# STATISTICAL ANALYSIS PLAN

TM003

A Randomized, Open-label, Single-dose, Parallel-arm, Phase 1 Study to Investigate the Pharmacokinetic Profile of a Fixed-Dose Combination Tablet of Tesofensine and Metoprolol (Tesomet) and Co-Administration of Tesofensine Plus Commercial Metoprolol in Adult Healthy Subjects

**Version: Final 1.0**

**Date: 19/Jan/2018**

## REVISION HISTORY

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| Draft 1.0 | 29/Nov/2017 | Kees Duineveld | New Document |
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| Final 1.0 | 19/Jan/2018 | Kees Duineveld | Finalized |

## SIGNATURE PAGE – SANIONA A/S

**Declaration**

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

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## SIGNATURE PAGE - PAREXEL

**Declaration**

The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

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# ABBREVIATION AND ACRONYM LIST

| Abbreviation / Acronym | Definition / Expansion |
|---|---|
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| Anti-HBc | Hepatitis B core antibody |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| AUC | Area under the concentration-time curve |
| $AUC_{0-48}$ | AUC from time zero to 48 hours |
| BLQ | Below the lower limit of quantification |
| BMI | Body Mass Index |
| Bpm | Beats per minute |
| CPK | Creatine phosphokinase |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| $C_{max}$ | Maximum observed concentration |
| CS | Clinically significant |
| CV | Coefficient of variation |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| ER | Extended Release |
| FDC | Fixed-dose combination |
| gCV | Geometric CV |
| GGT | Gamma glutamyl transferase |
| gMean | Geometric Mean |
| Hb | Hemoglobin |
| HBsAg | Hepatitis B surface antigen |
| HCT | Hematocrit |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |

| Abbreviation / Acronym | Definition / Expansion |
|---|---|
| HR | Heart rate |
| IMP | Investigational Medicinal Product |
| IR | Immediate release |
| LDH | Albumin Lactate dehydrogenase |
| LLOQ | Lower limit of quantification |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCS | Not clinically significant |
| NK | Not known |
| NS | No Sample |
| PK | Pharmacokinetic |
| PT | Preferred Term |
| QTc | QT interval corrected for HR |
| QTcB | QT interval corrected for heart rate using Bazett's correction |
| QTcF | QT interval corrected for heart rate using Fridericia's correction |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SOC | System Organ Class |
| TSH | Thyroid-stimulating hormone |
| $t_{½}$ | Apparent terminal elimination half-life |
| TEAE | Treatment-emergent adverse event |
| TFL | Tables, Listings and Figures |
| $t_{max}$ | Time corresponding to occurrence of $C_{max}$ |
| WHO-DD | World Health Organisation - Drug Dictionary |
| WBC | White blood cell |
| $\lambda_z$ | Terminal elimination rate constant |

# STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final CSP 1.0, dated, 15/Sep/2017.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum.

## 1. STUDY OBJECTIVES

### 1.1 Primary Objective

- To evaluate the pharmacokinetic (PK) profile and relative bioavailability of a single dose of the Tesomet fixed-dose combination (FDC) tablet and co-administration of tesofensine plus commercial metoprolol

### 1.2 Secondary Objective

- To evaluate the PK profile and relative bioavailability of a single dose of the Tesomet FDC tablet in fed state
- To evaluate the PK profile of a single dose of the high and low dose of the Tesomet FDC tablet
- To evaluate overall safety and tolerability of the Tesomet FDC tablet and co-administration of tesofensine plus commercial metoprolol in adult healthy volunteers

## 2. STUDY DESIGN

This is a randomized, open-label, parallel-arm study in 60 healthy male subjects who meet the inclusion and none of the exclusion criteria for the study. Each subject will participate in a screening period, a baseline period (the day preceding drug administration), a single-dose treatment period with

an on-site observation period of at least 48 hours after the dose and an end-of-study (EoS) safety evaluation 7 days after dosing over the phone.

