in fact a multi-regulated variable depending on many compensating pathways. Consequently, combinations of drugs, working through different mechanisms, are required to reduce BP in most people with hypertension. Thus, monotherapy is likely to be an inadequate therapy in most patients. Indeed, almost all patients in RCTs have required the combinations of drugs to control their BP[11].

Nebivolol (a beta-blocker [BB]) and Amlodipine (a calcium channel blocker [CCB]) are antihypertensive drugs widely prescribed as monotherapies in clinical practice. Both drugs have specific benefit-risk profiles with different mechanism of action.

Nebivolol is a third-generation lipophilic β-1 receptor-selective blocker with nitric oxide (NO)-mediated vasodilatory effects, devoid of intrinsic sympathomimetic effects as well as

membrane stabilizing activity and α1 receptor blocking properties. Nebivolol is administered as the racemate containing equal amounts of the d- and l-enantiomers. The d-isomer is the active β-blocking component; the l-isomer is responsible for enhancing production of NO. Nebivolol, at the recommended dosage (5 mg once daily) was similarly effective in lowering BP compared with other BB (atenolol and bisoprolol), angiotensin-converting enzyme inhibitors (lisinopril and enalapril), the angiotensin receptor blocker telmisartan, and calcium channel blockers (nifedipine and amlodipine)[9]. Nebivolol lowers BP by reducing peripheral vascular resistance and significantly increases stroke volume with preservation of cardiac output and maintains systemic flow and blood flow to target organs. In particular, nebivolol has also shown significant reduction in aortic pressure and wave reflection (markers of central BP) and improvements in endothelial dysfunction and arterial stiffness in hypertensive patients[9]. The high selectivity of nebivolol is witnessed by its high safety profile in patients affected by asthma or chronic obstructive pulmonary disease who are unable to tolerate traditional BB. Its antihypertensive efficacy and safety profile have been clearly proven in patients affected by chronic kidney diseases. Furthermore, the vasodilating properties of nebivolol mediated through endothelial release of NO offer an advantage over other BB in the patient with hypertension and erectile dysfunction. Moreover, it does not negatively influence glucose or lipid metabolism[10].

Amlodipine belongs to the dihydropyridine class of CCBs[7]. Amlodipine, like other CCBs, acts primarily by inhibiting extracellular calcium influx through cardiac and vascular smooth muscle cell membranes; this inhibition is achieved mainly by blockade of L-type 'voltage operated' calcium channels. Its main site of action is the peripheral vasculature, although it also produces vasodilation in coronary vascular beds. In patients with mild to moderate essential hypertension, amlodipine had a sustained and gradual onset of antihypertensive effect, when assessed by 24-hour ambulatory or intra-arterial BP monitoring[7]. Since the two drugs have distinct modes of action, they are well suited for use as combination therapy.

Current literature data has shown an additional antihypertensive effect when Nebivolol or Amlodipine is added to other antihypertensive treatment[10]. At the moment, the most studied association with nebivolol concerns its combination with hydrochlorothiazide and valsartan[9].

3.1 Assessment of Potential Risks and Benefits

The combination of a beta adrenergic blocker with a CCB is used when monotherapy is not fully effective at controlling symptoms In many cases, combination therapy improves rates of BP control and requires less time to achieve target BP with equivalent or better tolerability than higher-dose monotherapy. Patients with comorbidities may benefit from the effects of different antihypertensive medications classes. Approximately, 70% of patients with hypertension require 2 or more agents to achieve their target BP[7]. In a meta-analysis published in 2010, Fixed Dose Combinations of antihypertensive agents not only improved compliance by 21%, but also allowed for a 50% increase in persistence with therapy[10]. Beyond improving compliance, combination therapy in the setting of hypertension management allows for decreased BP variability. Variability in SBP and DBP is associated with an increased risk of myocardial infarction and stroke[11].

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

4 TRIAL OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the antihypertensive efficacy of the extemporaneous combination of nebivolol (NEB) 5 mg with amlodipine (AML) 5 mg or AML 10 mg in lowering the sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP, previously treated with NEB 5 mg or AML 5 mg monotherapies for at least 4 weeks.	Change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8).	The association between elevated DBP and increased mortality risk has been reported several times in literature especially in younger patients[14].
Secondary		
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg in lowering sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with NEB 5 mg or AML 5 mg monotherapies for at least 4 weeks.	• Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8).	A robust body of evidence demonstrated that the reduction of SBP decrease the risk of CV events and mortality[7].
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB/AML 5/10 mg versus extemporaneous combination NEB/AML 5/5 mg, in lowering sitting DBP and SBP between Visit 3 (Week 4) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with NEB 5 mg or AML 5 mg monotherapies for at least 4	• Change in mean sitting DBP and SBP between Visit 3 (Week 4) and 4 (Week 8) in patients receiving extemporaneous combination of NEB/AML 5/5 mg versus patients uptitrated to the extemporaneous combination of NEB/AML 5/10 mg.	

OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
weeks.		
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg by evaluating the patients who achieve BP goal (sitting BP <130/80 mmHg) at Visit 2 (Week 0), at Visit 3 (Week 4), and at Visit 4 (Week 8).	• Number and proportion of patients achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).	The proportion of patients at target is a very important clinical indicator of therapeutic success.
• To assess the compliance to the treatment (percentage of actual doses taken versus doses to be taken) at Visit 2 (Week 0), at Visit 3 (Week 4), and at Visit 4 (Week 8).	• Adherence to the treatments (% of doses taken/doses to be taken) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8).	Monitoring compliance is extremely important to better evaluate the efficacy and tolerability of the extemporaneous combination.
• To evaluate the safety and tolerability of the monotherapies (NEB 5 mg and AML 5 mg) and of the extemporaneous combinations (NEB 5 mg and AML 5mg or AML 10 mg) after 8 weeks of treatment.	• Safety and tolerability of the monotherapies (NEB 5 mg and AML 5 mg) and of the extemporaneous combinations (NEB 5 mg and AML 5mg or AML 10 mg) will be 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, Adverse events of special interest, clinically significant abnormal change in vital signs, electrocardiogram (ECG) (only at Visit 1 and Visit 4), laboratory parameters (if applicable) at Visit	Incidence of adverse drug reactions (ADRs), AEs, serious adverse events (SAEs), vital signs, physical examination, ECG needs to be studied to address safety and tolerability of the extemporaneous combination.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8).	
Exploratory		
• To assess change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8): ○ In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1.	• Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8): ○ In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1.	Evaluation of the antihypertensive efficacy of combination therapy in the sub-group of patients who switched from a different BB or CCB and in the sub-group of patients who were on nebivolol or on amlodipine at the inclusion in the study.
• To assess the change in mean sitting DBP and SBP between Visit 2 (Week 0) and Visit 3 (Week 4) for uncontrolled patients at Visit 3 (Week 4).	• Change in mean sitting DBP and SBP for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4).	To collect and analyze data not only in the overall population of patient but also in patients considered uncontrolled after 4 weeks of combined therapy.
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg by evaluating the number of patients achieving the BP goal (sitting BP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8): ○ In the group of patients who were on NEB 5 mg and AML 5	• Number and proportion of patients achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8): ○ In the group of patients who were on NEB 5 mg and AML 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.	To collect efficacy data stratifying the population of patients on the basis of the switching of the therapy.

OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**
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 AML 5 mg from any other BBs or CCBs at Visit 1 (Week -4).	○ In the group of patients who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1 (Week- 4).	
• To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with AML 5 mg or AML 10 mg by evaluating the number of patients divided into subgroups according to their hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting BP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8): ○ In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1.	• Number and proportion of patients divided into subgroups according to the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8): ○ In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1 (Week -4).	To collect efficacy data stratifying the population of patients on the basis of the switching of the therapy.

5 STUDY 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 8 weeks) to assess efficacy and safety of the extemporaneous combination of Nebivolol and Amlodipine in Grade 1 - 2 hypertension patients versus each monotherapy.

The study will be conducted in approximately 25 investigational clinical sites in Bulgaria, Poland, and Ukraine. The total study duration is 12 weeks including a run-in period of 4 weeks and an assessment period of 8 weeks.

Screening Visit 1 (Week -4): At Visit 1, after providing the informed consent, patients with Grade 1 - 2 hypertension (SBP ranging from ≥140 to ≤179 mmHg and DBP ranging from ≥90 to ≤109 mmHg) who were on treatment with any BBs or CCBs[c] including NEB 5 mg or AML 5 mg for at least one month prior to Visit 1 will be screened for eligibility. The eligibility for Grade 1 - 2 hypertension will be based on the 2018 ESC/ESH guidelines, and the BP criteria is defined as mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥90 mmHg and ≤109 mmHg.

Run-in period from Visit 1 (Week -4) to Visit 2 (Week 0): On the same day of the Screening visit, the eligible patients will enter into a run-in period of 4 weeks after screening, during which:

- Patients receiving NEB 5 mg or AML 5 mg will continue the same therapy for 4 weeks.
- Patients on any other BBs or CCBs[c] will be switched to NEB 5 mg or AML 5 mg.

Patients entering this phase in therapy with NEB 5 mg or AML 5 mg should be in a 1:1 ratio.

Assessment period from Visit 2 (Week 0) to Visit 4 (Week 8): After 4 weeks (±2 days) of run-in period of monotherapy, the BP will be further assessed (Visit 2). Patients with uncontrolled BP levels (sitting SBP/DBP ≥130/80 mmHg) at Visit 2, with the 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 5 mg

and AML 5 mg. Patients with controlled BP levels (sitting SBP/DBP <130/80 mmHg) and/or who do not tolerate the treatment or have an adherence range below 80% or above 120%, will be withdrawn from the study.

After 4 weeks ±2 days in the assessment period, patients BP will be further evaluated at Visit 3: patients with controlled BP levels (sitting SBP/DBP <130/80 mmHg) will continue the same extemporaneous combination, while patients with uncontrolled BP levels will be uptitrated from extemporaneous combination NEB/AML 5/5 mg to extemporaneous combination of NEB/AML 5/10 mg for further 4 weeks.

At the end of the assessment period (8 weeks ±4 days), the patients will attend an End of Treatment Visit 4. To correctly evaluate the additional effect of the combination therapy, the number of patients with uncontrolled BP on NEB or AML monotherapy needs to be balanced at Visit 2. In order to maintain a 1:1 ratio during the assessment period, a cap of 110 patients for each treatment arm (ie. NEB and AML) will be included at Visit 2 in order to maintain a balanced number of uncontrolled patients entering the assessment period for each drug. The evaluation will be done every 50 patients. If the rate of entrance in the assessment period for one of the 2 tested drugs will deviate more than 5%, a corrective measure will be initiated: according to the enrolment site statistics, one or more sites will be informed to enroll a greater number of patients being treated with the least represented drug in the assessment period.

A total number of 290 patients will be screened considering 25% of drop-out rate, to obtain approximately 216 completed patients at the end of the study (Visit 4).

Sitting BP will be measured at all visits before blood sampling. BP will be measured in both arms at the Screening visit (Visit 1) in order to detect possible between-arm differences. The arm with the higher mean DBP 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 to 12:00 a.m.), on the same arm, possibly by the same member of the site staff/personnel, and using the same calibrated equipment 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 two readings differ by >10 mmHg. The mean of the

three 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 (ie. 24 + 2 hour after the last drug intake). Study medication should be administered/consumed on the same time every day during the study; except the days of site visits, when study medication should be administered after all assessments mentioned as per study flow chart (Section 2.2). At Visit 1 (Week -4) and Visit 4 (Week 8), a 12-lead ECG will be performed.

Safety (AEs, SAEs) will be measured at all visits. In case of any abnormality of clinically relevant safety finding at any of the visits according to the Investigator, the patient will be contacted over phone within 24 hours to ensure their safety. Any patient having an ongoing AE or SAE at Visit 4, will be followed-up for further 2 weeks over a phone call.

5.1 Procedures and Study Visits

Patients will attend a total of 4 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 (Visit 1):

- Obtaining informed consent.
- Checking inclusion and exclusion criteria.

