STATISTICAL ANALYSIS PLAN

MEIN/19/ZoNe-HYP/001

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

NCT05257148

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final (Dated 14Dec2021) for Protocol MEIN/19/ZoNe-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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MODIFICATION HISTORY

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V1.0	14Dec2021	Aswin Nair	Not Applicable. First version

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE-i	angiotensin converting enzyme-inhibitors
ACS	Abnormal, Clinically Significant
ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse Event
AEOSI	adverse event of special interest
ANCS	abnormal, not clinically significant
ATC	anatomical therapeutic chemical
BB	beta blocker
BP	blood pressure
BMI	body mass index
CTMS	clinical trials management system
DBL	data base lock
DBP	diastolic BP
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ENR	enrolled
ITT	Intent-to-treat
MCMC	markov chain monte carlo
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
NEB	Nebivolol
PD	protocol deviation
PP	per protocol
PT	preferred term
SAE	serious adverse event
SAF	safety
SAP	statistical analysis plan
SBP	systolic BP
SD	standard deviation
SDTM	study data tabulation model
SOC	system organ class
TEAE	treatment emergent adverse events
WHO	world health organization
ZOF	zofenopril calcium

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol MEIN/19/ZoNe-HYP/001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on protocol version 1.0 dated 16JUL2020 and addendum version 1.0 dated 29OCT2020.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. PRIMARY OBJECTIVE

To assess the antihypertensive effect of the extemporaneous combination of zofenopril calcium(ZOF) 30 mg or nebivolol(NEB) 5 mg in lowering sitting diastolic blood pressure(DBP) after 8 weeks of treatment, in patients with uncontrolled blood pressure(BP) who were previously treated with NEB or ZOF monotherapies for at least 4 weeks

2.2. SECONDARY OBJECTIVES

The secondary objectives are,

- To assess the antihypertensive effect of the extemporaneous combination of NEB 5 mg and ZOF 30 mg in lowering sitting systolic blood pressure (SBP) after 8 weeks of treatment in patients with uncontrolled BP, after at least 4 weeks of treatment with NEB or ZOF monotherapies
- To evaluate the total number and percentage of patients who achieved the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3
- To assess compliance to the monotherapy and extemporaneous combination (actual doses taken versus planned doses to be taken)
- To evaluate the safety and tolerability of the ZOF and NEB monotherapies, and the extemporaneous combination of NEB 5 mg and ZOF 30 mg after 8 weeks of treatment

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are,

- To assess the antihypertensive efficacy at different time points in patients who
    1. received NEB or ZOF monotherapies before the run-in period,
    2. received any other ACE-i or BB monotherapies before the run-in period
- To assess the antihypertensive effect on patients, based on their hypertension grade, presence or absence of hypercholesterolemia, presence or absence of diabetes at Visit 2 and Visit 3

2.4. ESTIMANDS

Estimand	Definition	Attributes			
		Population	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
Primary Estimand		Intent-To-Treat (ITT)	Change in mean sitting DBP between Week 0 (Visit 2) and Week 8	The patients will not be permitted to use any of the Blood pressure modifying medications from Screening till the end of treatment.	Difference in mean DBP with P-value
Secondary Estimand 1		Intent-To-Treat (ITT)	Change in mean sitting SBP between Week 0 (Visit 2) and Week 8	The patients will not be permitted to use any of the Blood pressure modifying medications from Screening till the end of treatment.	Difference in mean SBP with P-value
Secondary Estimand 2		Intent-To-Treat (ITT)	The number of patients achieving BP goal (sitting BP ≤130/80 mmHg)	The patients will not be permitted to use any of the Blood pressure modifying medications from Screening till the end of treatment.	Difference in proportion of patients achieving BP goal between Week 0 (Visit 2) and Week 8 with P-value