Subjects will be admitted to the study center at least 24 hours prior to dosing. Each subject will then be randomized to one of the 4 treatment groups and receive one of the following treatments:

- Treatment A (Test 1): A Tesomet FDC tablet (20 mg immediate release [IR] metoprolol, 1 mg tesofensine, 80 mg extended release [ER] metoprolol) in fasted condition ("High" dose)
- Treatment B (Test 2): A Tesomet FDC tablet (5 mg IR metoprolol, 0.2 mg tesofensine, 20 mg ER metoprolol) in fasted condition ("Low" dose)
- Treatment C (Comparator): 1 mg tesofensine (2 tablets of 0.5 mg), 25 mg commercial IR metoprolol (1 tablet of 25 mg), 75 mg commercial ER metoprolol (1 ER tablet of 25 mg and 1 ER tablet of 50 mg), fasted condition
- Treatment D (Test 3): A Tesomet FDC tablet (20 mg IR metoprolol, 1 mg tesofensine, 80 mg [ER] metoprolol in fed condition ("High" dose)

# 3. ENDPOINTS

## 3.1 Pharmacokinetics Endpoints

The following PK parameters for tesofensine and metoprolol will be determined after dosing for all 4 treatments, as appropriate:

- $C_{max}$: Maximum tesofensine and metoprolol concentrations determined directly from the concentration-time profile
- $AUC_{0-48}$: Area under the concentration-time curve (AUC) from pre-dose (time 0) to 48 hours postdose calculated using the linear-log trapezoidal rule
- $T_{max}$: Time of maximum tesofensine and metoprolol concentrations determined directly from the concentration-time profile
- $\lambda_z$: The terminal elimination rate constant determined by selection of at least 3 data points on the terminal phase of the concentration-time curves
- $t_{½}$: Terminal elimination half-life calculated as: $\ln 2/\lambda_z$

### 3.2 Safety Endpoints

The following safety variables will be recorded at regular intervals during the study:

- Vital signs supine blood pressure (BP), pulse, body temperature and respiratory rate)
- Twelve-lead Electrocardiogram (ECG): Heart Rate (HR), PR interval, QRS interval, RR interval, QT interval and QT interval corrected for HR (QTc) (Bazett's correction [QTcB] and Fridericia's correction [QTcF])
- Clinical laboratory tests (hematology, clinical chemistry and urinalysis)
- Adverse event assessments
- Concomitant medication assessments
- Physical examinations

## 4. STUDY POPULATION

The study population will consist of 60 healthy male subjects.

Detailed lists of inclusion and exclusion criteria are shown in Sections 4.2 and 4.3 of the CSP.

## 5. STATISTICAL BASIS FOR SAMPLE SIZE

Formal sample size calculations were not performed. The number of subjects was chosen based on literature and experience from similar studies and is considered sufficient to meet the study objectives. No formal statistical test will be performed. Only descriptive statistics for PK and safety data by treatment group will be presented. The sample size chosen is therefore judged reasonable to gain knowledge regarding key parameters in each of the treatment groups.

## 6. RANDOMIZATION

A total of 60 subjects is planned for enrollment in the clinical study (N=15 will be randomly assigned to one of the 4 treatment groups). Withdrawn subjects may be replaced after mutual agreement between Principal Investigator and Sponsor.

Prior to dosing on Day 1, subjects will be assigned a randomization number in accordance with the randomization code generated by PAREXEL International. The randomization code will include 3-digit subject numbers starting with 101.

If subjects withdraw prematurely from the study and are replaced under the direction of the Sponsor, then a replacement randomization number will be assigned. A replacement randomization code will be generated such that replacement subjects are assigned to the same treatment as the discontinued subjects. The replacement randomization code will differ only in randomization numbers, which will be 4-digit numbers starting with a leading 1 followed by the digits from the randomization number of the replaced subject. For example, if Subject 102 withdraws and is replaced, then the randomization number for the replacement subject will be 1102.

# 7. STATISTICAL ANALYSIS CONVENTIONS

## 7.1 Analysis Variables

### 7.1.1 Demographic and Background Variables

The following demographic and anthropometric information will be recorded:

- Date of informed consent
- Medical history (including previous and current medical conditions and medications)
- History of blood or plasma donation
- Drug, alcohol, caffeine (or other stimulating beverages) and smoking history
- Special diet (vegetarian)
- Age (years)
- Gender
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, Black, Asian, Native Hawaiian or other Pacific Islands, American Indian or Alaska Native, Asian-Japanese, Asian-Korean, Other)
- Height, without shoes (cm)

- Body weight (kg)
- Body mass index (BMI) (kg/m$^2$)

All medical history will be coded using Version 20.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

### 7.1.2 Safety Variables

#### *7.1.2.1 Adverse Events*

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

All AEs will be coded using Version 20.1 of MedDRA.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g., those occurring during treatment-free periods (including Screening or post-treatment follow-up periods), in association with study-related procedures and assessments.

