STATISTICAL ANALYSIS PLAN

MEIN/22/NeRam-Hyp/001

Open-label, multicenter, multinAtionaL, inteRventional clinical Trial to assess Efficacy and safety of the exteMporaneous combInation of Nebivolol and Ramipril in hypertenSIve pAtients - ARTEMISIA study.

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0 (Dated 17Apr2024) for Protocol MEIN/22/NeRam-Hyp/001.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	15Dec2023	Chaitanya Trivedi	Not Applicable – First Version
2.0	12Mar2024	Chaitanya Trivedi	Chap 3.3 - change from planned analysis to due site GCP compliance related issue Chap 5.2 /16.1.3– introduction of a sensitivity mITT primary endpoint analysis Chap 16. 4 – new chapter added
3.0	17Apr2024	Chaitanya Trivedi	Updates in Chap 3 General design for formatting, 3.3 - change from planned analysis section 4 Planned analysis Section 5 Analysis set, 5.2 MITT Population (for site 507 related updates),16.1.4 (supplementary Analysis of Primary efficacy variable), 16.2.1(Secondary Efficacy variable), 16.2.1.3 (change in mean sitting DBP) and 16.4 Sensitivity analysis

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACE-i	Angiotensin-converting enzyme inhibitors
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BBs	Beta-Blockers
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats per minute
CHD	Coronary Heart Disease
COVID-19	Coronavirus Disease 2019
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENR	Enrolled
MMRM	Mixed Model Repeated Measure
ICF	Informed Consent Form
Mg	Milligram
Min	minute
mITT	Modified Intent-to-treat
NEB	Nebivolol
Pts	patients
PPAS	Per-Protocol Analysis Set
Q1	First Quartile
Q3	Third Quartile
Ram	Ramipril
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOP	Standard Operating Procedure
UPT	Urine Pregnancy Test

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol MEIN/22/NeRam-Hyp/001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 3.0, dated 13 July 2023.

The Inclusion and Exclusion criteria are detailed in the section 6.2 of the protocol.

2. STUDY OBJECTIVES AND ESTIMANDS

For the purpose of this study, uncontrolled BP is defined as sitting SBP/DBP ≥130/80 mmHg in patients < 65 years old and SBP/DBP ≥ 140/80 mmHg in patients ≥ 65 years old.

2.1. Primary Objective and Endpoint

The primary objective and endpoint is:

Primary Objective	Endpoint
To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5 mg, RAM 5 mg or RAM 10 mg in lowering sitting Systolic blood pressure (SBP) between Visit 2 (Week 0) and Visit 5 (Week 12) in patients with uncontrolled blood pressure (BP) previously treated with NEB 5 mg or RAM 5 mg monotherapies for at least 30 days.	Change in mean sitting SBP between Visit 2 (Week 0) and Visit 5 (Week 12).

2.2. Secondary Objectives and Endpoints

The secondary objectives are:

Secondary Objectives	Endpoint
To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg	Change in mean sitting DBP between Visit 2 (Week 0) and Visit 5 (Week 12).

with RAM 2.5 mg, RAM 5 mg or RAM 10 mg in lowering sitting Diastolic BP (DBP) between Visit 2 (Week 0) and Visit 5 (Week 12) in patients with uncontrolled BP previously treated with NEB 5 mg or RAM 5 mg monotherapies for at least 30 days.	
To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg in lowering sitting DBP and SBP between: • Visit 2 (Week 0) and Visit 3 (Week 4) • Visit 2 (Week 0) and Visit 4 (Week 8)	Change in mean sitting DBP and SBP between: • Visit 2 (Week 0) and Visit 3 (Week 4) • Visit 2 (Week 0) and Visit 4 (Week 8)
To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the standard BP goal (sitting BP < 140/90 mmHg) at Visit 5 (Week 12).	Number and proportion of patients achieving the standard BP goal (sitting BP < 140/90 mmHg) at Visit 5 (Week 12).
To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 5 (Week 12).	Number and proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 5 (Week 12).
To assess the adherence to the study treatment at Visit 2 (Week 0), at Visit 3 (Week 4), at Visit 4 (Week 8), and at Visit 5 (Week 12).	Adherence to treatment estimated as % of doses taken/doses to be taken at Visit 2 (Week 0), at Visit 3 (Week 4), at Visit 4 (Week 8), and at Visit 5 (Week 12).
To evaluate the safety and tolerability of the monotherapies (NEB 5 mg and RAM 5 mg) and of the Extemporaneous combinations (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg, NEB/RAM 5/10 mg).	Safety and tolerability of the monotherapies (NEB 5 mg and RAM 5 mg) and of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg, NEB/RAM 5/10 mg) measured by incidence, intensity (severity), seriousness of Adverse Events (AEs) during the study period, (screening, Run-in period and Assessment period), relationship to the study treatments, clinically significant abnormal change in vital signs, electrocardiogram (ECG), laboratory parameters and use of concomitant medications at Visit 2 (Week 0), Visit 3

	(Week 4), Visit 4 (Week 8) and Visit 5 (Week 12).

2.3. Exploratory Objectives and Endpoints

The exploratory objectives and Endpoints are:

• Exploratory Objectives	• Endpoints
To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the standard BP goal (sitting BP < 140/90 mmHg) at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8).	Number and proportion of patients achieving the standard BP goal (sitting BP < 140/90 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).
To assess the antihypertensive efficacy of the extemporaneous combination of NEB 5 mg with RAM 2.5/5/10 mg by evaluating the patients who achieved the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), at Visit 3 (Week 4), and at Visit 4 (Week 8).	Number and proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), and Visit 4 (Week 8).
To assess the antihypertensive efficacy in terms of sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population.	Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the overall population.
To evaluate sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) in patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies or who switched to NEB 5 mg or RAM 5 mg from any other beta blocker (BB) or angiotensin-converting enzyme inhibitors (ACEis) at Visit 1.	Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12) in the following subgroups: • in the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 and continued to be on the same therapies. • in the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BB or ACEi at Visit 1.

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

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

3. STUDY DESIGN

3.1. General Description

This is a Phase IV, interventional, multicenter, open-label, multinational study with 2 study periods (a Run-in period of 4 weeks and an Assessment period of 12 weeks) to assess the efficacy and safety of the extemporaneous combination of NEB and RAM in reducing SBP and DBP in hypertensive patients uncontrolled by monotherapy.

The trial will be conducted in approximately 26 investigational clinical sites in Bulgaria, Poland, and Hungary.

The total study duration is 16 weeks including a Run-in period of 4 weeks and an Assessment period of 12 weeks.

Note: For the purpose of this study, uncontrolled BP is defined as sitting SBP/DBP ≥130/80 mmHg in patients < 65 years old and SBP/DBP ≥ 140/80 mmHg in patients ≥ 65 years old.

Screening Visit 1 (Week -4):

Hypertensive patients with SBP ranging from ≥140 to ≤179 mmHg and/or DBP ranging from ≥90 to ≤109 mmHg on treatment, for at least 30 days prior to screening, with NEB 5 mg or any other BB, or RAM 5 mg or any other ACE-i will be screened for eligibility (Visit 1). Patients that did not meet eligibility criteria will be considered as screening failures and will not be re-screened.