- Recording of medical history.
- Recording of prior and concomitant medications.
- Collection of demographic data.
- Recording concurrent diseases and medical conditions.
- Dispensing of antihypertensive treatment with NEB 5 mg or AML 5 mg monotherapy and dispensing of tablets for 4 weeks (run-in period) to eligible patients.
- Dispensing of written instruction for self BP measurement and patient diary.
- Dispensing of BP device.
- Physical examination and vital signs.
- BP measurement.
- ECG.
- Laboratory tests (see Section 8.2.3) (a follow-up phone call will be made within 24 hours in case of any abnormality and clinically relevant results from the laboratory tests according to the Investigator).
- Urine pregnancy test (UPT) (only for female patients).
- AEs and SAEs assessment.
- The patients meeting all inclusion criteria and none of the exclusion criteria will enter into the run-in period on the same day and will receive monotherapy of NEB 5 mg or AML 5 mg:
    - Patients who are already on therapy with NEB 5 mg or AML 5 mg will be provided with the same medication ie, NEB 5 mg or AML 5 mg, respectively.
    - Patients taking any other BBs or CCBs[c] will be provided with NEB 5 mg or AML 5 mg.

2. **Start of the Assessment Period (Visit 2, Week 0):**

At the end of the run-in period (treatment with monotherapies for 4 weeks ±2 days), only the patients with uncontrolled BP (SBP/DBP >130/80 mmHg), who tolerated the treatment and whose adherence to the therapy ranges from 80% to 120%, will enter the 8-week assessment period.

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

The following procedures/assessments must be completed:

- Recording of concurrent diseases and medical conditions.
- BP measurement.
- Compliance assessment by return of NEB and AML tablets (also empty blisters) and accountability.
- Study treatment dispensing (patients will be provided with the extemporaneous combination NEB 5 mg/AML 5 mg).
- Recording of concomitant medications.
- Physical examination and vital signs.
- UPT (only for female patients).
- AEs and SAEs assessment.
- 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.

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

During the assessment period, patients with controlled BP at Visit 3 (Week 4) will continue to receive NEB/AML 5/5 mg while patients with uncontrolled BP (SBP/DBP >130/80 mmHg) will receive the extemporaneous combination NEB 5 mg/AML 10 mg dosing.

The following procedures/assessments must be completed:

- Recording of concurrent diseases and medical conditions.
- BP measurement.
- Compliance assessment by return of NEB and AML 5 mg tablets (also empty blisters) and accountability.
- Study treatment dispensing (patients will be provided with the extemporaneous combination NEB 5 mg/AML 5 mg [in patients with controlled BP] or NEB 5 mg/AML 10 mg [in patients with uncontrolled BP]).
- Recording of concomitant medications.
- Physical examination and vital signs.
- UPT (only for female patients).
- AEs and SAEs assessment.
- 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.

4. **End of the Assessment Period (Visit 4, Week 8):**

The end of assessment period will be considered as end of 8 week ±4 days treatment with the extemporaneous combination NEB 5 mg/AML 5 mg and NEB 5 mg/AML 10 mg.

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 performed within 24 hours in case of any abnormality and clinically relevant results from the laboratory tests according to the Investigator).
- UPT (only for female patients).
- Compliance assessment by study treatment (extemporaneous combination of NEB 5 mg/AML 5 mg and NEB 5 mg/AML 10 mg) return (also empty blisters) and accountability.
- AE and SAE assessment. In case of any patients having an ongoing AE or SAE at the end of the treatment, there will be a follow-up telephone call after 2 weeks to ensure patient safety.
- Return of written instruction for self BP measurement and patient diary dispensed at Visit 3 to the site.
- Return of BP device (dispensed at Visit 1) to the site.

6 SELECTION OF PATIENTS

6.1 Informed Consent Process

The patient's written informed consent to participate in the trial must be obtained before any trial-related activities are carried out. Adequate information must therefore be given to the patient by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations) The patient's written, dated and signed informed consent shall be obtained to the confidential disclosure, processing and transferring necessary documentation of the patient's health and personal data to the

Clinical 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).

The institution and the Investigator have the responsibility 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 HA and 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.

Initial informed consent signature must be provided at site. Should the patient need to re-consent if permitted by investigative site procedures and local regulations, in case of social restrictions (Coronavirus Disease-2019 [COVID-19] pandemic), the ICF can be mailed to the patient. The patient can sign the consent form at home and mail it to the study site. Alternatively, the PI or designee can visit the patient at home to present the changes to the study and obtain their signature on the ICF at the patient's home. If the patient 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 shared with the patient.

6.2 Inclusion and Exclusion Criteria

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

6.2.1 Inclusion Criteria

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

1. Male or female patients with Grade 1 - 2 hypertension with mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥90 mmHg and ≤109 mmHg at screening (in accordance with the 2018 ESC/ESH guidelines definition), ≥18 and <65 years of age, on monotherapy treatment either with BBs or CCBs for at least 4 weeks before Visit 1 (screening).
2. Patients are able to understand and have freely given written informed consent at Screening Visit.
3. Patients who are able to comply with all study procedures and who are available for the duration of the study.
4. Ability to take oral medication and willing to adhere to the drug regimen.
5. Female patients are eligible to participate if not pregnant, or not breastfeeding and if they refrain from donating or storing eggs. For females of reproductive potential: use of highly effective contraception (eg. method of birth control throughout the study period and for 4 weeks after study completion defined as a method which results in a failure rate of <1% per year) such as:
    - 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 the partner is the sole sexual partner of the trial patient and that the vasectomized partner has received medical assessment of the surgical success).
6. A male patient must agree to use contraception during the whole study period and for at least 1 week after the last dose of study treatment and refrain from donating sperms during this period.

6.2.2 Exclusion Criteria

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

1. Significant history of hypersensitivity to nebivolol, amlodipine, other BBs or other dihydropyridines, or any related products (including excipients of the formulations)as outlined in the relevant Investigators Brochures, summary of product characteristics (SmPC)[12,13] or local package inserts for NEB and AML.
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 <60mmHg.
5. Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring intravenous inotropic therapy.
6. Patients with secondary hypertension of any etiology including renal diseases, pheochromocytoma, Cushing's syndrome, hyperaldosteronism, renovascular disease, thyroid disorders.
7. Patients with 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 (eg. high grade aortic stenosis) or symptomatic coronary disease.
8. Patients with severe renal impairment or renal transplant.
9. Patients with clinically relevant hepatic impairment.
10. Patients with sick sinus syndrome, including sino-atrial block.
11. Patients with second- or third-degree heart block (without a pacemaker).
12. Patients with history of bronchospasm and bronchial asthma.
13. Patients with untreated pheochromocytoma.
14. Patients with bradycardia (heart rate <60 bpm; <50 bpm in patients already on BBs treatment).
15. Patient with metabolic acidosis.
16. Patients with severe peripheral circulatory disturbances.
17. Participation in another interventional study within the last 4 weeks before screening (Visit 1).
18. Patients with diseases that, in the opinion of the Investigator, prevent a careful adherence to the protocol.