Concomitant illnesses, which existed prior to entry into the clinical study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as part of the subject's medical history.

Any AE which started or increased in severity after first dosing of investigational medicinal product (IMP) is considered a treatment emergent AE (TEAE).

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known).
    - An AE that started or increased in severity on first dosing day of IMP with unknown start time will be considered a TEAE unless the end time is known and is before dosing time of the IMP

- Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings.

#### *7.1.2.2 Clinical Laboratory Tests*

The following safety laboratory parameters will be measured according to the schedule in Appendix 1:

- **Clinical Chemistry:** Alanine aminotransferase (ALT), Glucose, Albumin Lactate dehydrogenase (LDH), Alkaline phosphatase (ALP), Phosphorus, Aspartate aminotransferase (AST), Potassium, Blood urea nitrogen (BUN), Sodium, Calcium, Total bilirubin, Chloride, Total protein, Cholesterol, Triglycerides, Creatinine, Thyroid-stimulating hormone (TSH), Creatine phosphokinase (CPK), Uric acid, Gamma glutamyl transferase (GGT)

- **Hematology:** White blood cell (WBC) count, Neutrophils (percentage and absolute count), Red blood cell (RBC) count, Lymphocytes (percentage and absolute count), Hemoglobin (Hb), Monocytes (percentage and absolute count), Hematocrit (HCT), Eosinophils (percentage and absolute count), Mean corpuscular volume (MCV), Basophils (percentage and absolute count), Mean corpuscular hemoglobin (MCH), Platelet count, Mean corpuscular hemoglobin concentration (MCHC), RBC distribution width

- **Urinalysis:** Bilirubin, Blood, Glucose, pH, specific gravity, Ketones, Protein, Leukocytes, Urobilinogen, Nitrite

- **Viral Serology:** Hepatitis B core antibody (anti-HBc), Human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), (Types 1 and 2) antibodies, Hepatitis A virus antibodies (immunoglobulin M), Hepatitis C virus antibody (anti-HCV)

- **Drugs of abuse:** Amphetamines, Cocaine, Barbiturates, Opiates, Benzodiazepines, Phencyclidine, Cannabinoids, Cotinine, Ethanol

#### *7.1.2.3 Vital Signs*

The following vital signs measurements will be obtained according to the schedule in Appendix 1:

- Systolic blood pressure (SBP) [mmHg]

- Diastolic blood pressure (DBP) [mmHg]

- Pulse rate [bpm]

- Body temperature (oral) [°C]
- Respiratory rate [breaths per minute]

#### *7.1.2.4 Electrocardiograms*

The following ECG parameters will be recorded according to the schedule in Appendix 1:

- RR-interval [msec]
- PR (PQ)-interval [msec]
- QRS-interval [msec]
- QT-interval [msec]
- QT-interval corrected using the Bazett correction formula (QTcB) [msec]
- QT-interval corrected using the Fridericia correction formula (QTcF) [msec]
- Heart rate (HR) (beats per minute [bpm])

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS (Not clinically significant)' or 'Abnormal, CS (clinically significant)'.

#### *7.1.2.5 Physical Examination*

The physical examination will be performed according to the schedule in Appendix 1.

#### *7.1.2.6 Concomitant Medication*

Concomitant medication will be coded using the World Health Organisation-Drug Dictionary (WHO-DD) (Version **Jun2017**) and will be classified by Anatomical Therapeutic Chemical (ATC) categories up to level 2.

### 7.1.3 Pharmacokinetic Variables

Blood sampling for PK will be performed according to the schedule in Appendix 1.

Unless otherwise stated, derivation of pharmacokinetic (PK) parameters will be the responsibility of Early Phase, Quantitative Clinical Development (QCD), PAREXEL International. The following PK

parameters will be determined for tesofensine and metoprolol in plasma following single dose administration as appropriate:

**Table 1 Pharmacokinetic Parameters after Single Dose Administration**

| Parameter | Definition |
|---|---|
| $C_{max}$ | Maximum observed concentration |
| $T_{max}$ | Time corresponding to occurrence of $C_{max}$ |
| $t_{½}$ | Apparent terminal elimination half life |
| $\lambda_z$ | Terminal elimination rate constant |
| $AUC_{0-48}$ | AUC from time zero to 48 hours |
| $\lambda_z$ lower | First time point for $\lambda_z$ calculation |
| $\lambda_z$ upper | Last time point for $\lambda_z$ calculation |

#### *7.1.3.1 Pharmacokinetic Parameter Calculation Methods*

PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data using WinNonlin Professional (Version **6.3** or later) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.
- All below the limit of quantification (BLQ) values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. Thereafter BLQ values between evaluable concentrations will be substituted as missing, before the calculation of the PK variables. Terminal BLQ values will be disregarded.