Run-in period from Visit 1 (Week -4) to Visit 2 (Week 0):

On the same day of the Screening Visit, eligible patients will enter a Run-in period, during which:

- Patients receiving NEB 5 mg or RAM 5 mg will continue the same therapy for 4 weeks.

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

The study is designed in order to ensure that 1:1 ratio between patients in the NEB and RAM arms will be achieved.

Assessment period from Visit 2 (Week 0) to Visit 5 (Week 12):

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

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

After further 4 weeks ± 2 days (Week 8) the BP will be assessed again (Visit 4):
controlled patients will continue the same extemporaneous combination, while uncontrolled patients:if on NEB/RAM 5/2.5 mg, will be up-titrated to NEB/RAM 5/5 mg for further 4 weeks ± 2 days (Visit 5, Week 12);
if on NEB/RAM 5/5 mg, will be up-titrated to NEB/RAM 5/10 mg for further 4 weeks ± 2 days (Visit 5, Week 12).

At the end of the Assessment period (12 weeks ± 2 days), at Visit 5, the antihypertensive effect of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg or NEB/RAM 5/10 mg) will be evaluated.

To correctly evaluate the additional effect of the combination therapy, the number of patients with uncontrolled BP on NEB or RAM monotherapy needs to be balanced at Visit 2. To maintain a 1:1 ratio during the Assessment period, a cap of 110 patients for each treatment arm

(i.e., NEB and RAM) will be included at Visit 2 to maintain a balanced number of uncontrolled patients entering the Assessment period for each drug.

The evaluation will be done every 50 patients. If the entrance in the Assessment period for 1 of the 2 tested drugs will deviate more than 5%, a corrective measure will be initiated: according to the enrolment site statistics, 1 or more sites will be informed to enroll a greater number of patients being treated with the least represented drug in the Assessment period.

A total number of 270 patients will be screened, to obtain at least 215 completed patients at the end of the study (Visit 5) who have at least baseline and Week 12 assessments with primary efficacy data. For the sample size justification refer to section 12.2 of study protocol version 3.0.

Sitting BP will be measured at all visits before blood sampling. Blood Pressure will be measured in both arms at the Screening Visit (Visit 1) to detect possible between-arm differences. Three BP measurements will be performed for each arm. The arm with the higher mean DBP will be identified at screening and will be used in all subsequent visits for BP assessment. Blood pressure measurements should be performed as nearly as possible within the same time frame of the day (7:00 a.m. to 12:00 p.m.), on the same arm, possibly by the same trained member of the site staff/personnel and using the same calibrated automated device, provided by the Sponsor, at each visit.
Patients should be seated comfortably in a quiet environment for 5 minutes before beginning BP measurements.
Three BP measurements will be recorded, 1 to 2 minutes apart, and additional measurements only if the first 2 readings differ by >10 mmHg. The mean of the 3 recordings in sitting position will be used as the BP value for that visit. All BP measurements during the treatment phase will be performed as through readings (i.e., 24 + 2 hours after the last drug intake) using the same calibrated automated device, provided by the Sponsor. Study medication should be taken on the same time every day during the study; except the days of site visits, when study medication should be taken at the study center after all assessments mentioned as per study flow chart. At Visit 1 (Week -4) and Visit 5 (Week 12), a 12-lead ECG will be performed.

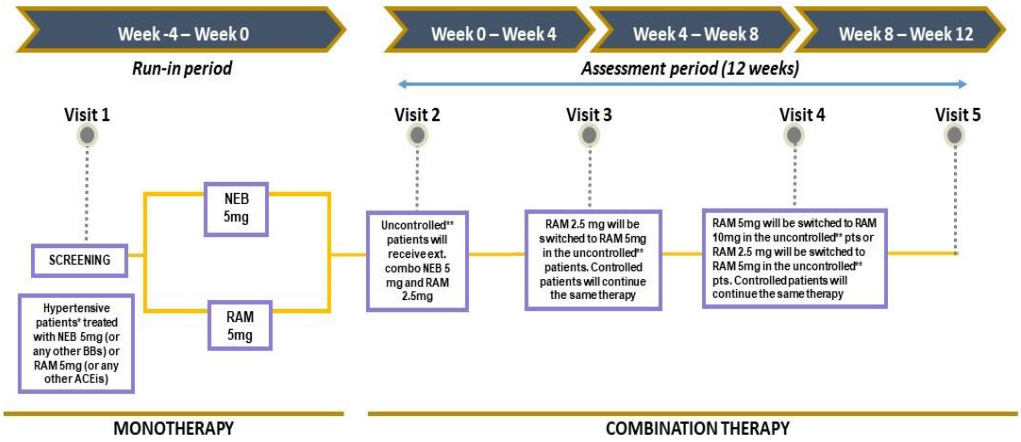
Safety (AEs, SAEs) will be measured at all visits. Any patient having an ongoing AE or SAE at the last visit, will be followed-up for further 2 weeks through a phone call to check about the status of the AE/SAE.

At any visit, in case of a clinically relevant laboratory test abnormality according to the Investigator's judgment, the patient will be contacted through a phone call within 24 hours.

3.2. Schedule of Events

Schedule of events can be found in Section 2.2 of the protocol.

Abbreviations: NEB = Nebivolol; BBs = Beta blockers; RAM = Ramipril; ACE-is = Angiotensin-converting enzyme inhibitors; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; pts = patients.
Note:
For the purpose of this study, uncontrolled BP is defined as sitting SBP/DBP ≥130/80 mmHg
There is no randomization procedure.



Patients treated with Ramipril or Nebivolol in dosages higher than 5 mg/daily will not be eligible.
* Systolic blood pressure ranging from ≥140 to ≤179 mmHg and diastolic blood pressure ranging from ≥90 to ≤109 mmHg.
** Sitting SBP/DBP ≥130/80 mmHg in patients < 65 years old and SBP/DBP ≥ 140/80 mmHg in patients ≥ 65 years old.

3.3. Summary of Change from Planned Analysis

After an Audit conducted by the Sponsor, the Site 114 has been closed for GCP non-compliance due to data quality issues. These data will be cleaned regularly, as for all other sites, but these will

not be included in the Modified Intent-to-Treat (mITT) and Per Protocol (PP) analysis sets. The Sponsor decision process and relevant assessment for the Site closurewill be summarized in the Clinical Study Report. To verify the impact of this exclusion on the study results, the primary efficacy analysis will be conducted both with data from site 114 and without data from site 114.

Data from this site will not be excluded from the safety analysis and sensitivity mITT analysis on primary efficacy endpoint (see chapter 16.4).