19. Patients using and not suitable for withdrawing the prohibited medications prior to the administration of study treatment.

6.2.3 Screening Failures

Screening failures are defined as patients who consent to participate in the clinical trial but do not meet one or more eligibility criteria required for participation in this trial during the screening procedures (Visit 1). Subjects who sign the ICF but do not start trial treatment for any reason will be considered Clinical Screening Failures. There will be no rescreening of screening failure patients in this study.

7 STUDY TREATMENT

The following study treatment are administered during:

- Run-in period (Visit 1 to Visit 2): NEB 5 mg tablets or AML 5 mg tablets in patients who were already receiving NEB 5 mg or AML 5 mg or who were on any other BBs or CCBs[c], respectively prior to enrolment into the study.
- Assessment period (Visit 2 to Visit 3): Extemporaneous combination of NEB 5 mg and AML 5 mg in patients with uncontrolled BP at Visit 2.
- Assessment period (Visit 3 to Visit 4): Extemporaneous combination of NEB 5 mg and AML 5 mg in patients with controlled BP at Visit 3 and extemporaneous combination of NEB 5 mg and AML 10 mg in patients with uncontrolled BP (sitting SBP/DBP >130/80 mmHg, who tolerated the treatment and whose adherence to the therapies ranges from 80% to 120%) at Visit 2.

Details on the study design is provided in Section 5.

Further details on study treatment is provided below in Table 7.1.

Table 7.1 Study Treatment Details

Study Treatment Name:	Nebivolol **Marketing Authorisation Holder**: A. Menarini Industrie Farmaceutiche Riunite srl, Via Sette Santi n. 3, 50131 Florence	Amlodipine Besylate **Marketing Authorisation Holder**: EG S.p.A. Via Pavia, 6 - 20136 Milano (MAH)
Dosage Formulation:	Tablet	Tablet
Unit Dose Strength(s)/Dosage Level(s):	5 mg once daily	5 mg/10 mg once daily
Route of Administration:	Oral	Oral
Dosing Instructions*:	1 tablet of study medication will be administered with a glass of water once daily	1 tablet of study medication will be administered with a glass of water once daily
Packaging and Labelling:	Study medication will be provided in a polyvinyl chloride (PVC)/Aluminum blister	Study medication will be provided in a Aluminum/PVC/polyethylene (PE)/ polyvinylidene chloride (PVDC) blister
Storage Conditions:	All study treatment must be stored in its original packaging and kept in a secure area (in a dry place and protected from light and in accordance with the label's instructions) with access limited to the Investigator and authorized site staff. No other special precautions are needed.	All study treatment must be stored in its original packaging and kept in a secure area (in a dry place and protected from light and in accordance with the label's instructions) with access limited to the Investigator and authorized site staff. No other special precautions are needed.

*The patients will take the monotherapy tablets or the extemporaneous combination of NEB and AML in the morning between 6 am to 10 am except on the visit days. On the visit days, the patients will take the monotherapy tablets or the extemporaneous combination of NEB and AML 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 Labelling

Study treatment dosage form, strength, formulation:

Nebivolol 5 mg: NEB 5 mg is white, round, cross-scored tablet with one-sided dividing cross score. The tablet can be divided in equal quarters.

Amlodipine besylate 5 mg: AML 5 mg is white, round tablet.

Amlodipine besylate 10 mg: AML 10 mg is white, round tablet with a score line on one side. A tablet may be divided into two equal doses.

Study treatment manufacturing:

The NEB 5 mg tablets and AML 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 are reported in relative SmPC.[12,13]

Study treatment packaging and labelling:

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

The study treatment packaging and labelling operations will be performed in compliance with all applicable regulatory requirements and Good Manufacturing Practice guidelines, as well as any additional national requirement and Standard Operative Procedures (SOPs).

The label wording will be in the local language for each country and will report the contents of the boxes and the instructions on how to administer and store the study medication.

Study treatment packaging description:

Both NEB 5 mg and AML 5/10 mg will be provided in dedicated treatment. Patient Kits to be dispensed at Visit 1 (beginning of the run-in period) and at Visit 2 (start of the assessment period) and Visit 3.

The Kits are labelled with labels of different colours, 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 one Patient Kit with nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- AML 5 mg: each trial participant is provided with one Patient Kit with amlodipine 5 mg 42 tablets (3 blisters with 14 tablets).

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

Visit 2 (Beginning of Assessment Period):

Each trial participant is provided with one Patient Kit made up by:

- NEB 5 mg: one box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- AML 5 mg: one box containing amlodipine 5 mg 42 tablets (3 blisters with 14 tablets).

The two boxes are then sealed together into a transparent plastic film in order to realize the treatment Patient Kit.

Trial participant must be carefully instructed by Investigator or designee to take simultaneously (at the same time): nebivolol 5 mg as one white round cross-scored tablet and amlodipine 5 mg as one white, round tablet, according to Study Protocol.

Visit 3 (Assessment Period):

Participants **with controlled BP** are provided with one Patient Kit made up by:

- NEB 5 mg: one box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- AML 5 mg: one box containing amlodipine 5 mg 42 tablets (3 blisters with 14 tablets).

The two boxes are then sealed together into a transparent plastic film in order to realize the treatment Patient Kit.

Trial participant must be carefully instructed by Investigator or designee to take simultaneously (at the same time): nebivolol 5 mg as one white round cross-scored tablet and amlodipine 5 mg as one white, round tablet, according to Study Protocol.

Participants **with uncontrolled BP** are provided with one treatment Patient Kit made up by:

- NEB 5 mg: one box containing nebivolol 5 mg 42 tablets (3 blisters with 14 tablets).
- AML 10 mg: one box containing amlodipine 10 mg 42 tablets (3 blisters with 14 tablets).