3. STUDY DESIGN

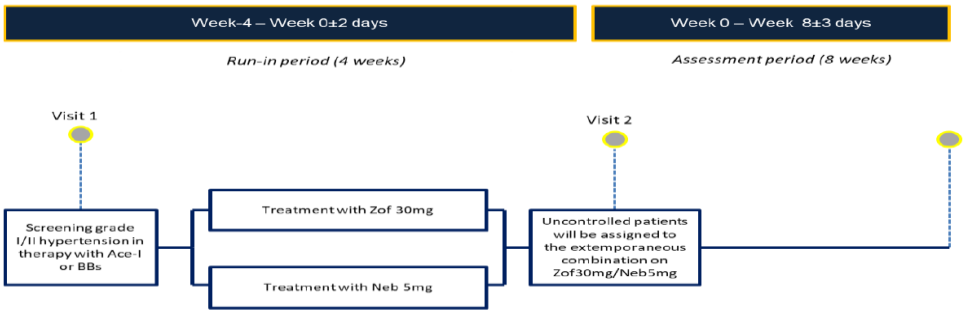
3.1. GENERAL DESCRIPTION

This is a phase IV, open-label, multicenter, multinational study with 2 study periods (a run-in period of 4 weeks and an assessment period of 8 weeks). Grade 1-2 hypertensive patients (blood pressure [BP] ranging from ≥140/90 mmHg to ≤179/109 mmHg) on treatment with any angiotensin converting enzyme-inhibitors (ACE-i) or beta blockers (BBs) including ZOF 30 mg or NEB 5 mg respectively will be screened for eligibility (Visit 1). On the same day, the eligible patients will enter into a run-in period after Screening, during which:

- Patients on ZOF 30 mg or NEB 5 mg will continue the same therapy for 4 weeks
- Patients on any other ACE-i will be assigned to monotherapy with ZOF 30 mg while patients on any other BB will be assigned to monotherapy with NEB 5 mg, respectively, for 4 weeks.

After the 4 weeks of monotherapy in the run-in period, if BP at Visit 2, remains uncontrolled (sitting SBP/DBP >130/80 mmHg) despite an adherence to the treatments ranging from 80% to 120%, the patients will start treatment (Week 0, Visit 2) with the extemporaneous combination of NEB 5 mg/ZOF 30 mg (NEB/ZOF) and will be assessed for further 8 weeks (assessment period). If the patients, at Visit 2 after the Run-In period, have controlled BP (sitting SBP/DBP ≤130/80 mmHg), and/or do not tolerate the treatment, and/or do not maintain the adherence to the therapy (range from 80% to 120%), these patients will not be continued further in the study. At the end of the assessment period (Visit 3) the antihypertensive effect of the extemporaneous combination of NEB 5 mg and ZOF 30 mg will be evaluated. A total number of 290 patients will be screened considering 25% of drop-out rate, to obtain approximately 216 completed patients at the end of the study.

Figure 1: Study Scheme



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

3.2. SCHEDULE OF EVENTS

Study Procedures/ Assessments	Visit 1 (Week -4)	Visit 2 (Week 0)[a]	Visit 3 (Week 8)
	Screening + Start of Run-in Period[b]	Start of Assessment Period	End of Assessment Period
Informed consent	X		
Inclusion/exclusion criteria	X		
Medical history	X		
Prior medication	X		
Demography (age, sex, race)	X		
Concurrent diseases and medical conditions	X	X	X
Antihypertensive treatment with NEB or ZOF monotherapy[c]	X		
Study drug dispensing[d]		X	
Study drug return and accountability (Compliance assessment)		X[e]	X[f]

Concomitant medications	X	X	X
Urine pregnancy test	X	X	X
Physical examination	X	X	X
Vital signs	X	X	X
Laboratory test[g]	X		X
Blood pressure	X	X	X
ECG	X	X	X
AE/SAE assessment	X	X	X[h]

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

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

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

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

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

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

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

g: To ensure patient safety, the patients will be contacted over phone within 24 hours, in case of any abnormality and clinically relevant laboratory test according to the Investigator's judgement at any visit

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

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

- 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 will be included in this population". In SAP, this has been updated to,

"The per-protocol (PP) population will contain all patients in the SAF population who have not experienced major protocol violations that could affect the efficacy analyses".

The primary endpoint analysis includes only 2 two consecutive visits, i.e. Baseline (week 0) and one post baseline (Week 8). The protocol suggested multiple imputation (MI) simulation method for imputing missing data is not applicable in this scenario. MI method may not be appropriate for a longitudinal study with only two time-points data. Thus, it has been agreed not to perform multiple imputation, and the primary analysis will be performed only on the observed data.