Moreover, also patients from Site 507 for whom "Primary efficacy source data are unavailable or unreliable" will not be included in the Modified Intent-to-Treat (mITT), as described in the chapters 5 and 16.4

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

- Separate Tables, Listings and Figures for final analysis are documented in TLF_Shells_Menarini_MEIN21AmNe-Hyp001_Final_V3.0. TLFs mock shells will be approved along with the SAP approval, and will not be changed without a SAP amendment.
- No interim analysis or analysis for DMC are expected to be executed.

4.1. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock and Sponsor Authorization of Analysis Sets.

5. ANALYSIS SETS

All population sets for analysis will be discussed with sponsor for statistical analysis during data review meeting and Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the database lock of the study.

After an Audit conducted by the Sponsor, the Site 114 has been closed for GCP non-compliance due to data quality issues. These data will be cleaned regularly, as for all other sites, but these will not be included in the Modified Intent-to-Treat (mITT) and Per Protocol (PP) analysis sets. The Sponsor decision process and relevant assessment for the Site closure will be summarized in the Clinical Study Report. To verify the impact of this exclusion on the study results, the primary efficacy analysis will be conducted both with data from site 114 and without data from site 114.

Data from this site will not be excluded from the safety analysis and sensitivity mITT analysis on primary efficacy endpoint (see chapter 16.4).

After two For Cause Audits (one conducted by CRO Indipendent QA Department and the other conducted by the Sponsor), patients from Site 507 for whom "Primary efficacy source data are unavailable or unreliable" will not be included in the Modified Intent-to-Treat (mITT) and so in the Per Protocol (PP) analysis sets. The Sponsor decision process and relevant assessment for the exclusion of these patients will be summarized in the Clinical Study Report. To verify the impact of this exclusion on the study results, the primary efficacy analysis will be conducted both with data from these patients and without data from these patients.

Data from these patients will not be excluded from the safety analysis and sensitivity mITT analysis on primary efficacy endpoint (see chapter 16.4).

5.1. All Subjects Enrolled Set [ENR]

The Enrolled (ENR) population will contain Patients who are enrolled into the study (i.e., signed ICF and met the eligibility criteria) and may or may not receive the study treatment (monotherapy and/or combination therapy).

5.2. Modified Intent-to-Treat Population [mITT]

The Modified Intent-to-Treat (mITT) population will contain all patients who are in the Enrolled population, receive at least one dose of combination therapy, and have at least baseline (Week 0) and Week 12 assessments with primary efficacy data. Data from Site 114 and data from patients of Site 507 excluded for primary efficacy source data unavailable or unreliable, will not be included in the Modified Intent-to-Treat (mITT) population (see chapter 3.3 and 5).

A sensitivity Modified Intent-to-Treat (mITT) primary endpoint analysis will be conducted for mITT population including all patients (see chapter 16.4).

5.3. Safety Analysis Set [SAF]

The Safety population will contain all patients who are in the Enrolled population and receive at least one dose of study medication (i.e., monotherapy and/or combination therapy).

5.4. Per Protocol Analysis Set [PPAS]

All patients included in the mITT population who do not have any major protocol deviations that could affect the primary efficacy analyses.

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It will appear in every listing where an assessment date or event date appears.

Reference start date (Day 1) is defined as the day of the first dose of combination therapy. Day before initiation of combination therapy will be consider from day -28 to day -1.

- If the date of the event is on or after the reference date, then:
- Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken same day or prior to reference start date (including unscheduled assessments) before first dose of study medication (monotherapy or combination therapy. Adverse Events (AEs) and medications commencing on the reference start date/time will be considered post-baseline, unless the start time of the AE is known to be prior to the first dosing of the study drug. Since there is no Lab assessment in Visit 2, Lab values collected at Visit 1 will be considered baseline for Lab data. For combination therapy related analysis, the baseline will be the measurements that are taken at Visit 2 (Week 0).

6.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries. Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. Windowing Conventions

Visit windowing will be consider as per protocol visit X ±2 days for this study.

6.5. Statistical Tests

The default significant level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.6. Common Calculations

For quantitative measurements, change from baseline will be calculated as:
- Test Value at Visit X – Baseline Value

And for change between Visit 3 and Visit 4 will be calculated as:
- Test Value at Visit 4 – Visit 3 Value

And for change between Visit 4 and Visit 5 will be calculated as:
- Test Value at Visit 5– Visit 4 Value

6.7. Software Version

All analyses will be conducted using SAS version 9.4 or higher (SAS Institute, Cary NC).

7. STATISTICAL CONSIDERATIONS

Summaries of continuous variables will include descriptive statistics (number of non-missing observations [n], mean, standard deviation [SD], median, minimum and maximum) and for categorical variables (the number of non-missing observations [n] and percentage), unless otherwise stated in the relevant section. Percentages will be based on the number of patients within the relevant analysis population and treatment arm, or the number of patients with data available where relevant.

If the original data has N decimal places, then the summary statistics will have the following decimal places:
Minimum and maximum: N
Mean, median, Q1, Q3, confidence intervals, ratios: N + 1
SD: N + 2
Percentages will be reported to one decimal place. P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001)

7.1. Adjustments for Covariates and Factors to be Included in Analyses

The following covariates and factors are used in the analyses.
- Treatment
- Age (eCRF page: Demography)
- Gender (eCRF page: Demography)
- Body Mass Index (eCRF page: Physical Examination)
- Baseline SBP
- For details of their inclusion in the models, see the specific analysis section

7.2. Multicenter Studies

This study will be conducted by multiple investigators at multiple centers internationally. Center pooling will not be carried out for use in analyses for this study.

7.3. Missing Data

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

7.4. Multiple Comparisons/ Multiplicity

Not Applicable.

7.5. Examination of Subgroups

Subgroup analyses will be conducted as stated in the exploratory analysis sections. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.
The following subgroups will be assessed and described within the exploratory analysis sections on ENR and mITT populations respectively.

- Hypertension grade at screening
- CHD
- Presence of diabetes (patients with or without diabetes) at screening
- Presence of hypercholesterolemia (patients with or without hypercholesterolemia) at screening

Hypertension grade at screening is derived as follows;
140 <= SBP < 160 or 90 <= DBP <100
160 <= SBP < 180 or 100 <= DBP <110

Patients with hypercholesterolemia at screening can be identified based on the clinical significance of the total cholesterol value collected in the blood chemistry laboratory data. If the total cholesterol at screening has clinical significance as per the investigator's input, then the patient will be considered for hypercholesterolemia and the details will be entered in the medical history data.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

9.1. Disposition

Patient disposition and withdrawals, including count and percentage of patients screened, screen failures, completed the study, discontinued the study, patient meets newly developed or not previously recognized and reason for discontinuation will be presented for the ENR population from eCRF page End of Study Treatment. Patient who discontinues from the study early will be asked to complete all the assessments of visit 5.
Number of patients in each population, including reasons for exclusion, will be presented for ENR population.
A listing of inclusion and exclusion criteria evaluation (met/not met) will be presented for the Screen Failures using ENR population. Subjects who withdraw prematurely can be part of any population (ENR, mITT or PP) depending on the individual follow-up characteristics and according to population derivation. Data collected on study patients up to the time of withdrawal must remain in the trial database.
If a patient does not meet one or more eligibility criteria required for participation in the trial during the screening procedures (Visit 1) should not be included in the ENR population**.** The patient disposition table will show the data referring to: Patient Screened (All patients), Patients Screen Failed, Patients Enrolled

> Screening Failures: Patients who consented to participate in the clinical trial by signing the ICF, but do not meet one or more eligibility criteria required for participation in the trial during the screening procedures (Visit 1), and subsequently are not assigned to the study treatment (monotherapy) or entered in the study are considered screening failures.