The two boxes are then sealed together into a transparent plastic film in order to realize the treatment Patient Kit.

Trial participant must be carefully instructed by Investigator or designee to take simultaneously (at the same time): nebivolol 5 mg as one white round cross-scored, tablet and amlodipine 10 mg as one white, round tablet (with one break on one side), 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.

An explanation will be given for any discrepancies.

At the conclusion of the study, the Drug Accountability Form will be completed after a final medication supply inventory.

All supplied (used or unused) study treatment must be accounted for and provided with relative return documentation duly filled in, signed, and dated as appropriate.

Any discrepancy (if any) must be investigated and satisfactorily explained.

Destruction of study medications will be carried out by manufacturer after written authorization of the Sponsor.

The following paragraph is applicable for all study visits (Visits 2, 3, and 4) 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 on 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 precautions.

Amlodipine 5/10 mg tablets: must be stored in the original package in order to protect against the light.

7.4 Study Product Compliance

Compliance with study treatment will be assessed at Visit 2 for monotherapy and Visit 3 and Visit 4 for the combination therapy. The PI must instruct patients to return the medications at each visit. The amount of study medication taken by the patient will be derived by counting the number of tablets in the blister returned and will be recorded in the source document and in the electronic case report form (eCRF).

Adherence to treatment will be measured through treatment compliance which will be calculated by using the below formula:

$$\frac{number\ of\ doses\ taken\ during\ the\ study}{number\ of\ doses\ to\ be\ taken\ during\ the\ study} \times 100$$

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.

7.5 Concomitant Therapy(ies)

Any medication that the patient was receiving at the time of enrolment, and the other regular or occasional use of any concomitant medication during the study will be recorded in the source documents and in the eCRF. 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 Prohibited 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 and agonists.
- Calcium antagonists.
- Angiotensin converting enzyme inhibitors.
- Diuretics.
- Centrally acting antihypertensive (eg. clonidine, methyldopa, guanfacine).
- Reserpine.
- Moxonidine.
- Chronic nitrate treatment (eg. isosorbide dinitrate or isosorbide mononitrate).
- Phosphodiesterase inhibitor and angiotensin II receptor blockers.

Moreover, special attention should be paid to contraindicated/not-recommended drugs as per Nebivolol and Amlodipine 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)/AML (5 mg/10 mg) in patients with Grade 1 - 2 hypertension versus each monotherapy after 8 weeks of treatment. Data for this variable will be collected from BP measurements.

BP measurements:

Sitting BP will be measured at all visits. Blood pressure will be measured in both arms at the Screening visit (Visit 1) in order to detect possible between-arm differences. 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 noon), on the same arm, possibly by the same site personnel, and using the same calibrated equipment 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 two readings differ by >10 mmHg. The mean of the three 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 (ie. 24 + 2 hour after the last study medication intake). Study medication should be administered/consumed on the same time every day during the study; except the days of site visits, when study medication should be administered after all assessments mentioned as per study flow chart (Section 2.2). At Visit 1 (Week -4) and Visit 4 (Week 8), a 12-lead ECG will be performed.

8.2 Assessment of Safety

Safety will be assessed through collection of treatment-emergent AEs, SAEs, AEs of special interest (AEOSI)-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.

8.2.1 Physical Examination

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

8.2.2 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 at least 10 minutes of rest; in sitting position in triplicate (spaced by at least 1 minute), and once in standing position. The mean of the 3 BP readings in sitting position will be recorded on the source documents and in the eCRF. Blood pressure and pulse measurements will be assessed with a completely automated device.

8.2.3 Clinical Laboratory Tests

All samples will be collected in accordance with standard laboratory procedures. The maximum volume of blood is approximately 40 mL, which will be the total blood collected during the study (Visit 1 and Visit 4).

A follow-up phone call after Visit 1 and Visit 4 will be performed within 24 hours only in case of clinically significant abnormality laboratory tests according to the Investigator 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.

The following hematology and serum chemistry laboratory tests will be performed at Visit 1 (Week -4) and Visit 4 (Week 8):

Hematology	**Serum Chemistry**
Red blood cell	ALT
White blood cell	Albumin
Hemoglobin	Alkaline phosphatase
Hematocrit	AST
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
International Normalized Ratio (INR)	Lactate dehydrogenase (LDH)
	Uric acid
	Prothrombin Time (PT)
	Partial Thromboplastin Time (PTT)

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

8.2.4 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. 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.

8.2.5 Urine Pregnancy tests

Urine pregnancy tests (when appropriate) will be performed at Visit 1, 2, 3, and 4, by determination of the urine β human chorionic gonadotropine, 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

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

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

9.2 Drug Relationship

The causal relationship between an AE and study treatments 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

An adverse drug reaction (ADR) is any untoward and unintended response to an investigational medicinal product (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:

- Certain
- Probable
- Possible
- Unassessable

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

- Unlikely

- Not related

9.4 Seriousness

An AE/ADR is considered serious when:

- Results in death
- Is life-threatening

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

- Requires inpatient 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 SAE/ADR.

9.5 Adverse Event/Adverse Drug Reaction Intensity

The intensity level of a serious or a non-serious AE or ADR is attributed according to the following definitions:

Mild: does not interfere with routine activities; in case of laboratory tests, when there is a mild abnormality.

Moderate: interferes with the routine activities; in case of laboratory tests, when there is a moderate abnormality.

Severe: makes it impossible to perform routine activities; in case of laboratory tests, when there is a significant abnormality.

9.6 Adverse Event/Adverse Drug Reaction Expectedness

An AE/ADR is considered unexpected when the nature, severity, or outcome of the AE/ADR is not consistent with the information provided in the Reference Safety Document (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.

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

Any AE(s) 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 recording pages/AE form any recognized AE identifying an ICSR, 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.

Any available information and diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall be recorded in and/or attached to the concerned eCRF pages/sections.

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

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

CRO Pharmacovigilance Officer: Will be reported through CRO's Pharmacovigilance group (AmNe_SO@IQVIA.com) 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

If the Investigator becomes aware of a SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a patient treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

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

Any further information and supporting documentation that 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 authorities and ECs as required, with these deadlines after the first knowledge, intended as the day when the CRO receives the notification of the SUSAR:

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

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

Furthermore, the following safety issues will be 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 treatment.