- 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 and visit 3. 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.
- The products involved in this study are well established in the market for many years with an excellent safety profile. The term AEOSI is mentioned in the study protocol by error and no adverse events of special interest (AEOSI) have been identified which require special monitoring during the study. Thus, no analysis is performed on AEOSIs in the study.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

4.2. 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 database lock of the study. A data review meeting will be conducted prior to database lock and confirm the patients in each analysis set population. Impact of Covid-19 pandemic on the missed data, missed visits or dropouts will be assessed during this meeting and appropriate decisions on population counts will be taken.

5.1. ENROLLED [ENR] POPULATION

The enrolled (ENR) population will contain all patients who are enrolled into the study and may or may not receive the study drug (extemporaneous combination)

5.2. INTENT-TO-TREAT [ITT] POPULATION

The intent-to-treat (ITT) population will contain all patients in the ENR population and receive at least 1 dose of study drug (combination therapy) and have at least 1 post baseline safety assessment

5.3. SAFETY [SAF] POPULATION

The safety (SAF) population will contain all patients who are in the ENR population and receive at least 1 dose of study drug (combination therapy)

5.4. PER PROTOCOL [PP] POPULATION

The per-protocol (PP) population will contain all patients in the SAF population who have not experienced major protocol violations that could affect the efficacy analyses. Patients with major protocol deviations which can affect the primary endpoint of the study, failure to satisfy inclusion or exclusion criteria, taking any prohibited medications affecting blood pressure during the study, serious non-compliance to dose regimen and visit schedule are excluded. Whether to include or exclude the patients from PP set will be finalized in the data review meeting prior to database lock.

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. Reference start date is defined as the day of the first dose of study drug (combination therapy) (Visit 2), (Day 1 is the day of the first dose of study drug) and will appear in every listing where an assessment date or event date appears.

- 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 (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.

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

The following table describes assignment of visit windows for the purposes of analysis:

Table A: Visit Window

Assigned Study Day (Inclusive)		Visit Assigned	Week Assigned
From	To		
	-29	Visit 1	Week -4
-2	2	Visit 2	Week 0
53	59	Visit 3	Week 8

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 from Visit 1 will be calculated as:

- Test Value at Visit X – Visit 1 Value

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS Enterprise Guide 7.1.

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

No adjustment for covariates will be performed for this study.

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

Missing efficacy and safety data will not be imputed.

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 ITT and PP populations.

- Country/Site
- Age (<40 years and ≥40 years)
- Gender (Male, Female, Other)
- Hypertension grade at screening (grade 1 and grade 2)
- Presence of diabetes (patients with or without diabetes)
- Presence of hypercholesterolemia (patients with or without hypercholesterolemia)
- Screening therapy (ACE-i, Beta blocker)
- Run-in period therapy (Monotherapies of ZOF 30 mg or NEB 5 mg)

Hypertension grade at screening is derived as follows;

- Grade 1 – 140 <= SBP < 160 or 90 <= DBP <100
- Grade 2 – 160 <= SBP < 180 or 100 <= DBP <110

Patients with presence of diabetes and hypercholesterolemia will be identified from the medical history data using the preferred terms. Presence of diabetes can be identified with the preferred terms "*Diabetes mellitus*" Or "*Type 2 diabetes mellitus*" and hypercholesterolemia with "*Dyslipidaemia*" or "*Hypercholesterolaemia*" or "*Hyperlipidaemia*". Patients under ACE-i and beta blocker can be identified from the concomitant medication data with anatomical therapeutic chemical (ATC) class "*Ace inhibitors, plain*" and "*Beta blocking agents, selective*" respectively.

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

All patients who provided informed consent will be considered for this study. Patient disposition and withdrawals, and reasons for exclusion from each analysis population, including inclusion and exclusion criteria will be presented for the ENR population.

9.2. PROTOCOL DEVIATIONS

All protocol deviations (PD) will be discussed and reviewed on a case-by-case basis before the DBL. All PDs authorized by Sponsor will be documented.
Individual PDs will be presented in a data listing. The number and percentage of patients with PDs will be summarized by deviation on ENR population. Additional Major and Minor PDs may be identified during data review and will be reflected in the Table and Listing as appropriate.
All PDs will be recorded and classified in Clinical Trial Management System (CTMS).