A patient who is in line with all I/E criteria at Visit 1, is enrolled (ENR population) and receive monotherapy, but then the results of the lab tests show that he cannot be enrolled must be considered a drop-out.

In case this study gets suspended or prematurely terminated, written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to study patients, Investigators, ECs, Sponsor and Regulatory Authorities with the reason(s) for the termination or suspension. Data will be analyzed till the communication from sponsor/authorities for suspension or termination of the study.

- Possible reasons for early termination or temporary suspension of the study include, but is not limited to:Study closure based on PI decision and/or,
- Study closure based on Sponsor decision and/or
- Study closure based on regulatory or other oversight bodies initiation and/or
- Review of serious, unexpected and related AEs and/or
- Non-compliance

- Lack of efficacy
- Lost to follow up
- Withdrawal by patient
- Patient meets newly developed or not previously recognized

9.2. Protocol Deviations

All protocol deviations (PD) will be discussed and reviewed on a case-by-case basis before the DBL at the data review meeting. All PDs reviewed by Sponsor will be documented.
Individual PDs will be presented in a data listing. The number and percentage of patients with Critical/Major PDs, patient who are excluded from the study will be summarized by deviation on ENR population. PD summary will be classified into "Monotherapy" and "Combination Therapy" based on the incidence date of PD. Additional Critical, Major and Minor PDs may be identified during data review and will be agreed upon with the Sponsor and reflected in the Tables and Listing as appropriate.
All PDs will be recorded and classified in IQVIA Clinical Trial Management System (CTMS) as per CS_WI_PL0038, Handling of Protocol Deviations and will be reviewed before the Data review Meeting (DRM). In DRM PDs will be categorized as minor/major/critical. Based on classification of identified PD the PP population will be confirm for the analysis.
The process by which the protocol deviation information will be obtained and used is to be discussed and agreed with the customer (refer to WI_PL0038, Handling of Protocol Deviations). For IQVIA managed clinical trials reference the Protocol Deviations Management Plan (CS_TP_PL0064): PDs category are also defined in the Artemisia PDMP.

9.3. COVID-19 IMPACT

The impact of COVID-19 on study related procedures are collected on 'COVID-19 Impact Log' in eCRF. Impact information which includes Assessment/Procedure Impacted, Type of Impact, and Reason for Impact will be presented in a summary table and a data listing for ENR population.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ENR population. No statistical testing will be carried out for demographic or other baseline characteristics.
The following demographic and other baseline characteristics will be reported for this study:

- Age (years)
- Age Category (<40 Years, ≥40 Years, <60 Years, ≥60 Years)
- Sex
- Childbearing potential
- Race
- Hypertensive Medication status at Screening (Visit 1)

NEB 5mg or RAM 5 mg
Other BBs or CCBs

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Presence of Type 2 diabetes mellitus at Screening (Yes/ No)
- Coronary Heart Disease (CHD) (Yes/No)
- Hypertension grade at Screening
- Presence of Hypercholesterolemia at Screening (with Hypercholesterolemia/ without Hypercholesterolemia)
- Mean sitting DBP at baseline (mmHg) selected arm (same dominant arm should be used throughout the study) component from vital sign page.
- Mean sitting SBP at baseline (mmHg) selected arm (same dominant arm should be used throughout the study) component from vital sign page.

10.1. Derivations

- BMI (kg/ m^2) = weight (kg)/ height (m)^2

11. MEDICAL HISTORY AND PROCEDURES

Medical History information will be presented by for the SAF Population.

- Medical History data captured on eCRF form "Medical History/Concurrent Diseases" and for medical procedures on eCRF form "Medical Procedures" will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 26. or latest) dictionary
    - Medical History conditions are defined as those conditions which were present prior to or at Screening.
    - Presented by SOC and PT.

A separate listing for Medical Procedures information collected on eCRF form "Medical Procedures" will be presented by Monotherapy and combination therapy for the SAF Population.

12. CONCURRENT DISEASE

Concurrent Disease will be presented for the SAF population.

- Concurrent Diseases will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 26.0 or latest) dictionary
    - Concurrent Diseases are conditions started prior to or at Screening and are ongoing at the date of Screening.
    - Presented by SOC and PT.

Concurrent Diseases conditions are defined as those conditions recorded in the eCRF form "Medical History/Concurrent Diseases"

13. PRIOR AND CONCOMITANT MEDICATIONS

Medications, recorded in the eCRF form "Prior and Concomitant Medications", will be presented for the SAF population and coded using WHO Drug dictionary Version 01SEP2022 or latest.
Frequency tabulations will be presented for prior and concomitant medications by primary therapeutic subgroup (3rd level ATC code) and preferred name for Monotherapy and Combination Therapy.
See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case, i.e., concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of monotherapy.
- 'Concomitant' medications are medications which:
    - started prior to, on or after the first dose of study medication,
    - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.
    - Concomitant medications that are started prior to the first dose of Combination Therapy will be summarized under "Monotherapy".

Concomitant medications that are started after the first dose of Combination Therapy will be summarized under "Combination Therapy"

14. STUDY MEDICATION EXPOSURE

Exposure to study medication for both Monotherapy and Combination therapy in days will be presented for the SAF population.
The date of first study medication administration will be taken from the eCRF "Exposure" form.
The date of last study medication will be taken from the eCRF "End of Study Treatment" form.
Interruptions, Adherence, and dose changes are not taken into account for duration of exposure.

14.1. Derivations

Duration of exposure (days) = date of last study medication administration – date of first study medication administration + 1.

15. STUDY MEDICATION ADHERENCE

Adherence with study treatment will be assessed at Visit 2 for monotherapy and Visit 3, Visit 4, and Visit 5 for the combination therapy and it will be presented for the SAF population.
A table consisting of summary statistics for percent Adherence along with the number and percent of patients with Adherence in each of the following groups:
Low: percentage of Adherence <80%

Normal: percentage of Adherence =>80% - <=120%
High: percentage of Adherence >120%

For patients who permanently stop the study medication, the “Date of Visit X(n)” will be replaced by the date of study withdrawal.

Adherence to study medication on SAF population for Monotherapy, and SAF population for Combination Therapy. By visit (Visit 2 for monotherapy and Visit 3, Visit 4 and Visit 5) and overall adherence will be produced for Combination Therapy.
A listing of drug accountability will be presented on SAF populations by phase to account for all drug distributed to each patient, including the box number, total number tablets dispensed, returned, consumed, lost (if any), percentage adherence and compliant (yes/no).
A listing of patient continuing the study (eCRF page: Subject Continuation) will be presented for SAF population for Subject's treatment adherence.