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 ADR or when a fatal or other serious outcome is the primary efficacy endpoint, agreement with competent authority will be reached to treat SAE as disease-related and not subjected 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 non-serious AE ICSR (whether or not thought to be related to the investigational drug), as specified above, no later than 5 calendar days after the first knowledge of the occurrence of the case.

Any further information and supporting documentation that become available (copies of laboratory reports, tests, procedures, etc.) shall be provided no later than 24 hours after the Investigator first becomes aware, to the CRO by e-mail or fax, to be forwarded to the Sponsor.

9.12 Management of any laboratory abnormality

Any laboratory test abnormality which occurs after IMP administration and is considered by the Investigator as an 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 (modality to be established) 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 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 eCRF as a SAE and managed as above described.

Eligibility of a woman of childbearing potential (WOCBP) will be considered as described in Section 6.2.1. 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 hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10 WITHDRAWAL CRITERIA

Withdrawal of monotherapies or the study treatment

Withdrawal from the monotherapies or study treatment refers to any patient who does not receive the complete course, ie. when no further planned dose is administered from the date of withdrawal. A patient withdrawn from the monotherapies or study 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 or monotherapies may be discontinued for any of the reasons below. In addition to the scheduled visits, patient who have been withdrawn from study treatment or monotherapies may also undergo additional medical follow-up at the discretion of the Investigator.

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

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 or liver enzyme parameters as described in Section 8.2.3.
- 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 4. 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

Considering a screen failure and a drop-out rate of 25% from Visit 1 to Visit 4 (End of Treatment), the number of patients to be screened are 290. Two-hundred and sixteen patients with uncontrolled hypertension, are planned to be included at screening in the assessment period lasting for 8 weeks. A total sample size of 216 patients is required to achieve 90%

power at 5% significance level assuming a difference in mean DBP from baseline to 8 weeks of 4 mmHg and a standard deviation (SD) for this difference of 10 mmHg. The mean change in DBP for null hypothesis is set at 2 mmHg.

12.3 Analysis Populations

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

- Enrolled population: Patients who are enrolled into the study (ie. signed ICF and met the eligibility criteria) and may or may not receive the study treatment (extemporaneous combination).
- Modified Intent-to-Treat (mITT) population: Patients who are in the Enrolled population and receive at least one dose of study treatment (combination therapy) and have at least baseline and Week 8 assessments with primary efficacy data.
- Safety population: Patients who are in the Enrolled population and receive at least one dose of study treatment (ie. monotherapy and/or combination therapy).
- Per-Protocol (PP) population: All patients included in the Safety population who do not have any major protocol deviations that could affect the analyses.

12.4 Analysis Variables

Analysis of Variables and Populations Used		
Efficacy		
	Analysis Variables	**Population Used**
Primary efficacy	Change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8).	mITT population, PP population
Secondary efficacy	Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8).	mITT population, PP Population
	• Change in mean sitting DBP and SBP between Visit 3 (Week 4) and 4 (Week 8) in patients under extemporaneous combination of NEB/AML 5/5 mg versus patients uptitrated to the extemporaneous combination of NEB/AML 5/10 mg. • Number and proportion of patients achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).	mITT population
	• Adherence to the treatments (% of doses taken/ doses to be taken) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).	Enrolled population, Safety population
	• Safety and tolerability of the monotherapies (NEB 5 mg and AML 5 mg) and of the extemporaneous combination (NEB 5 mg and AML 5mg or AML 10 mg).	Safety population
Exploratory efficacy	• Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8): o in the group of patients who were on NEB 5 mg and AML 5 mg at Visit 1 and continued on the same therapies. o in the group of patients who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1. • Change in mean sitting DBP and SBP for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4). • Number and proportion of patients achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8): o in the group of patients who were on NEB 5 mg and AML 5 mg at Visit 1 (Week -4) and continued on the same therapies. o in the group of patients who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1 (Week -4). • Number and proportion of patients divided into subgroups according	Enrolled Population

	to the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8): o in the group of patients who were on NEB 5 mg and AML 5 mg at Visit 1 (Week -4) and continued on the same therapies. o in the group of patients, who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1 (Week -4).	
Safety	Incidence, intensity (severity), seriousness of AEs during the study period, (screening, run-in period and assessment period), relationship to the study treatments, AEOSIs, abnormal/unexpected change in vital signs, ECG (only at Visit 1 and Visit 4), Laboratory parameters (if applicable), and use of concomitant medications at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).	Safety population
Abbreviations: AE = adverse event; AEOSI = adverse event of special interest; AML = Amlodipine; BB = beta-blocker; BP = blood pressure; CCB = calcium channel blocker; DBP = diastolic blood pressure; ECG = electrocardiogram; mITT = modified Intent-to-treat; NEB = nebivolol; PP = per-protocol; and SBP = systolic blood pressure.		

12.5 Statistical Analysis

12.5.1 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 + AML).

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, %).

12.5.2 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 DBP between Visit 2 (Week 0) and Visit 4 (Week 8).

The statistical hypothesis will be defined as below:

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

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

The above hypothesis will be tested as following:

- Change from baseline in sitting DBP from prior and post combination therapy will be 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, Q3, minimum, and maximum.

Additionally, a repeated measure general linear model (GLM) will be performed on the primary efficacy endpoint (change in mean sitting DBP) to test the covariate effects and the effects of interactions between the covariates. Age, gender, body mass index, and baseline DBP will be included in the GLM model as covariates. The GLM model will be explained in detail in the Statistical Analysis Plan (SAP), approved before database lock.

12.5.3 Sensitivity analysis

The primary 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.

12.5.4 Secondary (efficacy) analysis

Secondary efficacy variables will be summarized in a descriptive manner using both the mITT as well as the PP population.

- Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8).

- Change in mean sitting DBP and SBP between Visit 3 (Week 4) and Visit 4 (Week 8) in patients under extemporaneous combination of NEB/AML 5/5 mg versus patients uptitrated to the extemporaneous combination of NEB/AML 5/10 mg.
- Number and proportion of patients achieving the BP goal (sitting SBP/DBP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).

Change in sitting BP between visits will be compared 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.