9.3. COVID-19 IMPACT

The impact of COVID-19 on study related procedures are collected on 'COVID-19 Impact Form' in eCRF. Impact information will be presented in a summary table and a data listing.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ENR. 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)
- Sex
- Race
- Childbearing potential

- Weight (kg)
- Height (cm)

10.1. DERIVATIONS

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

11. MEDICAL HISTORY

Medical History information will be presented for the ENR.

- Medical History data captured on eCRF will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 23.1 or latest) dictionary
    - Medical History conditions are defined as those conditions which stop prior to or at Screening.
    - Presented by SOC and PT.

12. CONCURRENT DISEASES

Concurrent Diseases will be presented for the SAF by combination therapy.

- Concurrent Diseases will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 23.1) 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 "Concurrent Diseases and Medical Conditions".

13. MEDICATIONS

Medications will be presented for the SAF and coded using WHO Drug dictionary Version 01SEP2020 or latest**.** 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, the medication will be classified by the worst case, i.e. concomitant.
Frequency tabulations will be presented for prior and concomitant medications by primary therapeutic subgroup (3rd

level ATC code) and preferred name.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- '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.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication for both Monotherapy and Combination therapy in days will be presented for the ENR and SAF respectively.
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 will be presented for the ENR and SAF.
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 ENR population for Monotherapy and SAF population for Combination therapy.
A listing of drug accountability will be presented on ENR population 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

Compliance with study medication—based on the drug accountability data will be calculated as the number of tablets taken (total dispensed – total returned) divided by the prescribed number of tablets expressed as a percentage, see calculations below.

Mono/Combination Therapy and overall 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 patients who permanently stop the study medication, 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 Week 0 (Visit 2) and Week 8 (Visit 3).

16.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE(S)

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 ITT population. The above hypothesis will be tested as following-

- Change from baseline in sitting DBP from prior and post combination therapy will be compared using paired t-test. The p-value will be presented using paired t-test.

- The primary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, 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.

16.1.4. Sensitivity Analysis of Primary Efficacy Variable(s)

The primary sensitivity analysis will be conducted using the PP population.

16.2. Secondary Efficacy

16.2.1. Secondary Efficacy Variables & Derivations

- Change in mean sitting SBP

  Change in mean sitting SBP between Week 0 (Visit 2) and Week 8 (Visit 3)

- Number and proportion of patients achieving the BP goal

  Number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Week 0 (Visit 2) and Week 8 (Visit 3).

16.2.2. Analysis of Secondary Efficacy Variables

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

- Change in mean sitting SBP between Week 0 (Visit 2) and Week 8 (Visit 3):
  Change from baseline in sitting SBP from prior and post combination therapy will be compared using paired t-test. The p-value will be presented using a paired t-test comparing mean at baseline and mean at Week 8. The secondary endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum.
  Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.

- The number of patients achieving BP goal (sitting BP ≤130/80 mmHg) will be summarized for Visit 2 and Visit 3, along with percentage. A p-value using 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.

16.2.3. SENSITIVITY ANALYSIS OF SECONDARY EFFICACY VARIABLE(S)

The secondary sensitivity analysis will be conducted using the PP population for change in mean sitting SBP between Week 0 (Visit 2) and Week 8 (Visit 3).

16.3. EXPLORATORY EFFICACY

16.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

- Change in mean sitting SBP and DBP between Visit 1 and Visit 2 in the group of patients on ZOF 30 mg and NEB 5 mg and in the group of patients switched to ZOF 30 mg or NEB 5 mg from any other ACE-I and BB
- Change in mean sitting SBP and DBP between Visit 1 and Visit 3 in the group of patients on ZOF 30 mg and NEB 5 mg or in the group of patients switched to ZOF 30 mg or NEB 5 mg from any other ACE-i and BB
- Number and proportion of patients in the group of patients on ZOF 30 and NEB 5 mg and in the group of patients switched to ZOF 30 mg or NEB 5 mg from any other ACE-I and BB achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3
- Number and proportion of patients on combination therapy, divided into subgroups specified under section 7.5, achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 and Visit 3