- ranging between 80% to 120%?,
- subject tolerate the treatment?,
- subject present uncontrolled BP
- subject continue to the next visit?.

A patient who has taken at least 80% and no more than 120% of the required study medication intake since the last visit will be considered as adherent.

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

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

At the end of the Assessment period (12 weeks ± 2 days) at Visit 5, the antihypertensive effect of the extemporaneous combination (NEB/RAM 5/2.5 mg, NEB/RAM 5/5 mg or NEB/RAM 5/10 mg) will be evaluated.

15.1. Derivations

Monotherapy and Combination Therapy adherence with study drug based on the drug accountability data will be calculated as the number of doses taken during the study x 100 / number of doses to be taken during the study expressed as a percentage.
For Monotherapy, the expected number of doses to be taken = (Treatment End Date – Treatment Start Date) + 1.
For Combination Therapy, the expected number of doses to be taken = 2 * ((Treatment End Date – Treatment Start Date) + 1).
For patients who permanently stop the study medication (i.e., monotherapy and/or combination therapy), the expected number of tablets will be calculated up-to the date of study withdrawal.

16. EFFICACY OUTCOMES

16.1. Primary Efficacy

16.1.1. Primary Efficacy Variable(s) & Derivation(s)

The primary efficacy variable is Change in mean sitting SBP between Visit 2 (Week 0) and Visit 5 (Week 12). Blood pressure and pulse measurements will be assessed with the same calibrated automated device, provided by the Sponsor, at each visit.

16.1.2. Intercurrent Event Handling and Data Imputation for Primary Efficacy Variable(s)

Not Applicable.

16.1.3. Primary Analysis of Primary Efficacy Variable(s)

The primary objective of this study is to test the hypothesis that
H0: There is no change in the sitting SBP prior or post combination therapy.
H1: There is a difference in the sitting SBP prior or post combination therapy.

The above hypothesis will be tested as following:
Change from baseline in sitting SBP from prior and post combination therapy will be tested using paired t-test. The 2-sided p-value obtained from the paired t-test will be presented.

The primary efficacy analysis will be performed for the mITT population. Site 114 patient data will be removed from the mITT population due to site closure for GCP non-compliance issues. To verify the impact of this exclusion on the study results, the primary efficacy analysis will be conducted both with data from site 114 and without data from site 114.

Assumption of Normality will be investigated using Wilk-Shapiro test. If the p-value is greater than .05, it means we cannot reject the null hypothesis that a variable is normally distributed. 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.

Only those patients for whom we have SBP assessment results available at both Baseline (Week 0) and Week 12 will be considered. If baseline (Week 0) SBP value is missing the patient is not included in the mITT population.

16.1.4. Supplementary Analysis of Primary Efficacy Variable(s)

A repeated measure mixed model (MMRM) will be performed on the primary efficacy endpoint to test the covariate effects and the effects of interactions between the covariates for the only mITT population. The MIXED model will include change in mean sitting SBP as the dependent variable, repeated through visits Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12). Age (years), gender, body mass index (BMI), and baseline SBP are considered as the covariates.
The MIXED model is
SBP Change from Baseline = Visit + Age + Gender + BMI + baseline SBP + Age*Gender + Age*BMI + Age*baseline SBP + Gender*BMI + Gender*baseline SBP + BMI*baseline SBP + Age*Gender*BMI + Age*Gender*baseline SBP + Age*BMI*baseline SBP + Gender*BMI*baseline SBP + Age*Gender*BMI*baseline SBP
A PROC MIXED procedure, with an unstructured covariance matrix, is used for the analysis and the corresponding two-sided p-values for each of the covariates will be presented in a table.
If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity, compound symmetry, autoregressive with heterogeneity, toeplitz, and autoregressive. Smaller value of AIC and BIC will be considered for selection of best fit for covariance structure.

16.1.5. Sensitivity Analysis of Primary Efficacy Variable(s)

The sensitivity analyses will be conducted similar to the primary efficacy analysis including the paired t-test using the PP population.

16.2. Secondary Efficacy

Secondary efficacy variables will be analyzed using both the mITT as well as the PP population.

16.2.1. Secondary Efficacy Variables & Derivations

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

- Change in mean sitting DBP and SBP

Change in mean sitting SBP and DBP between Visit 2 (Week 0) and Visit 3 (Week 4).

- Change in mean sitting DBP and SBP

Change in mean sitting DBP between Visit 2 (Week 0) and Visit 5 (Week 12).
Change in mean sitting DBP and SBP between Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) in patients under extemporaneous combination of NEB/RAM 5/2.5 mg versus patients uptitrated to the extemporaneous combination of NEB/RAM 5/5 mg or NEB/RAM 5/10 mg.
Number and proportion of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12).
Number and proportion of patients achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12).

16.2.1.1. CHANGE IN MEAN SITTING SBP AND DBP BETWEEN VISIT 2 (WEEK 0) AND VISIT 3 (Week 4)

Change from baseline in sitting SBP and DBP from prior and post combination therapy will be compared using paired t-test. The p-value will be presented using a paired t-test comparing mean at baseline and mean at Week 4. The secondary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum. Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.
Additionally, the secondary end point of change in SBP and DBP between Visit 2 and Visit 3 will be analyzed using a repeated measures mixed model MMRM as described in Section **Error! Reference source not found.** with Age (Years), Gender, body mass index, and baseline BP (SBP or DBP) as covariates to identify the effect of covariates and interaction between the covariates.

16.2.1.2. CHANGE IN MEAN SITTING SBP AND DBP BETWEEN VISIT 2 (WEEK 0) AND VISIT 4 (Week 8)

Change from baseline in sitting SBP and DBP from prior and post combination therapy will be compared using paired t-test. The p-value will be presented using a paired t-test comparing mean at baseline and mean at Week 8. The secondary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum. Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.
Additionally, the secondary end point of change in SBP between Visit 2 and Visit 4 will be analyzed using a repeated measures mixed model MMRM as described in Section **Error! Reference source not found.** with Age (Years), Gender, body mass index, and baseline BP (SBP or DBP) as covariates to identify the effect of covariates and interaction between the covariates.

16.2.1.3. CHANGE IN MEAN SITTING DBP BETWEEN VISIT 2 (WEEK 0) AND VISIT 5 (WEEK 12)

Change from baseline in sitting DBP from prior and post combination therapy will be compared using paired t-test. The p-value will be presented using a paired t-test comparing mean at baseline and mean at Week 12. The secondary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum. Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.
Additionally, the secondary end point of change in DBP between Visit 2 and Visit 5 will be analyzed using a repeated measures mixed model MMRM as described in Section 16.1.4 with Age (years), Gender, body mass index, and baseline DBP as covariates to identify the effect of covariates and interaction between the covariates.

