STATISTICAL ANALYSIS PLAN

MEIN/21/AmNe-Hyp/001

Open-laBel, multicenter, multinatiOnal, inTerventional clinical Trial to assess efficacy and safety of the extemporaneous Combination of nEbivoLol and amLodipine in grade 1-2 hypertensive patlents versus each monotherapy – BOTTICELLI Study

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V1.0 (Dated 11Nov2022) for Protocol MEIN/21/AmNe-Hyp/001.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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Final V1.0	11Nov2022	Aswin Nair	Not Applicable – First Version

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AML	Amlodipine
ATC	Anatomical Therapeutic Chemical
BBs	Beta-Blockers
BP	Blood Pressure
CCBs	Calcium Channel Blockers
COVID-19	Coronavirus Disease 2019
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENR	Enrolled
GLM	General linear model
ICF	Informed Consent Form
mITT	Modified Intent-to-treat
NEB	Nebivolol
PP	Per-Protocol
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation

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/21/AmNe-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 1.0, dated 27 September 2021.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. Primary Objective

The primary objective is 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.

2.2. Secondary Objectives

The secondary objectives are

- 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 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.

2.3. Exploratory Objectives

The exploratory objectives are

- 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):
    1. 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.
    2. 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):
    1. 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.
    2. 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):
    1. 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.
    2. In the group of patients, who switched to NEB 5 mg or AML 5 mg from any other BBs or CCBs at Visit 1.

3. STUDY DESIGN

3.1. General Description

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). Patients with 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. 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 CCBsc 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. 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).

3.2. Schedule of Events

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

3.3. Changes to Analysis from Protocol

- The secondary and exploratory analysis use McNemar's test to analyze proportion of patients achieving BP goal (SBP/DBP <130/80 mmHg) between visit 2, visit 3, and visit 4. As per the entry criteria to the combination therapy, only those patients with uncontrolled BP (SBP/DBP > =130/80 mmHg) at visit 2 are eligible. So, the proportion of patients achieving the BP goal at visit 2 will be always zero. Thus, SAP has been updated with exact McNemar's test instead of McNemar's test when comparing the counts with respect to visit 2.
- As per protocol, the definition of Per Protocol Population is "All patients included in the Safety population who do not have any major protocol deviations that could affect the analyses.". In SAP, this has been updated to,
  "The Per-Protocol (PP) population will contain all patients included in the Safety population who do not have any major protocol deviations that could affect the primary efficacy analyses and have at least baseline (Week 0) and Week 8 assessments with primary efficacy data".
- As per protocol, the definition of ENR Population is "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)." In SAP, this has been updated to,
  "The Enrolled (ENR) population will contain all patients who are enrolled into the study (i.e. signed ICF and met the eligibility criteria) and may or may not receive the study medication (i.e., monotherapy and/or combination therapy). An enrolled patient who does not meet the inclusion/exclusion criteria might be included in the ENR population as per the investigator discretion.".
- As per protocol, Compliance to study medication will be summarized for Enrolled and Safety populations. In SAP, this has been updated to consider the summary based on SAF and mITT because Safety population will include monotherapy patients and thus analysis on ENR is not required.

- As per protocol, exploratory efficacy analyses will be summarized for Enrolled population. In SAP, this has been updated to include summary based on mITT population as well.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

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, Sponsor Authorization of Analysis Populations.

5. ANALYSIS POPULATION

Agreement and authorization of patients included/excluded from each analysis population will be conducted prior to the database lock of the study.

5.1. Enrolled [ENR] Population

The Enrolled (ENR) population will contain all patients who are enrolled into the study (i.e. signed ICF and met the eligibility criteria) and may or may not receive the study medication (i.e., monotherapy and/or combination therapy). An enrolled patient who does not meet the inclusion/exclusion criteria might be included in the ENR population as per the investigator discretion.

5.2. Modified Intent-to-Treat (mITT) Population

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 and Week 8 assessments with primary efficacy data.