PK parameters will be estimated according to the following guidelines:

- $C_{max}$ will be obtained directly from the concentration-time data.
- $T_{max}$ is the time at which $C_{max}$ is observed.
- $\lambda_z$ will be estimated at terminal phase by linear regression after log-transformation of the concentrations:

- Only those data points that are judged to describe the terminal log-linear decline will be used in the regression; the first and last time points used in the calculation of $\lambda_z$ will be listed.
- A minimum number of three data points in the terminal phase will be used in calculating $\lambda_z$ with the line of regression starting at any post-$C_{max}$ data point ($C_{max}$ should not be part of the regression slope).
- The adjusted correlation coefficient ($R^2$ adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the PK Scientist's best knowledge and judgment. ($R^2$ adjusted is the Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of $\lambda_z$).
- An appropriate number of decimal places should be used for $\lambda_z$ to enable the reported value of $t_{½}$ to be calculated.

- $t_{½}$ will be calculated as $\ln 2/\lambda_Z$.
- AUC is calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
  - $AUC_{0\text{-}48} = \int_0^{48} C(t)dt$ .
    - For concentration-time profiles where the last quantifiable concentration occurs prior to 48h, extrapolation to 48 hours will be accomplished for the calculation of $AUC_{0\text{-}48}$.

## 7.2 Analysis Populations

### 7.2.1 Randomized Set

The Randomized Set will consist of all subjects who have been randomized

### 7.2.2 Safety Population

The Safety Population will consist of all randomized subjects who received at least one dose of study drug. Subjects will be included in analyses according to the dose and study drug received.

### 7.2.3 Pharmacokinetic Population

All randomized subjects with at least one quantifiable tesofensine or metoprolol concentration. Subjects will be included in the analysis according to the dose and study drug received.

Data may be excluded from PK analysis (concentrations listed only) if any of the following criteria are fulfilled:

- Concomitant medication, which could render the plasma concentration-time profile unreliable
- Subject vomits within 2 x the reported median $t_{max}$ of the treatment in which the subject is analyzed for the analyte.
- Subject has moderate or severe diarrhea within 2 x the reported median $t_{max}$ for the analyte.
- Major protocol deviations which could affect the concentration profile

Any data excluded will be discussed in the Clinical Study Report (CSR).

## 7.3 Statistical Analysis Methods

### 7.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed and described using summary statistics. Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). All listings will include repeated and unscheduled measurements.

The following rules will apply to any repeated measurements:

- If the repeated measurement occurs prior to the first dose of study drug then the last obtained value of any repeated measurement will be used in the descriptive statistics.

- If the repeated measurement occurs after the first dose of study drug then the original value of any repeated measurements will be used in the descriptive statistics.

- All descriptive statistics will be presented by treatment (dose). The baseline for all measurements (where applicable) will be the last pre-dose measurement.

### 7.3.2 Rounding and Decimal Places

- The following rules will be followed with regard to the number of decimal places and presentation of data in the tables and listings of safety data:

    1. All data will be listed according to the number of decimal places presented in the source data
    2. Mean and median will be tabulated to one more decimal place than the source data
    3. Minimum and maximum values will be tabulated to the same number of decimal places as the source data
    4. Standard deviation will be tabulated to two more decimal places than the source data
    5. Coefficient of variation (CV)%, if applicable, will be presented to one decimal place
    6. Percentages will be displayed to two decimal places.

- The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK concentration data:

    1. The individual concentrations will be reported to the same precision as the source data (for example, if the source data is presented to five significant digits, the individual values will be presented to five significant digits)
    2. The mean, SD, geometric mean (gMean), geometric SD and median will be tabulated to one more significant digit compared to the source data.
    3. Minimum and maximum values will be tabulated to the same precision as the source data.
    4. Geometric CV% will be presented to one decimal place.