16.2.1.4. CHANGE IN MEAN SITTING DBP AND SBP BETWEEN VISIT 3 (WEEK 4) AND VISIT 4 (WEEK 8)

Change in sitting SBP and DBP between patients under extemporaneous combination of NEB/RAM 5/2.5 mg versus patients uptitrated to the extemporaneous combination of NEB/RAM 5/5 mg will be compared using independent samples t-test. The secondary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum. Assumption of normality will be investigated using Wilk-Shapiro test. If the data is found to be non-Normal, the independent samples t-test will be replaced by Wilcoxon rank-sum test.

16.2.1.5. CHANGE IN MEAN SITTING DBP AND SBP BETWEEN VISIT 4 (WEEK 8) AND VISIT 5 (WEEK 12)

Change in sitting SBP and DBP between patients under extemporaneous combination of NEB/RAM 5/5 mg versus patients uptitrated to the extemporaneous combination of NEB/RAM 5/10 mg will be compared using independent samples t-test. The secondary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum. Assumption of normality will be investigated using Wilk-Shapiro test. If the data is found to be non-Normal, the independent samples t-test will be replaced by Wilcoxon rank-sum test.

16.2.1.6. NUMBER AND PROPORTION OF PATIENTS ACHIEVING THE STANDARD BP GOAL

The number of patients achieving the BP goal (sitting BP < 140/90 mmHg) will be summarized for Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) along with percentage and 95% CI (Clopper Pearson). A p-value using McNemar's test, or exact McNemar's test proposed when one of the cell frequency is 0, will be presented to compare the proportion of patients achieving the Standard BP goal (sitting BP < 140/90 mmHg) between Visit 2 and Visit 3, Visit 2 and Visit 4, Visit 2 and Visit 5, and, as well as, between Visit 3, Visit 4 and Visit 5.

16.2.1.7. NUMBER AND PROPORTION OF PATIENTS ACHIEVING THE OPTIMAL BP GOAL(SITTING BP < 130/80 MMHG IN PATIENTS < 65 YEARS OLD/SITTING BP < 140/80 MMHG IN PATIENTS ≥ 65 YEARS OLD)

The number of patients achieving the BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) will be summarized for Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) along with percentage and 95% CI (Clopper Pearson). A p-value using exact McNemar's test will be presented to compare the proportion of patients achieving the BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) between Visit 2 and Visit 3, as well as Visit 2 and Visit 4 as well as Visit 2 and Visit 5. 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 3, Visit 4 and Visit 5.

16.3. Exploratory Efficacy

16.3.1. Exploratory Efficacy Variables & Derivations

Change in mean sitting DBP and SBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12):

- In the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.
- In the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACEs 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).
To assess change in mean sitting DBP and SBP, for uncontrolled patients at Visit 4 (Week 8), between Visit 2 (Week 0) and Visit 4 (Week 8) and between Visit 3 (Week 4) and Visit 4 (Week 8).
Number and proportion of patients achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12):
In the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.
In the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACEs at Visit 1 (Week 4).
Number and proportion of patients the optimal BP goal (sitting BP < 130/80 mmHg in patients <65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12):
In the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.
In the group of patients who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACEs at Visit 1 (Week 4).

Number and proportion of patients divided into subgroups according to the hypertension grade, CHD**,** the presence of diabetes and/or of hypercholesterolemia achieving the standard BP goal (sitting SBP/DBP < 140/90 mmHg) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12).
In the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.
In the group of patients, who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACEs at Visit 1.

Number and proportion of patients divided into subgroups according to the hypertension grade, CHD**,** the presence of diabetes and/or of hypercholesterolemia achieving the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) at Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12).
In the group of patients who were on NEB 5 mg and RAM 5 mg at Visit 1 (Week -4) and continued to be on the same therapies.
In the group of patients, who switched to NEB 5 mg or RAM 5 mg from any other BBs or ACEs at Visit 1.

16.3.2. Analysis of Exploratory Efficacy Variables

Exploratory efficacy variables will be summarized in a descriptive manner using ENR and mITT populations for Visits 1, 2, 3, 4 and 5.
Change in sitting DBP and SBP from Visit 1 (Week -4) will be using paired t-test. The p-value obtained from the paired t-test will be presented for the visits - Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12). Assumption of Normality will be investigated using Wilk-Shapiro test. If the data is found to be non-Normal, then paired t-test will be replaced by Wilcoxon signed rank test. A descriptive summary using n, mean, median, SD, Q1, Q3, minimum, and maximum is also presented.
Change in mean sitting DBP and SBP for uncontrolled patients between Visit 2 (Week 0) and Visit 3 (Week 4) will be using paired t-test. The p-value obtained from the paired t-test along with n, mean, median, SD, Q1, Q3, minimum, and maximum will be presented. Assumption of Normality will be investigated using Wilk-Shapiro test. If the data is found to be non-Normal, then paired t-test will be replaced by Wilcoxon signed rank test.
The number of patients achieving standard BP goal (sitting BP < 140/90 mmHg) will besummarized for Visits 2, 3, 4 and 5, along with percentage and 95% CI for the proportion. A p-value using exact McNemar's test will be presented to compare the proportion of patients achieving the standard BP goal (sitting BP < 140/90 mmHg) between Visit 2 and Visit 3 as well as Visit 2 and Visit 4 and as well as Visit 2 and Visit 5. A p-value using McNemar's test will be presented to compare the proportion of patients achieving the BP goal (sitting BP < 140/90 mmHg) between Visit 3 and Visit 4. A two-sided p-value using McNemar's test between Visit 3 vs. Visit 5 and between Visit 4 vs. Visit 5.

The number of patients achieving optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) will be summarized for Visits 2, 3, 4 and 5, along with percentage and 95% CI for the proportion. A p-value using exact 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 as well as Visit 2 and Visit 4 and as well as Visit 2 and Visit 5. 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 3 and Visit 4. A two-sided p-value using McNemar's test between Visit 3 vs. Visit 5 and between Visit 4 vs. Visit 5.

The number of patients achieving standard BP goal (sitting SBP/DBP < 140/90 mmHg) and the optimal BP goal (sitting BP < 130/80 mmHg in patients < 65 years old/sitting BP < 140/80 mmHg in patients ≥ 65 years old) will be summarized for Visits 2, 3, 4 and 5, along with percentage for each of the subgroup specified under section 7.5 of the SAP.

16.4 Sensitivity Analysis Including Data from Site(s) with Data Quality Issues

For Site 114 excluded for data quality issues, sensitivity analysis will be performed including data on the primary efficacy endpoint.

For the patients from Site 507 excluded for primary efficacy source data unavailable or unreliable data, sensitivity analysis will be performed including data on the primary efficacy endpoint.

Variable	Analysis set	Analysis type
Change in mean sitting SBP between Visit 2 (Week 0) and Visit 5 (Week 12)	mITT including all patients (all patients from Site 114 and Site 507)	Paired t-test

In the case of a significant difference between the results of the two primary efficacy analyzes (mITT vs. mITT including all patients), the efficacy outcome (primary, secondary and exploratory) variables will be analyzed using both the mITT as well as the "mITT including all patients" population. All results of the "mITT including all patients" analysis will be reported in the CSR.