Similar to the primary end point, the secondary end point of change in SBP between Visit 2 and Visit 4 will be analyzed using a repeated measures GLM. The same covariates as used in the primary analysis will be used for this analysis.

Change in sitting SBP and DBP between patients under extemporaneous combination of NEB/AML 5/5 mg versus patients uptitrated to the extemporaneous combination of NEB/AML 5/10 mg will be compared using independent samples t-test. If the data is found to be non-Normal, the independent samples t-test will be replaced by Wilcoxon rank-sum test.

The 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 BP goal (sitting BP <130/80 mmHg) will be summarized for Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8) along with percentage and 95% CI. A p-value using McNemar's test will be presented to compare the proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) between Visit 2 and Visit 3, Visit 2 and Visit 4 and, Visit 3 and Visit 4.

12.5.5 Exploratory (efficacy) analysis

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

- Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8):

  - In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1 (Week -4).
- To assess change in mean sitting DBP and SBP, for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4).
- Number and proportion of patients achieving the BP goal (sitting BP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8):
  - In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1 (Week -4).
- Number and proportion of patients divided into subgroups according to the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting BP <130/80 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8).
  - In the group of patients who were on NEB 5 mg and AML 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 AML 5 mg from any other BBs or CCBs at Visit 1.

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

The number of patients achieving BP goal (sitting BP <130/80 mmHg) will be summarized for Visits 2, 3, and 4, along with percentage. A p-value using McNemar's test will be presented to compare the proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) between Visit 2 and Visit 3, Visit 2 and Visit 4, and Visit 3 and Visit 4.

12.5.6 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 current 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.

12.5.7 Interim analysis and stopping rules

Not applicable.

12.5.8 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 protocol should be initiated without prior approval by EC/HA of a protocol amendment according to applicable Regulations, except in case of emergency or when the change involves only logistical or administrative aspects of the trial.

Any deviation from the protocol, SOPs, 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, ie. are likely to have an impact on the safety of the patients, or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the ECs and the country authorities (CAs) in the participating countries have to approve these amendments before implementation, according to applicable Regulatory Requirements.

Changes which have no significant impact on medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the EC/CA will be notified of this protocol amendment.

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

12.7 Statistical Analysis Plan

This study is an open-label study and SAP will be finalized prior to database lock. However, in case of any protocol amendment or any modification which may not affect the integrity of data or primary analysis but may lead to modification of SAP version, will be finalized prior to database lock. The SAP will describe in detail study endpoints and statistical analyses, including the analysis of the primary as well as additional endpoints. In case changes to the original primary endpoint or of the original primary analyses occurs during the study, these changes will be the subject of a substantial protocol amendment.

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

13 STUDY DISCONTINUATION AND CLOSURE

In case this study gets temporarily suspended or prematurely terminated, written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study patients, Investigators, ECs, Sponsor and Regulatory Authorities with the reason(s) for the termination or suspension.

The study patients will be contacted 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 compliance 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.

15.2 Electronic Case Report Forms

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

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

During the conduct of the clinical part of the study, the eCRF must be available and up-to-date, so that it always reflects the latest observations on the respective patient.

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

15.3 Quality Assurance

All clinical activities conducted under this protocol is subject to GCP regulations. This includes audits/inspections by the Sponsor, and/or by national/international HA representatives at any time. Principal Investigators must agree to the inspection of the study site, facilities, and of study-related records by the HA 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 (Patient information leaflet, ICF, the Investigator's Brochure 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 have to be followed. Any amendment to the protocol will be submitted to the ECs and HAs before implementation.

Furthermore, the HAs and ECs of the participating countries will be informed about the study start, the end of the study, or the premature study termination as appropriate and within the requested time period.

16.2 Patient's Insurance

For patients 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 patients in the ICF and/or provided as a separate document, in accordance with national requirements. The insurance policy will be submitted for approval to the ECs along with the other study documents.

A copy of the insurance certificate will be provided to each Investigator and will be filed in the Investigator's File at the sites and in the study's Trial Master File (TMF).

The Investigator must notify to Sponsor immediately upon notice of any claims or lawsuits.

17 PERSONAL DATA PROTECTION SECTION

17.1 General Principles on Personal Data Compliance

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

This section defines the appropriate technical and organizational measures that shall be implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfilment of patients' privacy rights.

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 (ie. the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014) and local laws (ie. the laws of the country where the study is conducted) as well as by the Sponsor's national legislation.

In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore the site, the PI, the local laboratory, the CRO shall cooperate with the Sponsor to allow the fulfilment of such obligations; (c) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the site, the PI, the local laboratory, and the CRO.

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 (eg. if pursuant to the local laws the Site is a data processor of the Sponsor, a Data Processing Agreement will be finalized; if pursuant to the local laws Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalized).

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

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 freedoms and the dignity of data patients. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws. The site, the PI, the Sponsor, the CRO, and the local laboratory as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the study, shall implement the following safety measures (physical, logical, organizational, technical, electronic, 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:

- The patient diary must be handed in person by the patient. In case the patient is not able to hand over the diary personally, collection must be carried out by a secure courier, which will collect the diary and deliver it in the hands of the PI or authorized staff (ordinary postal mail is prohibited). The patient diary must not include the patient's name but only patient code.
- In order to minimize the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- Any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least 3 "special"

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

- Adequate cryptographic protection measures shall be put in place for data "at rest" and "in transit" (these include, eg. file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorized to access them);
- High level security measures shall be implemented also on the files or databases which contain the "key" to match the patients' personal data (ie. name, surname, etc.) with their respective "Patient IDs" (as defined at point (iv) below);
- Backup processes and other measures that ensure rapid restoration of business-critical systems shall be implemented;
- Updated Antivirus and firewall programs shall be installed on the IT devices.

The site shall, regularly test and update the measures listed above.

The site shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.

The CRO shall ensure that the selected sites for the study have implemented the above listed measures.

(ii) TRANSMISSION OF DATA:

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

(iii) SECURITY OF THE CENTRALIZED DATA BASE

The centralized database held by the Sponsor shall have the following safeguards in place:

- Appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of

patients' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study.

- Appropriate measures to ensure that the authentication credentials are periodically updated (ie. password change).