- The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK parameters:

    1. Individual PK parameters will be presented to three significant digits, with the exception of $t_{max}$, which will be presented to two decimal places. In addition, parameters directly derived from source data (e.g. $C_{max}$) shall be reported with the same precision as the source data

2. The mean, gMean, median and SD values will be reported to one more significant digit than the source data, except for CV% which will be presented to one decimal place. For $t_{max}$, the median, minimum and maximum will be presented to two decimal places

### 7.3.3 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.3 or later. The PK analysis will be performed using WinNonlin Professional Software Version 6.3.

### 7.3.4 Missing Data

There will be no imputation of missing data.

### 7.3.5 Interim Analysis

Not applicable.

### 7.3.6 Disposition

Subject disposition will be listed. The number and percentage of subjects entering and completing the clinical study will be presented by treatment.

Subjects excluded from the safety and PK analysis sets and data excluded from the PK analysis will be listed including the reason for exclusion. Subject disposition will be summarized by treatment and will include the following information: number of subjects randomized, dosed and in PK analysis set, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all subjects randomized.

Subject discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

A randomization listing will be presented and include the following: each subject's randomization number and the treatment to which the subject has been randomized

### 7.3.7 Protocol Deviations

All protocol deviations will be recorded by the Investigator and will be listed by subject. All protocol deviations will be discussed between PAREXEL (physician, Data Manager, Biostatistician, PK

Scientist/Analyst) and also the Sponsor during the data review meeting before database lock in order to determine whether these may warrant exclusion of a subject from the statistical analyses.

### 7.3.8 Demographic Data

All demographic data will be presented using the safety population. Demographic characteristics will be summarized by treatment and for all subjects using both the safety population and the PK population.

### 7.3.9 Concomitant Medication

Prior medications are those that started and stopped prior to the first dose of investigational medicinal product (IMP). Concomitant medications are those taken after first dosing (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed by subject and will include the following information: reported name, WHO-DD Preferred Term (PT), ATC code, the route of administration, dose, frequency, start date/time, duration and indication.

### 7.3.10 Exposure to the Investigational Medicinal Product

A listing of drug administration will be created and will include the date and time of administration, consumption of breakfast and for treatment D the time of breakfast.

### 7.3.11 Pharmacokinetic Concentrations and Variables

The analysis of the PK data will be based on the PK population.

Concentrations below the lower limit of quantification (LLOQ) will be indicated by BLQ in the listings.

Pharmacokinetic concentration data will be listed by subject including actual sampling times relative to dosing. Plasma concentrations will be summarized by analyte and treatment and timepoint. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric SD, geometric CV% (calculated as: $gCV\%=SQRT(e^{s^2}-1)*100$; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

Pharmacokinetic parameters will be listed by subject and summarized by treatment. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, CV%, geometric mean, median, minimum and maximum values. For $t_{max}$, only median, minimum and maximum values will be presented. Additional summary by will be provided using dose normalized $C_{max}$ and $AUC_{0-48}$. For the dose normalized summary, the parameters for treatment B will multiplied with a factor 4 for metoprolol and with a factor 5 for tesofensine. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

Individual plasma concentration versus actual times will be plotted for each analyte in linear and semi-logarithmic scale. Mean plasma concentrations versus nominal times will also be presented in linear and semi-logarithmic scale by analyte, SD will be added in the plot for the linear scale. All treatments will be overlaid on the same plot.

#### *7.3.11.1 Exploratory Model for Relative Bioavailability*

Relative bioavailability will be estimated for tesofensine and metoprolol by the ratios of the gMeans (test/comparator [T/C]) for $AUC_{0-48}$ and $C_{max}$. Comparator will be treatment C. Additionally, their two-sided 90% CIs will be provided.

The statistical model will be a one way analysis of variance (ANOVA) on the logarithmic scale including fixed effects for treatment. For each endpoint, the difference between the expected means for log(T)-log(C) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). CIs will be calculated based on the residual error from ANOVA. The differences between the test and reference product and the CIs will be back-transformed to the original scale, resulting in point estimates of the T/C gMean ratios and 90% CIs.

#### *7.3.11.2 Handling of Values Below the Limit of Quantification in Concentration Summaries and Listings*

**Handling of values BLQ in listings and for the calculation of descriptive statistics at each time point:**

All concentrations BLQ or missing data will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis.

Values that are BLQ will be substituted with zero for the calculation of descriptive statistics of concentration by time point.

