Statistical Analysis Plan

Protocol No.: TM005

A 24-WEEK PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, SINGLE-CENTER SAFETY AND EFFICACY STUDY TO EVALUATE OVERALL SAFETY AND TOLERABILITY OF COADMINISTRATION OF TESOFENSINE AND METOPROLOL IN SUBJECTS WITH HYPOTHALAMIC INJURY-INDUCED OBESITY (HIO), AND WITHA 24-WEEK OPEN-LABEL EXTENSION, IN TOTAL 48 WEEKS

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STATISTICAL ANALYSIS PLAN APPROVAL

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Version History

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Version 1.0	17.05.2019	Initial Version

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LIST OF ABBREVIATIONS

Table 1: Abbreviations

AE	Adverse Event
°C	Degrees Celsius
ADR	Adverse Drug Reaction
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CRF	Case Report Form
CRO	Contract Research Organization
CSS	Composite Satiety Score
DB	Double-Blind
DBL	Database Lock
DBP	Diastolic Blood Pressure
DEXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
HbA1C	Hemoglobin A1c
HR	Heart Rate
ICH	International Conference on Harmonization
IMP	Investigation Medicinal Product
kg	Kilogram
l	Liter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention-to-treat
mL	Milliliter
N	(No) Number
PK	Pharmacokinetic
PPP	Per Protocol Population
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus

TEAEs	Treatment Emergent Adverse Events
Tmax	Time of the Maximum Plasma Drug Level
VAS	Visual Analogue Scale
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of the data collected under TM005.
The scope of this SAP includes presentation of disposition, demographic and other baseline data, safety and efficacy analyses.
Mock tables, figures, and listings (TFLs) shells will be provided in separate supporting documents.
This SAP should be read in conjunction with the study protocol and case report forms (CRFs).
This version of the SAP has been developed using Protocol Version 2.0 dated 11-JAN-2019 and eCRFs.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To examine overall safety and tolerability of coadministration of 0.5 mg tesofensine/50 mg metoprolol treatment over 24 weeks in subjects with HIO

2.1.2 Secondary Objectives

- To examine the effect on satiety and appetite from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on bodyweight from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on body composition from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on quality of life from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine effect on craving for something sweet, salty, savory and fatty from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on thirst from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine effect on glycaemic control and lipid profile from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 following coadministration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO

- To examine the effect on HR and BP from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To establish profile of trough values of tesofensine and metoprolol following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO:
    - o Active arm: the first 24 weeks and then continuously up to week 48.
    - o Placebo arm: start of treatment at week 25 and then continuously up to week 48.
- To evaluate the effect on BP and HR from Baseline to week 24 by 24 hours (24H) home monitoring of BP and 48 H home monitoring of HR.
- To evaluate overall safety and tolerability from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO.

2.2 Study Endpoints

2.2.1 Primary Endpoint

Safety and tolerability will be judged from all safety data collected in the period, including number and type of treatment emergent adverse events, laboratory data, blood pressure and heart rate.

2.2.2 Secondary Efficacy Endpoints

• Change in satiety and appetite using the composite satiety score (CSS) from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48
• Change in body weight from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48
• Change in body composition i.e. body fat and lean body mass by Dual-energy X-ray absorptiometry (DEXA) from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48
• Change in quality of life by the use of the SF-36 questionnaire from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48
• Change in craving for something sweet, salty, savory and fatty by the use of Visual Analogue Scale (VAS) scales from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48
• Change in thirst by the use of a VAS scale from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48
• Change on glycaemic control and lipid profile from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48
• Change in waist circumference from Baseline to week 24, from Baseline to week 48 and from week 24 to week 48

2.2.3 Secondary Safety and PK Endpoints

• Change on HR and BP from Baseline to week 48 and from week 24 to week 48
• Trough values of tesofensine and metoprolol
  o Active arm: the first 24 weeks and then continuously up to week 48.
  o Placebo arm: start of treatment at week 25 and then continuously up to week 48.
• Change of 24H BP/48H HR and QT from Baseline to V5 and V8 and from V5 to V8 measured by home monitoring
• Number and type of AE's from week 24 to week 48

3. OVERALL STUDY DESIGN AND PLAN

3.1 General Study Design

This is a double-blind, randomized, placebo-controlled, single-center study followed by an open-label extension period.
The study will have two parts:

- Part 1: 24 weeks double-blind treatment, followed by
- Part 2: 24 weeks open-label extension – all subjects still participating at the end of Part 1 will be given an option to continue for additional 24 weeks on the active drug if evaluated eligible by the Investigator.

As an integral part of the study all subjects will undergo regular dietary and physical activity counseling during the study.
A Clinical Study Report (CSR) will be prepared following the completion of the 24-week double-blind part of the study and a separate CSR following finalization of the 24-week open labeled study part, including data and analysis from Baseline to week 24 and week48.