(iv) PSEUDONYMIZATION

All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymization" process). The PI shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to a an alphanumerical code ["Patient ID"], whose format shall not make it possible to identify the patient directly or indirectly, so as to ensure that only anonymous data are transmitted to the Sponsor, the centralized laboratory and/or the CRO. The site/PI shall securely store a separate list (eg. identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.

(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 (eg. X-ray, ECG) shall bear Patient ID, and in no case will they bear other information that may lead to the direct or indirect identification of the patient, especially when, in accordance with this protocol, samples shall be forwarded and shared outside the clinical site (eg. in case of centralized reading or local laboratory analysis).

(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 afore mentioned measures shall be provided by the Sponsor, the site and/or the CRO to the competent authorities (including data protection authorities) and ECs if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, the site,

the PI, the CRO, and the 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 (ie. the list that where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived care of the 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 authorities.

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 Paolo Fabrizzi for cloud data within the Sponsors' organization as responsible person 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 (eg. an unauthorized access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (eg. cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability, alteration, theft, copy or dissemination of personal data.

Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the study, shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the Clinical Operations Director, the Sponsor's Data Protection Officer (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 (eg. 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 (eg. 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 have been provided, the Sponsor and/or the site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

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

For Data Breach affecting personal data of patients enrolled within the 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 pseudo-anonymization

Prior to patients' enrolment in the study, the PI and/or the Site (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The PI is responsible to archive the signed ICF in accordance with the security measures described above. Among other things, the ICF (or the separate form) shall inform 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 (eg. 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 researches/secondary use of data (if any). In such a case the future scientific purposes/secondary use shall include the future/further scientific processing activities/purposes.

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 General Data Protection Regulation 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 with regard to 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 patients' data outside the European Union

The study performance entails transferring patients 'personal data (coded data) outside the EU. To this extent, the Sponsor, the site, the PI, the local laboratory, the CRO, undertake to export such data in compliance with adequate safeguards/legal basis as required by the Regulation 679/2016 including the Commission Decisions, the Standard Contract Clauses, the Privacy Shield, and patients' specific consent.

17.9 Exercise of patients' 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 (IF APPLICABLE: including his/her biological samples, unless they have been permanently anonymized), thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study. If the Site, the PI, the 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 course of the study for further medical and scientific research purposes. These may include, eg.: retrospective clinical studies; clinical studies pertaining to the patients' pathology/medical condition(s)or similar conditions; studies which compare the data of this Study with those from other sources to identify the factors involved in a disease; registration of new drugs.

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

18 DATA HANDLING AND RECORDS KEEPING

Unless other laws require archiving for a longer period, the site and the PI shall archive the content of the clinical trial file, including the relevant patients' personal data, for at least

25 years after the end of the clinical trial. However, medical records shall be archived in accordance with the national laws of the country where the study is performed.

The Investigator should keep all study-related documents, as specified in ICH E6 (GCP) Section 8 and by the applicable regulatory requirement(s), in the Investigator's File.

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

The content of the Investigator's File shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility.

The Sponsor must be notified in writing of the name and address of the new custodian.

19 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.

20 REFERENCES

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21 PROTOCOL APPROVAL PAGE

Study Title: Open-la**B**el, multicenter, multinati**O**nal, in**T**erventional clinical **T**rial to assess eff**I**cacy and safety of the extemporaneous **C**ombination of n**E**bivo**L**ol and am**L**odipine in grade 1-2 hypertensive pat**I**ents versus each monotherapy – **BOTTICELLI Study**

Code: MEIN/21/AmNe-Hyp/001

EUDRA-CT number: 2021-005077-10

The signers confirm that they have read and approved the protocol

Study Medical Expert: MARCO MIRODDI

Signature & Date: _____ 29/09/2021

Corporate Medical Director: LORENZO MELANI

Signature & Date: _____ 29/09/2021

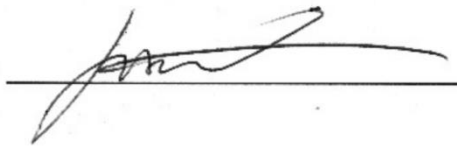
Coordinating Investigator: MASSIMO VOLPE

Signature & Date: _____ 30/09/2021

Sponsor: **Menarini International Operations Luxembourg SA** **Protocol Version_1** ***of 27/09/2021***

Study Code: **MEIN/21/AmNe-Hyp/001**

Statistician: GIORGIO REGGIARDO

Signature & Date:  28/09/2021

22 INVESTIGATOR'S APPROVAL PAGE

I understand that all information concerning the product Menarini International Operations Luxembourg SA supplied ..... in connection with this Study Protocol are confidential information. This information includes: Study Protocol, Investigator's Brochure, electronic Case Report Form, Other documents

_____.

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 Ethics Committee 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: _____

23 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 patients, 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 BOTTICELLI study. The following mitigation measures will be implemented in study-related procedures as a result of the COVID-19 pandemic. Clinical investigators should document in site files and in source documents as appropriate how restrictions related to COVID-19 originated changes to the study conduct, duration of changes, and which patients 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 patient needs to re-consent in study participation. Initial informed consent signature must be provided at

	site during Visit 1 (screening). Each patient must be provided with new information that might impact their willingness to participate in the study in a timely manner. Should the patient need to re-consent if permitted by investigative site procedures and local regulations, the informed consent form can be mailed to the patient. The patient can sign the consent form at home and mail it to the study site. Alternatively, the PI or designee can visit the patient at home to present the changes to the study and obtain the informed consent form signature at the patient's home. If the patient 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 patient.
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 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 study treatment, which will be collected by the designated site staff on the earliest possible time or agreed with the patient 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 PI continues to be responsible for reviewing all study -related assessments. The patient may not be able to reach the site to perform blood pressure (BP) measurement for primary and secondary analysis, clinical laboratory tests, vital sign and physical examination, electrocardiogram (ECG), or other assessments required by the study flow chart. In such cases, these assessments will be performed by the health care professionals (study staff or qualified designee) at patient's home, if allowed per country regulations.
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 site 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 IQVIA procedures and must documented in the monitoring plan.
Abbreviations: COVID-19 = Coronavirus Disease 2019; eCRF = electronic case report form; GCP = Good Clinical Practice; ICH = International Council for Harmonisation; PI = Principal Investigator.	