5.3. Safety (SAF) Population

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 (PP) Population

The Per-Protocol (PP) population will contain all patients included in the Safety population who do not have any major protocol deviations that could affect the primary efficacy analyses and have at least baseline (Week 0) and Week 8 assessments with primary efficacy data.

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 is defined as the day of the first dose of study (combination therapy) (Visit 2), (Day 1 is the day of the first dose of study drug).

- 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 (i.e., 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). For safety analysis, if the measurement at visit 2 is missing or not collected, then visit 1 data will be considered.

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

No visit window conventions are applicable 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

6.7. Software Version

All analyses will be conducted using SAS Enterprise Guide version 8.2.

7. STATISTICAL CONSIDERATIONS

Summaries will include descriptive statistics for continuous variables (sample size [n], mean, standard deviation [SD], median, minimum and maximum) and for categorical variables (frequency [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/factors are used in the analyses.

- Treatment
- Age
- Gender
- Body Mass Index
- Baseline DBP

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
- 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 presence of diabetes and hypercholesterolemia at screening will be identified from the medical history data using the preferred terms. Presence of diabetes can be identified using the preferred terms "Diabetes mellitus" Or "Type 2 diabetes mellitus" and hypercholesterolemia using "Dyslipidaemia" or "Hypercholesterolaemia" or "Hyperlipidaemia" or "Type IIa hyperlipidaemia" or "Type V hyperlipidaemia".

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 will be presented for All Patients.
Number of patients in each population, including reasons for exclusion, will be presented for ENR population.
A listing of inclusion and exclusion criteria will be presented for the Screen Failures.

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 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 Table and Listing as appropriate.
All PDs will be recorded and classified in Clinical Trial Management System (CTMS) before the Data review Meeting.

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)
- Sex
- Childbearing potential
- Race
- Hypertensive Medication status at Screening (Visit 1)
  - NEB 5mg or AML 5 mg
  - Other BBs or CCBs
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Presence of Type 2 diabetes mellitus at Screening (Yes/ No)
- Hypertension grade at Screening
- Presence of Hypercholesterolemia at Screening (with Hypercholesterolemia/ without Hypercholesterolemia)
- Mean sitting DBP at Screening (mmHg)
- Mean sitting SBP at Screening (mmHg)

10.1. Derivations

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

11. MEDICAL HISTORY AND PROCEDURES

Medical History information will be presented by Monotherapy for the ENR Population.

- Medical History data captured on eCRF form "Medical History/Concurrent Diseases" will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 24.1 or latest) dictionary
  - Medical History conditions are defined as those conditions which stopped 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 for the ENR 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 24.1) 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 01SEP2020 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, compliance, 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 COMPLIANCE

Compliance to study medication (i.e., monotherapy and/or combination therapy) will be presented for the mITT and SAF populations.
A table consisting of summary statistics for percent compliance along with the number and percent of patients with compliance in each of the following groups:

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

on SAF population for Monotherapy, and mITT as well as SAF populations for Combination Therapy. By visit (Visit2 and Visit 3) and overall compliance will be produced for Combination Therapy.
A listing of drug accountability will be presented on mITT and 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 compliance and compliant (yes/no).

15.1. Derivations

Monotherapy and Combination Therapy compliance with study drug based on the drug accountability data will be calculated as the number of tablets taken x 100 / expected number of

tablets which should have been taken expressed as a percentage.
For Monotherapy, the expected number of tablets to be taken = (Treatment End Date – Treatment Start Date) + 1.
For Combination Therapy, the expected number of tablets 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 & Derivation

The primary efficacy variable is Change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8).

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

Not Applicable.

16.1.3. Primary Analysis of Primary Efficacy Variable

The primary objective of this study is to test the hypothesis that

H0: There is no change in the sitting DBP prior or post combination therapy.
H1: There is a difference in the sitting DBP prior or post combination therapy.