Data from Site 114 and from those patients from Site 507 for whom primary efficacy data are unavailable or unreliable will not be excluded from the safety analysis.

17. QUALITY OF LIFE ANALYSIS

Not applicable.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.
The primary safety endpoint will be summarized with counts and percentage of patients reporting any TEAEs and patients with at least one or any TEAE with corresponding 95% CI using exact binomial method, with two-sided p-value will be presented.

18.1. Adverse Events

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 26.0 or latest.
Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the date/time of the first administration of study medication (i.e., monotherapy and/or combination therapy) or worsen if an AE started prior to the start of first administration of study medication.
TEAEs that occurred or worsened on or after the date/time of the first administration of Monotherapy but before the date/time of the first administration of Combination Therapy will be summarized under "Monotherapy".
TEAEs that occurred or worsened on or after the date/time of the first administration of Combination Therapy will be summarized under "Combination Therapy".
Related Adverse Events: adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (i.e. no answer to the question "Relationship with study treatment"). all AEs occurred after the study drug intake (monotherapy and/or combination), regardless of the causality relationship (related or not-related), have to be reported in AE pages of eCRF and should be managed.
Serious Adverse Events (SAE): serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
Adverse Events Leading to Treatment Discontinuation: adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e., treatment emergent.
An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates.
Listings will include TEAEs and Non-TEAEs.

18.1.1. All TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication (i.e., monotherapy and/or combination therapy).

The following tables will be created:
The overall summary of AEs table will include the following categories:

- TEAEs
- Related TEAEs
- TEAEs leading to permanent treatment discontinuation
- Related TEAEs leading to permanent treatment discontinuation
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death
- Related TEAEs leading to death

18.1.1.1. SEVERITY

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication (i.e., monotherapy and/or combination therapy) with a missing severity will be classified as severe. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

18.1.1.2. RELATIONSHIP TO STUDY MEDICATION

Relationship, as indicated by the Investigator, is classed as "Not Related", "Related" (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship to study medication (i.e., monotherapy and/or combination therapy) as "Certain Related", "Probable Related", "Possible Related" or "Unassessable" to study medication. TEAEs with a missing relationship to study medication will be regarded as "Probable Related" to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

18.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication (i.e., monotherapy and/or combination therapy) are those events for which "Action Taken with Study Treatment" is recorded as "Drug withdrawal" on the Adverse Event page of the eCRF.
For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

18.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be prepared.

18.1.4. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as “Fatal” for the Outcome field on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

18.2. Deaths

If any patients die (eCRF page: End of Study Treatment) during the study, the information will be presented in a summary table and a data listing using SAF population. If a patient died during Monotherapy (eCRF page: End of Study Treatment, Variable: Reason treatment not completed), then the data will be summarized under Monotherapy, else the summary will be provided under Combination Therapy.

18.3. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology (eCRF page: Local Laboratory Results: Hematology), Serum Chemistry (eCRF page: Local Laboratory Results: Chemistry), Urine Pregnancy Test (eCRF page: Urine Pregnancy Test), and Coagulation (eCRF page: Local Laboratory Results: Coagulation). A list of laboratory assessments to be included in the outputs is included in protocol Section 8.2.3.
Presentations will use SI Units.
The following summaries will be provided for laboratory data:
Quantitative data will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each nominal visit over time. Changes from baseline at each nominal visit over time will also be presented in boxplots. End of Treatment visit will be summarized separately. Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, High).

All lab tests (at screening and any further scheduled control during the study), should be recorded in “lab test pages of the CRF” and only a new and clinically significant (CS) or a CS worsening of lab test after stud drug administration (monotherapy and/or combination therapy), should be recorded in the CRF AE pages.

If both central and local labs are collected for a patient, these summary statistics by visit will be based only on the central lab collected data, while summaries of worst during-treatment abnormalities will be based on both local and central lab data.

- Actual and change from baseline by visit (for quantitative measurements) for Monotherapy and Combination Therapy using SAF population.
- shifts from baseline normal to at least one result above normal
- shifts from baseline normal to at least one result below normal

- A patient may present a lab test change from baseline also after monotherapy. In this case if the patient doesn’t start the combination phase (for any reason), a clinically significant change compared to baseline lab after the monotherapy should also be recorded and evaluated.

- All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information on the eCRF.
- Urinalysis: all urinalysis parameters
- Pregnancy test
- Listings of laboratory results will be provided for all laboratory parameters. These listings will be sorted by parameters and assessment dates or visits for each patient; laboratory values that are outside the normal range will be flagged along and corresponding normal ranges will be provided.
- In addition, listings of abnormal values will be provided for chemistry, hematology and urinalysis parameters. If there is at least one abnormal result for any parameter, all the data for that parameter will be included in the listing.
- For all tests not mentioned above but present in the clinical data, a listing of patients with at least one result for the relevant test will be provided.

A by-patient listing of all laboratory data and pregnancy test data will be presented for both Monotherapy and Combination therapy using the SAF population.

18.4. ECG Evaluations

The following ECG (eCRF page: 12 Lead ECG) parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- RR Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) [derived]
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)
    - The 12-lead Electrocardiogram (ECG) assessment will be performed during screening (baseline) and at the Discontinuation / End-of-Treatment visit. For each of the ECG parameters, descriptive statistics at baseline and at the Discontinuation / End-of-Treatment visit and changes from baseline will be summarized by treatment group.

    - The incidence and percentage of patients with the worst potentially clinically significant abnormalities (PCSA) for ECG parameters will be summarized during the on-treatment period. Each patient will be counted only once within each category. As ECG assessments are only performed during screening and at the Discontinuation/End-of-Treatment visit, the denominator to calculate percentages for each PCSA category is the number of patients with Discontinuation/End of Treatment visit.

Test	Potentially Clinically Significant Abnormalities (PCSA) Criteria

Heart Rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
PR Interval	≥ 220 ms and increase from baseline ≥ 20 ms
QRS	≥ 120 ms
QTcF and QTcB absolute	>450 ms >480 ms >500 ms
QTcF and QTcB change from baseline ○	Increase from baseline > 30 ms Increase from baseline > 60 ms

QTc will be corrected based on Fridericia's formula for QTcF and Bazett's formula for QTcB (QTcF= QT/$\sqrt[3]{RR}$ and QTcB= QT/$\sqrt{RR}$) where RR=60/heart rate. Baseline QTcF and QTcB will be derived from the visit that ECG parameters are flagged as baseline.

QT Scale	Male (msec)	Female (msec)
Very Short QT	330	340
Short QT	360	370
Normal QT	390	400
Long QT	450	460
Very Long QT	470	480

A QTc interval of at least 480 milliseconds is a predictor for increased risk for symptoms, whereas a QTc of at least 00 milliseconds predicts an increased risk of life-threatening cardiac events.
A categorical summary of QTcF interval and QT interval corrected by Bazett's formula (QTcB) will be provided using counts and percentages at Baseline and maximum postbaseline by treatment for the following categories:

- Result ≤450 msec;
- Result >450 and ≤480 msec;
- Result >480 and ≤500 msec;
- Result >500 msec;
- Change from Baseline ≤30 msec;
- Change from Baseline >30 and ≤60 msec;
- Change from Baseline >60 msec.