16.3.2. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

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

- Change in mean sitting SBP and sitting DBP between Visit 1 and Visit 3 will be analyzed as following:
- Change from baseline in sitting SBP and DBP from prior (Visit 1) and post (Visit 3) combination therapy will be compared using paired t-test. The p-value will be presented using a paired t-test comparing mean at baseline and mean at Week 8. The exploratory endpoint will be presented in a descriptive manner using n, mean, median, SD, Q1, Q3, and minimum and maximum. Assumption of normality will be investigated using Wilk-Shapiro test. If violation is observed, then paired t-test will be replaced by Wilcoxon signed rank test.
- The number of patients achieving BP goal (sitting BP ≤130/80 mmHg) will be summarized for Visit 2 and Visit 3, along with percentage. 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.
- The number of patients achieving BP goal (sitting BP ≤130/80 mmHg) will be summarized for Visit 2 and Visit 3, 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 Safety Analysis 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 23.1.
Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication (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 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.

18.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication 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. Adverse Drug Reaction

An adverse drug reaction (ADR) is any untoward and unintended response to a study treatment related to any dose administered. The definition implies a reasonable possibility of a causal relationship between the event and the study

treatment. In eCRF, if related, as indicated by the Investigator, is classed as “Certain Related”, “Probable Related”, “Possible Related”, “Un-assessable”, and if unrelated then classed as “Unlikely related”, “Not related”. 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

Treatment-emergent Adverse Events leading to discontinuation of study medication are those events where for ‘Reason treatment not completed’ recorded as ‘Adverse event’.
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” 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.

18.3. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry and Pregnancy test. A list of laboratory assessments to be included in the outputs is included in protocol Section 10.2.3. Laboratory evaluations will be summarized for Combination therapy by SAF population. Presentations will use SI Units.
The following summaries will be provided for laboratory data:

- A descriptive summary of lab parameters by visit.
- The Shift from screening (visit 1)according to the lab result summary will be provided for laboratory data
- A by-patient listing of all laboratory data and pregnancy test data will be presented.

18.4. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study. The following ECG parameters will be reported for this study:

- PQ Interval (PR) (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

ECG parameters will be summarized descriptively using the safety population for the Combination therapy. All ECG data will be listed.

18.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Sitting [/ Standing/ Supine] Systolic Blood Pressure (mmHg)
- Sitting [/Standing/ Supine] Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{o}C)

The following summaries for both Monotherapy and Combination therapy, will be provided for vital signs data:

- Actual and change from baseline by visit.

18.6. PHYSICAL EXAMINATION

The following summaries will be provided for physical examination data for combination therapy by visit on SAF:

- Summary of Physical examination
- Shift from baseline according to the physical examination findings.

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 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 and Graphs	For Listings (include if different to tables)
Monotherapy	NEB 5mg	NEB 5mg	NEB 5mg
Monotherapy	ZOF 30mg	ZOF 30mg	ZOF 30mg
Combination therapy	NEB+ZOF	NEB+ZOF	NEB+ZOF

PRESENTATION OF VISITS

Visit 1 Week -4

Visit 2 Week 0

Visit 3 Week 8

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 Week 0 (Visit 2)	BL(W0) or W0(V2)
Week 8 (Visit 3)	W4 (V3)

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)

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 <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, 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 <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, 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 <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, 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 <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, 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 <= end of treatment, assign as concomitant If start date > end of treatment, 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)	20 Dec 2021 11:44:56 UTC
Jean Dorothee Müller	Document Approval (I certify that I have the education, training and experience to perform this task)	21 Dec 2021 12:23:14 UTC
Jisho Jose	Document Approval (I certify that I have the education, training and experience to perform this task)	21 Dec 2021 12:36:30 UTC
Paolo Fabrizzi	Document Approval (I certify that I have the education, training and experience to perform this task)	22 Dec 2021 15:36:26 UTC
Giorgio Reggardio	Document Approval (I certify that I have the education, training and experience to perform this task)	03 Jan 2022 14:51:48 UTC