3.2 Sample Size Estimation and Power

As this is an exploratory study formal sample size or power calculation was not performed.

3.3 Study Population

In total, a minimum of 12 and a maximum of 25 subjects with HIO. HIO is defined as obesity developed in relation to damage to the hypothalamus, whether it is from an injuring trauma, bleeding, infarction, tumor, surgery or irradiation.

3.4 Treatment Administered

Part 1 – the double-blind part: The active medication arm will be given co-administration of 0.5 mg tesofensine/50 mg metoprolol daily for 24 weeks. The placebo arm will receive matching placebo tablets.
Part 2 – the open-label extension part: All active participants at the end of the double-blind part will be given the active medication 0.5 mg tesofensine/50 mg metoprolol daily for 24 weeks.

3.5 Randomization

During the Part 1 subjects will be randomized into either the active medication or matching placebo in 2:1 ratio.

There will be 2 stratification groups (subjects with T2DM and without diabetes). Each stratification group will be randomized in 2:1 ratio.

Stratified block randomization will be performed.

Randomization of eligible subjects to one of the study medication groups will be done at Baseline visit Day 1, following successful completion of all baseline assessments, using a study medication number defined by the assignment list.

Subjects will be randomly allocated to either study medication group in a 2:1 randomization by selecting the lowest available randomization number at the time of randomization.

The randomization codes will be generated within the Biometrics Department of the sponsor's Contract Research Organization (CRO) by a randomization statistician and IMP kits for patients will be packaged according to this list. The randomization codes and the complete generation procedure will be filed at a secure place by sponsor's CRO statistician until the study database is closed. Study statistician, data managers and statistical programmers will not have access to the randomization list prior to the database lock. The only person on site with access to the code break sealed envelopes will be the principle investigator. The study medication number consists of four digits. In part 1, all kits assigned to a subject will have the same randomization number. In part 2, kits assigned to a subject will have different study medication numbers between visits. This procedure will be checked by the monitor.

3.6 Blinding and Unblinding

Part 1 - It is double-blind, placebo-controlled study, i.e. investigators, site staff and subjects will be blinded as to whether they will be allocated to active or placebo treatment. This will be achieved by the following procedures:

The IMP will look similar to placebo with regard to size, color and general appearance

The labelling of the IMP will identify the study and the investigational product but will not indicate the contents. When a patient is ready for randomization, the investigator picks the lowest available randomization number from one of two lists; one list for patients with DM and one list for patients without DM

In general, emergency un-blinding is to be done only when absolutely necessary for the clinical management of an individual subject and where stopping the blinded medication is not sufficient in the opinion of the investigator. If possible, the justification for the un-blinding should be discussed with the sponsor prior to unblinding to ensure that unblinding is truly necessary and that appropriate steps for subject's welfare and management are being taken.

4. STATISTICAL METHODS

4.1 General Considerations

All analyses will be performed in two steps – first after the completion of the double-blind part, then following the completion of the open-label extension part. As the primary endpoint is at week 24, no data will be changed that could affect the endpoints after unblinding. During the open-label extension all subjects will receive the study drug. The treatment arms during the open-label extension will be based on the treatments assigned during the double-blind phase, and analysis will be done from Baseline to week 24 and 48 and from week 24 to week 48.
All primary and secondary endpoints will be summarized by treatment and visit using descriptive statistics.

Continuous endpoints will be summarized by non-missing counts, mean, median, standard deviation, minimum and maximum value. Categorical endpoints will be summarized by frequency counts (N) and percentages (%). Moreover, complete listings of individual values for all endpoints will be provided. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit.

Formatting for Dates and Times

- Dates only – ddmmmyyyy;
- Times only – hh:mm or hh:mm.ss (as appropriate);
- Dates and times – ddmmmyyyy hh:mm or ddmmmyyyy hh:mm:ss (as appropriate).

The minimum and maximum will be reported with the same degree of precision (i.e, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and P values will be reported.

4.2 Definitions of Analysis Sets

The following analysis sets are defined in accordance with the ICH-E9 guidance1:

Modified Intention-to-treat Population (mITT):

Includes all randomized subjects that have non-missing baseline assessment and at least one post-baseline assessment. Subjects will be included into mITT population separately for the double-blind and open-label phase. Subjects in the mITT Population will contribute to the evaluation 'as randomized'.

Per Protocol Population (PPP):
Includes all randomized subjects without any major protocol violations. Subjects in the PPP will contribute to the evaluation 'as randomized'.

Safety Analysis Set:
Includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set will contribute to the evaluation 'as treated'.