The primary efficacy analysis will be performed for the mITT population. 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.
- Only those patients for whom we have DBP assessment results available at both Week 4 and Week 8 will be considered.

16.1.4. Supplementary Analysis of Primary Efficacy Variable

A repeated measure general linear model (GLM) will be performed on the primary efficacy endpoint to test the covariate effects and the effects of interactions between the covariates for the mITT population. The GLM model will include change in mean sitting DBP as the dependent variable, repeated through visits Visit 3 (Week 4) and Visit 4 (Week 8). Age (Years), gender, body mass index (BMI), and baseline DBP are considered as the covariates.
The GLM model is
Change from Baseline = Visit + Age + Gender + BMI + baseline DBP + Age*Gender + Age*BMI + Age*baseline DBP + Gender*BMI + Gender*baseline DBP + BMI*baseline DBP + Age*Gender*BMI + Age*Gender*baseline DBP + Age*BMI*baseline DBP + Gender*BMI*baseline DBP + Age*Gender*BMI*baseline DBP
A PROC MIXED procedure, with an unstructured covariance matrix, is used for the analysis and the corresponding p-values for each of the covariates will be presented in a table.

16.1.5. Sensitivity Analysis of Primary Efficacy Variable(s)

The sensitivity analyses will be conducted similar to the primary efficacy analysis including the repeated measure GLM 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

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

- Change in mean sitting DBP and SBP

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

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).

16.2.2. Analysis of Secondary Efficacy Variables

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

Change from baseline in sitting SBP from prior and post combination therapy will be compared using paired t-test. The p-value will be presented using a paired t-test comparing mean at baseline and mean at Week 8. The secondary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum. Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.

Additionally, the secondary end point of change in SBP between Visit 2 and Visit 4 will be analyzed using a repeated measures GLM as described in Section 16.1.4 with Age (Years), Gender, body mass index, and baseline SBP as covariates to identify the effect of covariates and interaction between the covariates.

16.2.2.2. 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/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. 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.

16.2.2.3. Number and proportion of patients achieving the BP goal

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 (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) between Visit 2 and Visit 3 as well as Visit 2 and Visit 4. 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.

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) 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.

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 and 4.

- 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) and Visit 4 (Week 8). 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 BP goal (sitting BP < 130/80 mmHg) will be summarized for Visits 2, 3, and 4, 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. 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.
- The number of patients achieving BP goal (sitting BP < 130/80 mmHg) will be summarized for Visits 2, 3 and 4, along with percentage for each of the subgroup specified under section 7.5 of the SAP.

17. QUALITY OF LIFE ANALYSIS

Not Applicable.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF population.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

18.1. Adverse Events

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 25.0 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".

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 subjects 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).

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 subject 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 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, 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, Serum Chemistry, Urine Pregnancy Test, and 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:

- Actual and change from baseline by visit (for quantitative measurements) for Combination Therapy using SAF population.
- 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 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 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 Combination therapy. All ECG data will be listed for both Monotherapy and Combination Therapy using the SAF population.

18.5. Vital Signs

The following 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 (°C)

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.
- 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:

- Shift from baseline according to the physical examination findings.
- Physical Examination parameters will be summarized using the SAF population for the 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.

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:
Global Bios > Processes > GBIOS Processes - Implementation Guidelines and Templates > General Guidelines and Templates > Output Conventions.

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	AML 5mg	AML 5mg
Combination Therapy	NEB+AML (5mg)	NEB+AML (5mg)
Combination Therapy	NEB+AML (10mg)	NEB+AML (10mg)

Presentation of Visits

Visit 1 (Week -4)
Visit 2 (Week 0)
Visit 3 (Week 4)

Visit 4 (Week 8)
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)
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-subject 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 GLM

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

START DATE	STOP DATE	ACTION
	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
	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

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures

Signer Full Name	Meaning of Signature	Date and Time
Aswin Nair	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Nov 2022 12:53:50 UTC
Jean Dorothee Müller	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Nov 2022 14:15:25 UTC