**Graphical presentation:**

Any BLQ values prior to the last quantifiable concentration will be plotted at zero for individual linear/linear graphs and excluded from log/linear graphs. All BLQ values after the last quantifiable concentration will be excluded from individual linear/linear and log/linear graphs.

For graphs of arithmetic means all BLQ mean concentrations will follow the rules of summary statistics. Graphs of geometric means include only time points with minimum concentration greater than zero. Any arithmetic mean that is BLQ will be excluded from log/linear presentation of arithmetic means.

### 7.3.12 Safety Analysis

The analysis of the safety variables will be based on the safety population.

#### *7.3.12.1 Adverse Events*

The following listings will be produced:

- All pre-treatment AEs and TEAEs.
- Withdrawals due to AEs (if applicable).
- SAEs (if applicable).

The following information will be included in the listings: AE number, reported term, System Organ Class (SOC), PT, start and end date/time, intensity, causality, action taken, outcome, classified as serious and treatment emergence.

Numbers of TEAEs will be summarized by treatment (including category any treatment), SOC, PT, and also by treatment, SOC, PT and severity and also by treatment (including category any treatment), SOC, PT and causality to treatment. In addition serious TEAES will be summarized by treatment, SOC and PT.

#### *7.3.12.2 Clinical Safety Laboratory Tests (hematology, biochemistry and urinalysis)*

Laboratory values (hematology, biochemistry and urinalysis) will be listed by subject and study time point including changes from baseline (with the exception of urinalysis). The baseline for the laboratory values will be the last observation prior to dosing, these are expected to be the results obtained on Day -1.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal NCS or abnormal CS. Clinically significant laboratory values will be recorded by the Investigator as AEs.

Descriptive statistics (for non-categorical data including hematology and biochemistry) will be presented by treatment for both individual values (N, mean, SD, median, minimum, maximum) and changes from baseline.

Shift tables of laboratory range classification from baseline to Day 2 will be presented for clinical chemistry, hematology and urinalysis laboratory parameters.

#### *7.3.12.3 Vital Signs*

Vital signs data will be listed by subject including changes from baseline. The baseline for the vital signs measurements will be the last observation prior to dosing, these are expected to be the pre-dose measurements on Day 1.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by treatment.

Spaghetti plots of SBP, DBP, pulse rate and respiratory rate will be presented by treatment, using time points Day -1 to Day 3, both inclusive.

#### *7.3.12.4 Twelve-Lead Electrocardiogram*

All ECG parameters obtained from the ECG measurement will be listed by subject for each treatment and time point including changes from baseline. The baseline for the ECG measurements will be the last observation prior to dosing, this is expected to be the pre-dose measurement obtained on Day 1.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by treatment.

Spaghetti plots of QTcF, QTcB and HR will be presented by treatment, using time points Day -1 to Day 3, both inclusive.

A categorical QTc analysis will be performed. QTcF and QTcB will be summarized in four categories: ≤450ms, interval >450ms and ≤480 ms, interval >480 ms and ≤500 ms, >500 ms. Change from baselines will be summarized in three categories, ≤30 ms, interval >30 ms and ≤60 ms, >60 ms.

#### *7.3.12.5 Physical Examination*

The abnormal results of the physical examination will be listed by subject and time-point.

# 8. REFERENCES

1. SAS® Version 9.2 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. WinNonlin Professional Software Version 6.3. http://www.pharsight.com

# 9. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

**Subject Disposition**

**Table 14.1.1** Subject Analysis Sets (Randomized Population)

**Table 14.1.2** Subject Disposition by Treatment (Randomized Population)

**Baseline and Demographic Data**

**Table 14.1.3** Subject Demographics (Safety Population)

**Table 14.1.4** Subject Demographics (Pharmacokinetic Population)

**Pharmacokinetic Data**

**Table 14.2.1** Summary of Tesofensine Plasma Concentrations (unit) versus Nominal Sampling Times by Treatment (Pharmacokinetic Population)

**Table 14.2.2** Summary of Metoprolol Plasma Concentrations (unit) versus Nominal Sampling Times by Treatment (Pharmacokinetic Population)

**Table 14.2.3** Summary of Tesofensine Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)

**Table 14.2.4** Summary of Metoprolol Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)

**Table 14.2.5** Summary of Dose Normalized Tesofensine Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)

**Table 14.2.6** Summary of Dose Normalized Metoprolol Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)

**Table 14.2.7** Statistical Analysis of Pharmacokinetic Parameters of Tesofensine in Plasma

(Pharmacokinetic Population)

**Table 14.2.8** Statistical Analysis of Pharmacokinetic Parameters of Metoprolol in Plasma (Pharmacokinetic Population)

**Safety Data**

**Table 14.3.1.1** Summary of Treatment Emergent Adverse Events (Safety Population)

**Table 14.3.1.2** Treatment Emergent Adverse Events by Treatment, System Organ Class and Preferred Term (Safety Population)

**Table 14.3.1.3** Treatment Emergent Adverse Events by Treatment, System Organ Class, Preferred Term and Causality (Safety Population)

**Table 14.3.1.4** Treatment Emergent Adverse Events by Treatment, System Organ Class, Preferred Term and Severity (Safety Population)

**Listing 14.3.2.1** Serious Adverse Events (Safety Population)

**Listing 14.3.2.2** Adverse Events Leading to Withdrawal (Safety Population)

**Listing 14.3.4.1** Abnormal Clinical Chemistry Values (Safety Population)

**Listing 14.3.4.2** Abnormal Hematology Values (Safety Population)

**Listing 14.3.4.3** Abnormal Urinalysis Values (Safety Population)

**Table 14.3.5.1** Clinical Chemistry (Safety Population)

**Table 14.3.5.2** Hematology (Safety Population)

**Table 14.3.5.3** Clinical Chemistry Shift Table (Safety Population)

**Table 14.3.5.4** Hematology Shift Table (Safety Population)

**Table 14.3.6.1** Vital Signs (Safety Population)

**Table 14.3.6.2** Electrocardiograms (Safety Population)

**Table 14.3.6.3** Categorical Analysis Electrocardiograms (Safety Population)

# 10. FIGURES

**Figure 14.2.1** Subject Profiles for Tesofensine Plasma Concentration Time Data (Linear Scale) (Pharmacokinetic Population)

**Figure 14.2.2** Subject Profiles for Metoprolol Plasma Concentration Time Data (Linear Scale) (Pharmacokinetic Population)

**Figure 14.2.3** Subject Profiles for Tesofensine Plasma Concentration Time Data (Semi-logarithmic Scale) (Pharmacokinetic Population)

**Figure 14.2.4** Subject Profiles for Metoprolol Plasma Concentration Time Data (Semi-logarithmic Scale) (Pharmacokinetic Population)

**Figure 14.2.5** Mean (± Standard Deviation) Profiles for Tesofensine Plasma Concentration Time Data (Linear Scale) (Pharmacokinetic Population)

**Figure 14.2.6** Mean (± Standard Deviation) Profiles for Metropolol Plasma Concentration Time Data (Linear Scale) (Pharmacokinetic Population)

**Figure 14.2.7** Mean Profiles for Tesofensine Plasma Concentration Time Data (Semi-logarithmic Scale) (Pharmacokinetic Population)

**Figure 14.2.8** Mean Profiles for Metoprolol Plasma Concentration Time Data (Semi-logarithmic Scale) (Pharmacokinetic Population)

**Figure 14.3.1** Spaghetti Plots of Vital Signs (Safety Population)

**Figure 14.3.2** Spaghetti Plots of ECG Parameters (Safety Population)

# 11. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

**Subject Disposition**

**Listing 16.2.1.1** Withdrawals from the Study (Randomized Set)

**Listing 16.2.1.2** Informed Consent (Randomized Set)

**Listing 16.2.1.3** Study Visits (Safety Population)

**Listing 16.2.1.4** Failed Inclusion and Exclusion Criteria (Safety Population)

**Listing 16.2.2** Protocol Deviations (Safety Population)

**Listing 16.2.3** Assignment to Analysis Populations (Randomized Set)

**Baseline and Demographic Data**

**Listing 16.2.4.1** Subject Demographics (Safety Population)

**Listing 16.2.4.2** Medical History (Safety Population)

**Listing 16.2.4.3** Subject Habits (Safety Population)

**Listing 16.2.4.4** History of Blood or Plasma Donation(Safety Population)

**Concomitant Medication**

**Listing 16.2.4.5** Prior and Concomitant Medication (Safety Population)

**Exposure**

**Listing 16.2.5.1** Exposure to Investigational Medicinal Product (Safety Population)

**Listing 16.2.5.2** Individual Blood Sampling Times and Concentrations (Safety Population)

**Pharmacokinetic Data**

**Listing 16.2.6.1** Pharmacokinetic Parameters of Tesofensine (Pharmacokinetic Population)

**Listing 16.2.6.2** Pharmacokinetic Parameters of Metoprolol (Pharmacokinetic Population)

**Safety Variables**

**Listing 16.2.7** Adverse Events (Safety Population)

**Listing 16.2.8.1** Clinical Chemistry (Safety Population)

**Listing 16.2.8.2** Hematology (Safety Population)

**Listing 16.2.8.3** Urinalysis (Safety Population)

**Listing 16.2.8.4** Serology (Safety Population)

**Listing 16.2.8.5** Drugs of Abuse (Safety Population)

**Listing 16.2.9.1** Vital Signs (Safety Population)

**Listing 16.2.9.2** Electrocardiogram Parameters (Safety Population)

**Listing 16.2.9.3** Abnormal Physical Examinations

# 12. DOCUMENTATION OF STATISTICAL METHODS

Appendix 16.1.9.1: WinNonlin outputs

Appendix 16.1.9.2: Statistical Analysis of Pharmacokinetic Parameters of Tesofensine in Plasma (Pharmacokinetic Population)

Appendix 16.1.9.3: Statistical Analysis of Pharmacokinetic Parameters of Metropolol in Plasma (Pharmacokinetic Population)

# 13. APPENDIX 1: SCHEDULE OF ASSESSMENTS

| Evaluation | Screening | | Treatment Period | | | Safety FU Phone call |
|---|---|---|---|---|---|---|
| | Day -30 to Day -2 | Admission Day -1 | Baseline / Day 1 | Day 2 | Discharge Day 3 | Day 8 |
| Admission | | X | | | | |
| In-house stay[a] | | X | X | X | X | |
| Ambulatory visits | X | | | | | |
| Informed consent | X | | | | | |
| Medical history | X | | | | | |
| Demographics | X | | | | | |
| Inclusion/exclusion criteria | X | | | | | |
| Physical examination | X | X | | | X | |
| Height and body weight, BMI | X | | | | | |
| Viral serology | X | | | | | |
| Supine blood pressure and pulse[b] | X | X | X | X | X | |
| Body temperature, respiratory rate[c] | X | X | X[d] | X | X | |
| Clinical laboratory tests (clinical chemistry, hematology and urinalysis) | X | X | | X | | |
| Urine drug screen, cotinine and alcohol test | X | X | | | | |
| 12-lead ECG[d] | X | X | X | X | X | |
| Randomization | | | X | | | |
| Study drug administration[e] | | | X | | | |
| Blood sampling for PK[f] | | | X | X | X | |
| Prior/concomitant medications | X | X | X | X | X | X |
| AE monitoring | X | X | X | X | X | X |
| Discharge | | | | | X | |

AE = adverse event; BMI = Body Mass Index; ECG = electrocardiogram; FU = Follow-up; PK = pharmacokinetics

[a] Subjects will be admitted in the morning of Day -1 and will leave the study center on Day 3 after completion of all study-related assessments.

[b] At Screening and on Day -1. On Day 1 at pre-dose and 1, 2, 4, 8, 12 and 16 hours post-dose, on Day 2 at 24, 30 and 36 hours post-dose and on Day 3 at 48 hours post-dose.

[c] Once daily, on in-house days in the morning.

[d] At Screening and on Day -1. On Day 1 at pre-dose and 1, 6 and 12 hours post-dose, on Day 2 at 24 hours post-dose and on Day 3 at 48 hours post-dose.

[e] In Treatment Groups A, B and C, dosing will be performed after an overnight fast of at least 10 hours before dosing and subjects will fast until 4 hours post-dose. At 4 hours after dosing a light standardized meal will be served.
In Treatment D, subjects will be required to eat an FDA standardized high-fat breakfast within a period of 30 minutes before dosing. The Investigator or a designee will administer the treatment to the subjects 30 minutes after start of the breakfast and within 5 minutes of completing the meal.
The Investigator or a designee will administer the appropriate treatment with 240 mL water to the subjects as per randomization schedule. If more water is needed for the intake of the 5 tablets in Group C, up to further 200 mL water may be taken.

[f] Blood sampling at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36 and 48 hours post-dose.