4.3 Statistical Definitions and Algorithms

4.3.1 Baseline

The last observation recorded prior to the first dose of treatment will be used as the baseline observation for all calculations of change from baseline.

4.3.2 Pooling of Centers

Not applicable as this is a single-center study.

4.3.3 Handling of Dropouts and Missing Data

Data queries will be generated either in the eCRF or sent to investigator via email for missing and doubtful data. The responsible investigator will answer the query and confirm or correct data.
"Last observation carried forward (LOCF)" approach will be used as the main method for handling of missing data. Additionally, data without imputation will be used for sensitivity analysis.

4.3.4 Analysis Software

All summaries and statistical analyses will be generated using SAS® version 9.3 or later.

5. PROTOCOL DEVIATIONS AND DISPOSITION OF SUBJECTS

5.1 Disposition of Subjects

Subject disposition will be tabulated including the numbers of screened subjects, screening failures, subjects exposed to study product, subjects completing the study and subjects in the mITT population, PPP and Safety Analysis Set. Subjects withdrawn from the study will be listed including the primary reason for withdrawal. The primary reasons for withdrawal will be summarized.

5.2 Protocol Deviations

Protocol deviations will be listed. Protocol deviations will be tabulated by treatment group and overall for the Safety Population.

6. BACKGROUND INFORMATION

6.1 Demographics and Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height in cm, weight in kg, and BMI will be presented by treatment group and overall. These analyses will be conducted for the Safety population.

6.2 Medical History

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v.<21.1>), will be tabulated by treatment group. This analysis will be conducted for the Safety Population.

7. PRIOR AND CONCOMITANT MEDICATIONS

Medications that started prior to the start of the study drug will be considered prior medications whether or not they were stopped prior to the first dose of study drug. Any medications (other than the study drug) continuing or starting post the first dose of study drug will be considered to be concomitant. If a medication starts prior to the first dose of study drug and continues after the first dose of study drug it will be considered both prior and concomitant.

Prior and concomitant medications will be summarized descriptively by treatment group and overall using counts and percentages.

Prior medications will be presented separately from concomitant medications.

Medications will be coded using WHODrug v. B3.

8. COMPLIANCE AND EXPOSURE

Study drug administration data will be listed.

Study medication compliance (determined by calculating returned bottles and count of returned tablets) data will be summarized by treatment group, overall, and by visit for the Safety Population.

9. SAFETY AND TOLERABILITY ANALYSIS

All Safety analysis will be performed on the Safety Analysis Set.

Continuous data will be summarized separately for double-blind and open-label (Baseline to week 24, Baseline to week 48 and from week 24 to week 48) parts using non-missing counts, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized separately for double-blind and open-label (Baseline to week 24, Baseline to week 48 and from week 24 to week 48) parts using counts and percentages.

9.1 Analysis of Primary Endpoint

No inferential statistical test will be performed for the primary endpoint.

Safety and tolerability will be judged based on the following:

• The number and type of Treatment Emergent Adverse Events (TEAEs) during the first 24 weeks

• Change in laboratory data (hematology and blood chemistry) from Baseline to week 24

• Change in blood pressure and heart rate from Baseline to week 24

Each TEAE will be evaluated for duration, severity, seriousness, and causal relationship to the study drug. The action taken and the outcome will also be reported. The TEAEs will be summarized overall. The number and percentage of subjects experiencing any TEAE will be

summarized and presented by system organ class and preferred term. The TEAEs will also be presented by severity, by relationship to study drug, and by seriousness.

Laboratory data, BP and HR will be listed. Any abnormalities will be reported, clinically relevant or significant abnormalities will be additionally flagged.
Changes in Laboratory data, BP and HR from Baseline to week 24 will be summarized descriptively by treatment arms. Shift tables will also be provided. BP and HR from both Visit measurements as well as from home monitoring will be analyzed. Figures of BP and HR from Baseline to week 24 from both Visit measurements as well as from home monitoring will be prepared.

9.2 Analysis of Secondary Safety Endpoints

Secondary safety analysis will be performed the same way as the primary safety analysis.
Treatment allocation during double-blind and open-label part is described in Section 4.1 General Considerations.

The number and type of AEs from week 24 to week 48 will be analyzed.

Changes in blood pressure and heart rate from baseline to week 48 and from week 24 to week 48 from both Visit measurements as well as from home monitoring will be summarized descriptively by treatment arms. Figures of BP and HR from Baseline to week 48 and from week 24 to week 48 from both Visit measurements as well as from home monitoring will be prepared.

Changes in 24H BP/48H HR and QT from Baseline to week 12 and week 24 and from week 12 to week 24 measured by home monitoring will be tabulated. Figures of mean values of BP and HR from Baseline, week12 and week 24 will be prepared. Data describing potential changes in heart rhythm and diagnosis will be tabulated and summarized.

9.3 Additional Description of Safety Analysis

9.3.1 Adverse Events

Adverse events will be coded using the MedDRA version 21.1 thesaurus.

A TEAE will be defined as an adverse event encountered after the first dose of IMP given.

In the AE data listings, all AEs will be displayed. Four groups will be presented; from Baseline to week 24 on active medication (A), from baseline to week 24 on placebo (P), from week 24-48 on AA and from week 24-48 on PA. Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the study drug. The action taken and the outcome must also be recorded. AEs that are not treatment emergent will be flagged.
All adverse events, grouped by MedDRA system organ class and preferred term, will be summarized by treatment group and overall. In the case of multiple occurrences of the same within the same subject, each subject will only be counted once for each system organ class or preferred term.

The number and percent of subjects reporting treatment emergent AEs, grouped by MedDRA system organ class and preferred term, will be tabulated by severity, relationship to study drug, and by treatment group.

In the summaries showing severity and relationship to study medication at each level of summarization (System Organ Class and Preferred Term) subjects who reported more than one adverse event will be counted only once for the maximum severity (mild, moderate, severe) and strongest relationship (not related, unlikely, possible, probable, definitely related).

If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = definitely related).

A treatment related AE is any AE with a relationship to the study drug of possible, probable, and definitely related.

A summary of incidence rates (frequencies and percentages) of AEs leading to discontinuation of study drug, grouped by MedDRA system organ class and preferred term, will be prepared by treatment group and overall.
A data listing of AEs leading to discontinuation of study drug will also be provided, displaying details of the event(s) captured on the CRF.
Any deaths that occur during the study will be listed.
Serious adverse events will be listed. The number and percent of subjects reporting SAEs, grouped by MedDRA system organ class and preferred term, will be tabulated by severity, relationship to study drug and by treatment group. The same split of four groups as for AEs will be prepared.

9.3.2 Clinical Laboratory Evaluations

Laboratory test results will be listed.

Laboratory values that are outside the normal range will be flagged in data listings.

Laboratory test results will be summarized descriptively by treatment and visit as both observed values and change from baseline values.

The number of subjects with clinical laboratory values below, within, or above the normal range by visit and in relation to baseline will be tabulated for each clinical laboratory analyte by treatment group (shift table).

9.3.3 Electrocardiograms

ECG results (normal/abnormal) will be listed. Clinically significant abnormalities will be flagged.

Descriptive summaries will be presented for ECG measures of QT interval and HR. These summaries will be presented by visit and treatment group.

The number and percentage of subjects with normal and abnormal ECG results will be summarized by treatment group.

9.3.4 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for body temperature, pulse rate, and blood pressure.

Clinically relevant abnormalities of BP and HR should be flagged.

Vital signs values that are outside the normal range will be flagged in data listings. Shift tables will also be provided.

9.3.5 Physical Examination

Physical examination results(normal/abnormal) will be listed and summarized by body system, by time points and treatment group.

10. PHARMACOKINETIC ANALYSIS

Trough values of tesofensine and metoprolol will be listed and summarized descriptively. A figure with the concentrations of tesofensine and metoprolol versus time will be prepared.

11. EFFICACY ANALYSIS

Analyses of efficacy endpoints will be based on the mITT Population.
Additionally, sensitivity analysis may be performed on the PPP in case mITT and PPP differ.

Continuous secondary efficacy endpoints will be compared between treatment arms by means using Analysis of Covariance (ANCOVA) including treatment as fixed factor and baseline value as covariate. Estimates and 95% confidence intervals of treatment differences will be calculated. During the double-blind phase changes from Baseline to week 24 will be compared between treatment arms.

During the open-label extension, the treatment arms will be based on the treatments assigned during the double-blind phase.
First, changes from Baseline to week 24 then between Baseline and week 48 will be compared between treatment arms. Additionally, changes from week 24 to week 48 may be compared between treatment arms. When comparing changes from Baseline to week 48 and from week 24 to week 48 the Baseline value will still be Day 1 value.

12. INTERIM ANALYSIS

No interim analysis is planned.

13. CHANGES IN THE PLANNED ANALYSIS

The Statistical Analysis Plan (SAP) will be finalized before the database lock. Should any additional changes of the statistical analysis be implemented, they will be described in the corresponding section of the final study report.

14. MOCK TABLES, LISTINGS AND FIGURES (TLFS)

The study TLF shells will be provided in a separate document, which will show the content and format of all tables, listings, and figures in detail.
All ICH required data in the database will be presented in data listings.
Data will be displayed as described in this SAP and in the supporting, separate TFL shells document(s).
If there is no data available for a table or listing (e.g., no deaths occurred in the study), the planned output will be displayed as “No data to report”.

15. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.