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements).
- Shift from baseline of ECG Interpretation Results.

ECG parameters recorded in eCRF form "12 Lead ECG", will be summarized using the SAF population for the monotherapy and Combination therapy. All ECG data will be listed for both Monotherapy and Combination Therapy using the SAF population.
A listing of abnormal 12-lead ECGs will be provided with all relevant information and derived variables.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes.

18.5. Vital Signs

The following Vital Signs (eCRF page: Vital Signs) measurements will be reported for this study:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature (^{0} C)
- All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each planned visit over time. Discontinuation/End of Treatment visit will be summarized separately. The changes computed will be the differences from baseline.
- The maximum on-treatment change from baseline will be calculated and categorized by vital sign measurement. Missing values will define a separate category. A summary of maximum shift from baseline by category will be provided by treatment arm.
- Categories of Change from Baseline for Vital Sign Parameters

Parameters	Categories of Change from Baseline
• Body temperature increase	• < 1 Ċ , 1-<2 Ċ , 2-<3 Ċ, ≥ 3 Ċ
• Weight increase	• <10%, ≥ 10%
• Weight decrease	• <10%, ≥ 10%
Heart rate increase from baseline • <100 bpm ; ≥ 100 bpm	• ≤20 bpm, >20 – 40 bpm, >40 bpm
Heart rate decrease from baseline • <100 bpm ; ≥ 100 bpm	• ≤20 bpm, >20 – 40 bpm, >40 bpm
SBP increase from baseline • <130 mmHg; ≥ 130 mmHg for age <65	• ≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline • <130 mmHg; ≥ 130 mmHg, for age <65	• ≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP increase from baseline • <140 mmHg; ≥ 140 mmHg for age ≥65	• ≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline • <140 mmHg; ≥ 140 mmHg, for age ≥65	• ≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP increase from baseline • <80 mmHg; ≥ 80 mmHg	• ≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP decrease from baseline • <80 mmHg; ≥ 80 mmHg,	• ≤20 mmHg, >20 – 40 mmHg, >40 mmHg

Respiration rate increase from baseline <20 • breaths/min; ≥ 20 breaths/min	• ≤5 breaths/min, >5 – 10 breaths/min, >10 breaths/min
Respiration rate decrease from baseline <20 • breaths/min; ≥ 20 breaths/min	• ≤5 breaths/min, >5 – 10 breaths/min, >10 breaths/min

- bpm = beats per minute; DBP=diastolic blood pressure; SBP=systolic blood pressure, min=minute.

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit for Monotherapy and Combination therapy using the SAF population.

Blood pressure and pulse measurements will be assessed with the same calibrated automated device, provided by the Sponsor, at each visit.
A by-patient listing of all vital signs data will be presented for both Monotherapy and Combination therapy using the SAF population.

18.6. Physical Examination

The following summaries will be provided for physical examination data for combination therapy by visit on SAF population:
The Physical examination will include general appearance, skin and mucosa, Superficial lymph nodes, head and neck, chest, abdomen, Musculoskeletal system, height, weight, BMI and Neurological system.

- Shift from baseline according to the physical examination findings from eCRF page (Physical Examination).

Physical Examination parameters will be summarized using the SAF population for the Monotherapy and Combination therapy. All Physical Examination data will be listed for both Monotherapy and Combination Therapy using the SAF population.

18.7. Other Safety Assessments

No other safety assessment will be collected for this study.

19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments
- Contacts

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

20. REFERENCES

Dobson, A. J. (2002). *An introduction to generalized linear models, 2nd ed.* Chapman & Hall/CRC.

EMA. (n.d.). *Guideline on Missing Data in Confirmatory Clinical Trials.* Retrieved December 15, 2011, from European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

Little, R., & Yau, L. (1996). Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. *Biometrics* , vol 52, 1324-1333.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following:

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in the given order:

Therapy	Treatment Group	For Tables, Listings and Figures
Monotherapy	NEB 5mg	NEB 5mg
Monotherapy	RAM 5mg	RAM 5mg
Combination Therapy	NEB+RAM (2.5mg)	NEB (5mg) + RAM (2.5mg)
Combination Therapy	NEB+RAM (5mg)	NEB (5mg) + RAM (5mg)
Combination Therapy	NEB+RAM (10mg)	NEB (5mg) + RAM (10mg)

Presentation of Visits

For outputs, visits will be represented as follows and in that order:
Visit 1 (Week -4)
Visit 2 (Week 0)
Visit 3 (Week 4)
Visit 4 (Week 8)
Visit 5 (Week 12)
Early Termination

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening (Visit 1)	Scr (V1)
Baseline (Week 0) or Visit 2 (Week 0)	BL (W0) or V2 (W0)
Visit 3 (Week 4)	V3 (W4)
Visit 4 (Week 8)	V4 (W8)
Visit 5 (Week 12)	V5 (W12)
Early Termination	ET

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):
- Treatment group (Monotherapy and Combination Therapy),
- Center-patient ID,
- Date (where applicable).

Reference Code

- Paired t-test

```
ods trace on;
proc ttest data=input_data h0=0;
   paired VISITX*VISITY;
   ods output TTests=test;
run;
ods trace off;
```

- Normality assumption check

```
ods trace on;
proc univariate data=indata normal plot;
   var change from baseline;
   histogram /normal kernel(color=red);
   ods output TestsForNormality=norm(where=(test="Shapiro-Wilk"));
   run;
ods trace off;
```

- Wilcoxon Signed Rank Test

```
ods trace on;
proc univariate data=indata mu0=0 loccount;
   var change from baseline;
   ODS Output TestsForLocation=test LocationCounts=LOCC_one;
run;
```

- Exact McNemars Test

```
ods trace on;
ods output McNemarsTest=McNemarsTest;
proc freq data=indata order=data;
   tables VISITX*VISITY/agree alpha=0.05 ;
   exact mcnem;
   weight ZZZ/zeros;
run;
```

- Independent sample t-test

```
ods trace on;
proc ttest data=indata h0=0;
class xxx;
var change from baseline;
run;
ods trace off;
```

- Wicoxon Rank Sum Test

```
ods trace on;
proc npar1way data=indata wilcoxon;
   by by_variables;
   class xxx;
   var change from baseline;
   ods output WilcoxonTest=wt;
run;
```

- Repeated measures Mixed Model

```
proc mixed data=indata;
class visit sex;
model change from baseline = Visit Age Gender BMI baseline_SBP Age*Gender
Age*BMI_Age*baseline_SBP Gender*BMI Gender*baseline_SBP BMI*baseline_SBP
Age*Gender*BMI_Age*Gender*baseline_SBP Age*BMI*baseline_SBP Gender*BMI*baseline_SBP
Age*Gender*BMI*baseline_SBP;
repeated visit;
    run;
```

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment

START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant