Clinical Study Protocol

A Phase 1 Study to Examine Pharmacodynamic Interaction Between Tesofensine and Metoprolol on 24-hours Mean Heart Rate

Sponsor:	Saniona A/S Baltorpvej 154 DK-2750 Ballerup Denmark
Contract Research Organization:	PAREXEL International GmbH Early Phase Clinical Unit Klinikum Westend, Haus 31 Spandauer Damm 130 14050 Berlin, Germany
Principal Investigator:	Dr. med. Astrid Breitschaft
PAREXEL Study Number:	238081
Sponsor Study Number:	TM004
EudraCT Number:	2018-000660-28
IMP Names:	Tesofensine, metoprolol
Development Phase:	Phase 1, pharmacodynamic interaction
Version (Date) of Previous Protocol:	Final 1.0 (03 April 2018)
Date of Protocol:	Final 2.0, 14 June 2018, incorporates Amendment No. 01

This clinical study will be conducted in accordance with the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (GCP) (E6), the Declaration of Helsinki (Version 1996), the protocol and with other applicable regulatory requirements.

Confidentiality Statement

SUMMARY OF CHANGES OF AMENDMENT 1

The final Version 1.0 of this protocol (protocol final version f1.0, dated 03 April 2018) was submitted to the German Authorities (BfArM) and the Berlin Ethics Committee. In addition, typographical errors were also corrected and linguistics as well as administrative changes were made by means of this amendment.

This amendment 1.0 serves to incorporate the following items as requested by the BfArM and the Ethics Committee:

A restriction with regard to the maximum number of subjects that might be replaced due to other reasons than adverse events (AEs) related to the investigational medicinal products has been added (up to 25% in the study).

To specify in more detail which aspects of the medical history and which exact findings during physical examination will lead to exclusion of a subject, threshold values for HbA1c to exclude diabetic subjects (inclusion criterion 7) and creatinine to exclude subjects with renal impairment (exclusion criterion 7) as well as threshold values for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (exclusion criterion 4) to exclude subjects with liver diseases have been added.

A rationale has been added to justify the inclusion of subjects with a body mass index (BMI) of up to 40 kg/m^2, in order to clarify that the obese subjects to be included will have to be otherwise healthy and without comorbidities.

To clarify that no comorbidities shall be expected, wording was added that subjects to be include, though overweight, are healthy.

Pregnant and lactating females have been excluded from participation.

Contraindications, warnings and precautionary measures listed in the Summary of Product Characteristics (SPC) of metoprolol have been added to the exclusion criteria.

With regard to concomitant medications restrictions it was added that the use of any prescribed or non-prescribed drugs is prohibited before admission also for five half-lives of the respective drug, if this is results in more than 2 weeks.

The psychodiagnostic self-rating instruments (Generalized Anxiety Disorder Assessment [GAD-7] and Patient Health Questionnaire-9 [PHQ-9]) have been added to the Screening-procedure, to ensure that no subjects with disposition to neuropsychiatric disorders (like anxiety disorders or depression) or to suicidal ideation or self-harm will be included.

Pregnancy tests have been added for the end of trial visits as well as during Follow-up to test for absence of pregnancy throughout the complete period where highly effective methods of contraception have to be used. In addition it has been added that a pregnancy test will be performed whenever clinically indicated.

A stopping criterion has been added to ensure termination of the study in case of occurrence of psychiatric AE.

References have been added referring to the Investigator Brochure (IB) of tesofensine.

The risk-benefit assessment section has been updated to reflect that psychiatric events occurred in an age group and population completely different from the one to be included in this study. No serious or severe cardiovascular AEs have been reported to date.

These changes affected the following sections:

Protocol Amendment No. 1

Sections Affected	Changes and Reasons
Protocol Synopsis Study Design, Inclusion Criteria, Exclusion Criteria, Criteria for Evaluation,	Added to study design that dosing of tesofensine will be performed "approximately 30 minutes" after start of breakfast. Exchanged "within" with "approximately" in study design with regard to metoprolol-dosing 30 minutes after start of a standard breakfast. Changed that subjects will be withdrawn due to other reasons than "tesofensine related AEs" to " investigational medicinal product (IMP)-related AEs" in the study design, and added that that only "(up to 25% in the study)" subjects withdrawn due to other reasons than IMP-related AEs will be replaced. Inclusion criterion 3 (on the inclusion of obese but healthy subjects) has been added. The previous inclusion criterion 4 on BMI has been deleted. An inclusion criterion requiring HbA1c < 6.5% at Screening has been added. "Metabolic acidosis" has been added to exclusion criterion 1. Threshold values for specific liver function tests have been added (exclusion criterion 4) It has been added to exclusion criterion 5 that for diastolic blood pressure (DBP) and systolic blood pressure (SBP) value-determination the mean of triplicate measurements will be used. Exclusion criterion 6 on cardiac parameters (QTc) has been amended, now using the mean of 3 measurements to determine electrocardiogram (ECG) parameters. The previous exclusion criterion 13 has been moved here as well (to exclude clinically significant cardiac arrhythmia). Also added were several cardiac conditions to reflect the contraindications stated in the SPC of metoprolol. Subjects with a creatinine value above the upper limit of normal (ULN) are now excluded by criterion 7. Exclusion criterion 9 (on use of any prescribed or non-prescribed drugs) has been amended by addition of "or five half-lives of the drug, whichever is longer ". Exclusion criterion 16 has been amended (on participation in any clinical study) has been amended by addition of "or five half-lives of the drug, whichever is longer" and deletion of "provided that the clinical study did not entail a biological compound with a long t1/2 ". The psychodiagnostic self-rating instruments (PHQ-9 and GAD-7) have been added (criterion 17). Exclusion of pregnant or lactating subjects was added (criterion 21). Those contraindications for metoprolol that have not explicitly been mentioned in other exclusion criteria have now been added as exclusion criterion 24. Exclusion criterion 25 has been amended to exclude also a rare hereditary problem of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency. The last exclusion criterion (number 30) has been amended to exclude ultrarapid CYP2D6 metabolizers in addition to poor metabolizers Secondary Endpoints have been clarified, to reflect that maximum and minimum heart rate (HR)24 are abbreviated by HRmax and HRmin.

List of Abbreviations and Definition of Terms	Updated.
Introduction, Section 1	Third paragraph has been updated by adding that 2 of the 3 studies with co-administation of tesofensine and metoprol have been completed. Added a reference to the Tesofensine IB.
Introduction, Pharmacokinetics, Section 1.1	Changed reference in section on tesofensine from Tesomet IB to Tesofensine IB.
Introduction, Pharmacokinetics, Section 1.1.3	Changed title of section by deleting "Tesomet" and keeping part in brackets. Added a reference to the Tesofensine IB.
Introduction, Rationale for the Clinical Study, Section 1.2.1	Added study number "NS2330-001, (“TIPO-1”)" to first sentence in second paragraph and moved last 3 sentences of same paragraph directly behind the first sentence. Added a paragraph on long-term studies. Number of subjects that have been included in studies on tesofensine (examining the metabolic and weight loss effects in patients) has been changed from 800 to 900. Added a reference to the Tesofensine IB.
Introduction, Rationale for the Clinical Study, Section 1.2.3	Number of studies in which tesofensine tablet and metoprolol tablet have been co-administered to humans has been changed from 3 to 4. Added that studies Q-21125 and TM001 have been completed and that "third" refers to study TM003.
Risk-Benefit Assessment, Section 1.3	Reference to "Tesomet"-IB changed to "Tesofensine IB". Wording has been added with regard to low risk of metoprolol administration, since healthy subjects will be included. In addition paragraphs have been added discussing psychiatric and cardiovascular risks based on previous studies. In addition it has been added that at Screening the psychodiagnostic self-rating instruments (PHQ-9 and GAD-7) will be performed to exclude subjects with a predisposition to neuropsychiatric disorders like anxiety disorders or depression or to suicidal ideation or self-harm. A reference to the Tesofensine IB has been added.
Overview, Section 3.1	Corrections were made to reflect that dosing of tesofensine will be performed "approximately 30 minutes" after start of breakfast. In addition, with regard to metoprolol-dosing "within 30 minutes after start of breakfast" has been exchanged with "approximately…".
Figure 1 and Figure 2	An addition has been made to Day 23, to reflect that before each PK sample or at corresponding time of the day resting 12-lead ECG, blood pressure (BP) and pulse will be assessed.
Endpoints, Section 3.2	Secondary Endpoints have been clarified, to reflect that maximum and minimum HR24 are abbreviated by HRmax and HRmin
Justification of the Study Design, Section 3.3	Changes have been made to reflect that not only poor, but also ultrarapid metabolizers will be excluded from participation in this study.
Stopping Criteria and Termination of the Clinical Study, Section 3.4	A psychiatric stopping criterion has been added
Study Population, Section 4	A paragraph has been added to explain that subjects with obesity grade 1 and 2 will be included and why this is justified, with regard to safety.
Number of subjects, Section 4.1	Added that only "(up to 25% in the study)" subjects will be withdrawn due to other reasons than to IMP-related AEs and that only healthy subjects will be included.
Inclusion Criteria, Section 4.2	Inclusion criterion 3 (on the inclusion of obese but healthy subjects) has been added. The previous inclusion criterion 4 on BMI has been deleted.

	An inclusion criterion requiring a HbA1c < 6.5% at Screening has been added.
Exclusion Criteria, Section 4.3	"Metabolic acidosis" has been added to exclusion criterion 1. Threshold values for specific liver function tests have been added (exclusion criterion 4) It has been added to exclusion criterion 5 that for DBP and SBP value-determination the mean of triplicate measurements will be used. Exclusion criterion 6 on cardiac parameters (QTc) has been amended, now using the mean of 3 measurements to determine ECG parameters. The previous exclusion criterion 13 has been moved here as well (to exclude clinically significant cardiac arrhythmia). Also added were several cardiac conditions to reflect the contraindications stated in the SPC of metoprolol. Subjects with a creatinine value above ULN are now excluded by criterion 7. Exclusion criterion 9 (on use of any prescribed or non-prescribed drugs) has been amended by addition of "or five half-lives of the drug, whichever is longer ". Exclusion criterion 16 has been amended (on participation in any clinical study) has been amended by addition of "or five half-lives of the drug, whichever is longer " and deletion of "provided that the clinical study did not entail a biological compound with a long t1/2 ". The psychodiagnostic self-rating instruments (PHQ-9 and GAD-7) have been added (criterion 17). Exclusion of pregnant or lactating subjects was added (criterion 21). Those contraindications for metoprolol that have not explicitly been mentioned in other exclusion criteria have now been added as exclusion criterion 24. Exclusion criterion 25 has been amended to exclude also a rare hereditary problem of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency. The last exclusion criterion (number 30) has been amended to exclude ultrarapid CYP2D6 metabolizers in addition to poor metabolizers.
Subject Withdrawal and Replacement, Section 4.4	Changed to reflect that subjects will be withdrawn due to other reasons than "tesofensine related AEs" to "IMP-related AEs" in the study design, and added that that only "(up to 25% in the study)" subjects will be withdrawn due to other reasons than to IMP-related AEs
Administration of Investigational Medicinal Products, 5.6	Added to study design that dosing of tesofensine will be performed "approximately 30 minutes" after start of breakfast. Exchanged "within" with "approximately" in study design with regard to metoprolol-dosing 30 minutes after start of a standard breakfast
Compliance, Section 5.7	Wording adapted (no change of content)
Blinding and Breaking the Blind, Section 5.8	Specified that a glass of water corresponds to 240 mL. It has been added that subjects can drink an additional 200 ml of water if needed for swallowing the tablets.
Medical History, Demographic and Other Baseline Information, Section 6.1	A third bullet has been added to medical history i.e. family history of psychiatric disorders.
Recording of Adverse Events, Section 6.2.1.2	It has been added that causality of AEs will be assessed separately for tesofensine and metoprolol
Assessment of Adverse Events, Section 6.2.1.3	It has been added that causality of AEs will be assessed separately for tesofensine and metoprolol

Reporting of Serious Adverse Events, 6.2.1.4	The address (email and FAX) to send the SAE Report Form to has been changed from PAREXEL to KLIFO Pharmacovigilance Service. "Year of birth" has been changed to "Age". It has been added that details can be found in the SMP.
Pregnancy, Section 6.2.1.6	A section on pregnancy has been added.
Clinical Laboratory Assessments, Table 3	HbA1c has been added (only Screening).
Vital Signs, Section 6.2.3	It has been added that measurements will be taken as triplicates and that mean of these 3 values will be used to assess eligibility.
Standard 12-lead Electrocardiograms, Section 6.2.4	It has been added that measurements will be taken as triplicates and that mean of these 3 values will be used to assess eligibility.
Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder Assessment (GAD-7), Section 6.2.6	A section on PHQ-9 and GAD-7 has been added.
Pharmacodynamic Variables 6.4	Added the following: “With regard to HRmin and HRmax the minute in which the minimum and the minute in which the maximum HR occurred will be determined over the 24 hour period”.
Schedule of Assessments, Table 5 and Table 6	The psychodiagnostic self-rating instruments (PHQ-9 and GAD-7) have been added at Screening. The footer has been updated, with regard to footnote d and e (referring to days on which triplicate measurements will be performed). HbA1c has been added to Screening. It has been added that a pregnancy tests will be performed whenever deemed necessary and that additional tests will be performed on Day 24 and at the Follow-up (FU) call at home. Only to the Flowchart of Cohort 3 a BP and pulse-measurement has been added for Days 4 and 5.
Interim Analyses; Section 8.11	Details have been added.
Reference list, Section 10	The IB of Tesofensine has been added.

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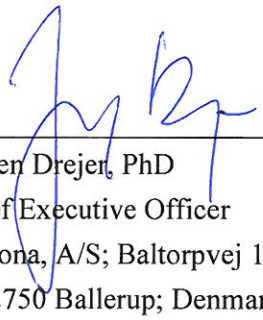
Declaration of Sponsor or Responsible Medical Expert

Protocol Title: A Phase 1 Study to Examine Pharmacodynamic Interaction Between Tesofensine and Metoprolol on 24-hours Mean Heart Rate

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert



June 15th 2018

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Declaration of the Principal Investigator and Deputy Principal Investigator

Protocol Title: A Phase 1 Study to Examine Pharmacodynamic Interaction Between Tesofensine and Metoprolol on 24-hours Mean Heart Rate

This clinical study protocol was subjected to critical review and has been released by the Sponsor. The information it contains is consistent with current risk and benefit evaluation of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

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PROTOCOL SYNOPSIS

Protocol Title	A Phase 1 Study to Examine Pharmacodynamic Interaction Between Tesofensine and Metoprolol on 24-hours Mean Heart Rate
Study Numbers	PAREXEL Study No.: 238081 Sponsor Protocol No.: TM004
Development Phase	Phase 1, pharmacodynamic interaction
Sponsor	Saniona A/S
Principal Investigator	Dr. med. Astrid Breitschaft
Study Center	PAREXEL International GmbH Early Phase Clinical Unit Berlin Klinikum Westend, Haus 31 Spandauer Damm 130 14050 Berlin, Germany The study will be conducted at a single center (PAREXEL International GmbH, Early Phase Clinical Unit Berlin).
Study Objectives	**Primary objective:** To determine the optimal dose of metoprolol to mitigate the effect of tesofensine on heart rate (HR) **Secondary objectives:** • To confirm that addition of metoprolol mitigates the effect of tesofensine on HR • To examine the concentration-response relationship between tesofensine and metoprolol on HR and blood pressure (BP) • Assess the time dependence of tesofensine effect on HR by comparing HR data under tesofensine alone • Safety and tolerability of tesofensine alone and co-administration of tesofensine and metoprolol
Study Design	This is a randomized, open-label for tesofensine and single-blind for metoprolol, parallel-arm study in 60 male and female subjects who meet the inclusion and none of the exclusion criteria for the study. Each subject will participate in a Screening Period (Day -28 to Day -3), a Baseline Period (Day -2 to Day -1) and a Treatment Period (Day 1 to Day 24) and will have 2 Follow-up phone calls (Day 30 and Day 50). The Treatment Period will comprise: • In Cohorts 1 and 2, an initial in-house stay (Day -2 to Day 3) until the last loading dose of tesofensine has been administered on Day 3 or In Cohort 3, an initial in-house stay until the third loading dose tesofensine has been administered on Day 3 • In Cohorts 1 and 2, a home-dosing period (Day 4 to Day 12, once daily dosing to achieve steady state of tesofensine with an ambulatory visit in the clinical unit on Day 7) or In Cohort 3, 2 ambulatory visits on Days 4 and 5 with administration of the 4th and 5th loading dose, followed by a home-dosing period (Day 6 to Day 12, once daily dosing to achieve steady state of tesofensine with an ambulatory

	visit in the clinical unit on Day 7) and • A second in-house stay (Day 13 to Day 24). Safety evaluations will be performed on Day 30 and Day 50 (end-of-study [EoS]) after last dosing over the phone. A total of 60 subjects will be randomly assigned to one of the following treatment cohorts: **Cohort 1** (20 subjects): tesofensine 0.25 mg once daily for 23 days (loading dose of 1.0 mg for the first 3 days) **Cohort 2** (20 subjects): tesofensine 0.50 mg once daily for 23 days (loading dose of 2.0 mg for the first 3 days) **Cohort 3** (20 subjects): tesofensine 0.75 mg (0.25 mg + 0.50 mg) once daily for 23 days (loading dose of 2.0 mg [4 tablets of 0.50 mg] for the first 5 days) Dosing of tesofensine will be performed approximately 30 minutes after start of breakfast. Timing and quantity of meals will be consistent on pharmacokinetic (PK) and pharmacodynamic (PD) days, i.e., on Day -1, Day 13, Day 14, Day 15, Day 17, Day 18, Day 20, Day 21 and Day 23. In addition, each subject will receive a single dose of 25 mg, 50 mg or 100 mg metoprolol extended release (ER) in random order in the morning of Day 15, Day 18 and Day 21, respectively, approximately 30 minutes after start of a standard breakfast and together with the tesofensine dose. For each subject assessments (24-hour ECG, blood sampling for PK of metoprolol and tesofensine [Day 15, Day 18 and Day 21 only], blood sampling for PK of tesofensine [Day 13, Day 14 and Day 23 only] and 12-lead ECG, BP and pulse before each blood sampling for PK) will be performed to examine the dose-response relationship in combination of tesofensine and metoprolol: o On the day before start of investigational medicinal product (IMP) dosing (on Day -1) At tesofensine steady state o On Day 14 and 15 (before and after the 1st metoprolol dose) o On Day 17 and 18 (before and after the 2nd metoprolol dose) o On Day 20 and 21 (before and after the 3rd metoprolol dose) o And on Day 23 (tesofensine alone) In addition, safety assessments will be performed throughout the study. Day 16, Day 19 and Day 22 will be wash-out days for metoprolol. At each dosing of metoprolol, a metoprolol placebo tablet will be administered in addition to the metoprolol tablet in order to mask the dose level of metoprolol. On in-house dosing days (i.e., Day 1 to Day 3, Day 7 and Day 13 to Day 23 and, in addition in Cohort 3, Day 4 and Day 5), the Investigator or a designee will administer the IMP(s), i.e., tesofensine, metoprolol and placebo, to the subjects approximately 30 minutes after start of the breakfast. From Day 4 to Day 6 (Cohorts 1 and 2) or on Day 6 (Cohort 3) and from Day 8 to Day 12 (all cohorts), subject will self-administer a single dose of tesofensine approximately 30 minutes after start of a breakfast. For each of the treatment groups, blood samples will be collected pre-dose and at designated time points post dosing. Pharmacodynamic (PD) assessments (24-hour Holter-ECG, 12-lead ECG, BP and pulse) will be performed pre-dose and at designated time points post dosing. Subjects will be discharged from the clinical unit after the 48 hours post-dose assessments have been completed on Day 3. Subjects will have a home-dosing period (from Day 4 to Day 6 [Cohorts 1 and 2] or on Day 6 [Cohort 3] and from Day 8 to Day 12 [all

	cohorts]) with once daily dosing to achieve steady state of tesofensine with an ambulatory visit in the clinical unit (on Day 7) and a second in-house stay (Day 13 to Day 24). At the Safety Follow-up phone calls (on Day 30 and Day 50), subjects will be asked regarding adverse events (AE), and concomitant medications. The total duration for each subject will be up to 78 days, including Screening and Follow-up period.
Investigational Medicinal Products	• Tesofensine, film-coated tablet, 0.25 mg: o Oral dose of 4 tablets once daily from Day 1 to Day 3, Cohort 1 only (loading dose of 1.0 mg) o Oral dose of 1 tablet once daily from Day 4 to Day 23, Cohort 1 only o Oral dose of 1 tablet once daily from Day 6 to Day 23, Cohort 3 only • Tesofensine, film-coated tablet, 0.50 mg: o Oral dose of 4 tablets once daily from Day 1 to Day 3, Cohort 2 only (loading dose of 2.0 mg) o Oral dose of 4 tablets once daily from Day 1 to Day 5, Cohort 3 only (loading dose of 2.0 mg) o Oral dose of 1 tablet once daily from Day 4 to Day 23, Cohort 2 only o Oral dose of 1 tablet once daily from Day 6 to Day 23, Cohort 3 only o Metoprolol, 25 mg ER tablet (Metoprololsuccinat "Orion" 25 mg, depottabletter; each tablet contains 23.75 mg metoprolol succinate equivalent to 25 mg metoprolol tartrate; manufacturer: Orion Corporation, [Finland]) o Single oral dose of 1 tablet in each subject of Cohort 1, Cohort 2 and Cohort 3, on Day 15, Day 18 or Day 21 • Metoprolol, 50 mg ER tablet (Metoprololsuccinat "Orion" 50 mg, depottabletter; each tablet contains 47.5 mg metoprolol succinate equivalent to 50 mg metoprolol tartrate; manufacturer: Orion Corporation, [Finland]) o Single oral dose of 1 tablet in each subject of Cohort 1, Cohort 2 and Cohort 3, on Day 15, Day 18 or Day 21 • Metoprolol, 100 mg ER tablet (Metoprololsuccinat "Orion" 100 mg, depottabletter; each tablet contains 95 mg metoprolol succinate equivalent to 100 mg metoprolol tartrate; manufacturer: Orion Corporation, [Finland]) o Single oral dose of 1 tablet in each subject of Cohort 1, Cohort 2 and Cohort 3, on Day 15, Day 18 or Day 21 • Metoprolol placebo film-coated tablet; manufacturer: Solural Pharma ApS (Denmark) o Single oral dose of 1 tablet in each subject at each metoprolol dosing i.e., on Day 15, Day 18 and Day 21 Each subject will receive tablets for all days with self-administration of tesofensine. Subjects in Cohort 1 will receive 0.25 mg tablets, subjects in Cohort 2 will receive 0.50 mg tablets and subjects in Cohort 3 will receive 2 containers – one with 0.25 mg tablets and one with 0.50 mg tablets.
Number of Subjects	A total of 60 subjects are planned for enrollment. The subjects will be randomly assigned to one of the 3 treatment cohorts with 20 subjects per

	cohort. Reasonable efforts will be made to achieve gender balance; at least 8 subjects of each gender will be included into each cohort. Subjects withdrawn due to other reasons than IMP-related AEs may be replaced (up to 25% in the study) after mutual agreement between Principal Investigator and Sponsor. Overweight and obese subjects will be included in order to investigate the effects in the target population.
Study Population	**Inclusion Criteria** Subjects who meet the following criteria will be considered eligible to participate in the clinical study: 1. Subject voluntarily agrees to participate in this study and signs an Independent Ethics Committee (IEC)-approved informed consent prior to performing any of the Screening procedures. 2. Male and female subjects between 18 to 60 years of age, inclusive, at Screening. 3. Overweight and obese subjects with a body mass index (BMI) between ≥ 27 and < 40 kg/m^2 at Screening but otherwise healthy. 4. Non-smokers (or other nicotine use) as determined by history (no nicotine use over the past 6 months) and by urine cotinine concentration (< 500 ng/mL) at Screening and admission. 5. No clinically relevant deviation or finding in pre-study medical evaluation (medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory evaluations). 6. HbA1c < 6.5% at Screening. 7. Subject is willing to adhere to the contraception requirements details in Section 7.5.2 of the clinical study protocol. **Exclusion Criteria** Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study: 1. Subject has history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic (e.g., diabetes, metabolic acidosis), urologic, pulmonary (e.g., asthma or chronic obstructive pulmonary disease), neurologic, dermatologic, psychiatric, renal, and/or other major disease or malignancy as judged by the Investigator. 2. Subject has any disorder that would interfere with the absorption, distribution, metabolism or excretion of drugs. 3. Subject has a clinically significant abnormality following the Investigator's review of the physical examination, ECG and clinical study protocol-defined clinical laboratory tests at Screening or admission to the clinical unit or has any concurrent disease or condition that, in the opinion of the Investigator, would make the subject unsuitable for participation in the clinical study. One re-test is allowed, if (a) test result(s) is outside the limits. 4. History or presence of liver disease or liver injury, as indicated by abnormal liver function tests including: • aspartate aminotransferase (AST) > 1.2 x upper limit of normal (ULN) • alanine aminotransferase (ALT) > 1.1 x ULN 5. Subject has a pulse < 50 or > 90 bpm; systolic blood pressure (SBP) < 90 mmHg or > 140 mmHg; diastolic blood pressure (DBP) < 50 mmHg or > 90 mmHg (using the mean of triplicate measurements) at Screening or admission. One re-test is allowed, if (a) test result(s) is outside these limits. 6. History of any clinically significant cardiac arrhythmia. Subject has a

	corrected QT interval using Fridericia's formula (QTcF) interval > 450 msec or 2nd or 3rd degree atrioventricular (AV) block, high-grade sinoatrial block or PQ interval > 0.24 seconds at Screening (using the mean of triplicate measurements). If a mean ECG parameter of a triplicate ECG exceeds the limits above, an additional triplicate ECG may be taken. If this also gives an abnormal result, the subject will be excluded. Also the following cardiac conditions will lead to exclusion of the subjects: Untreated heart failure (pulmonary oedema, impaired blood flow or hypotension) and continuous or intermittent treatment leading to an increased contractility of the heart muscle (beta-receptor agonism); Sick sinus syndrome; cardiogenic shock; severe peripheral arterial circulatory disturbances. 7. Has a creatinine value exceeding the ULN. 8. Subject has positive test for hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (indicative of active hepatitis B), hepatitis A virus antibodies (immunoglobulin M), hepatitis C virus (HCV) antibodies or human immunodeficiency virus (HIV) 1 and/or -2 antibodies. 9. Use of any prescribed or non-prescribed drugs (including vitamins, natural and herbal remedies, e.g., St. John's Wort) in the 2 weeks prior to admission, or 5 half-lives of the drug, whichever is longer, except for the occasional use of paracetamol (up to 2 g/day) or other non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraception for female subjects. 10. Subject has history of alcohol and/or illicit drug abuse within 2 years of entry. 11. Subject has positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids) or alcohol test at Screening or at admission. 12. History of drinking > 168 g (males) and > 84 g (females) pure alcohol per week (10 g pure alcohol = 259 mL of beer [5%] or 35 mL of spirits [35%] or 100 mL of wine [12%] within 3 months prior to admission to the clinical unit. 13. Subject consumes more than 600 mg caffeine per day (e.g., more than 3 cups of coffee containing 200 mg caffeine per cup) within the 4 weeks before admission or the subject is unwilling to avoid consumption of coffee and caffeine-containing beverages within 48 hours prior to admission until discharge from the clinical unit. 14. Subject is unwilling to avoid use of alcohol or alcohol-containing foods, medications or beverages, within 48 hours prior to Screening and from admission until discharge from the clinical unit. 15. Any significant blood loss, donated one unit (450 mL) of blood or more, or received a transfusion of any blood or blood products within 60 days, or donated plasma within 7 days prior to the admission to the clinical unit. 16. Participation in any clinical study within 3 months or 5 half-lives of the drug, whichever is longer, prior to the expected date of IMP administration, or participation in more than 3 clinical studies within 12 months. 17. Subject with a relevant history or with a present psychiatric disorder, including depression, suicidal ideation, or eating disorders (e.g., bulimia or anorexia nervosa). Subjects with a medical history of relevant psychiatric disorders or known and relevant family history or evidence of anxiety disorders or depression as judged by the Investigator using the Generalized Anxiety Disorder Assessment (GAD-7) and Patient Health Questionnaire-9 (PHQ-9) at Screening. Any of the following will lead to exclusion of the subject: • Subject has a GAD-7 mood scale score ≥ 10 • Subject has a score ≥ 10 on the PHQ-9 questionnaire • Subject selects a response of "1, 2 or 3" to question number 9 on the

	PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9). 18. Use of any agent used for weight loss within the last 3 months. 19. More than 5% weight loss within the last 3 months. 20. Hypo- or hyperthyroidism. 21. Subject is pregnant or lactating. 22. Subject is unwilling to abstain from vigorous exercise from 48 hours prior to admission until discharge. 23. Subject has a history of hypersensitivity to the IMPs or any of the excipients or to medicinal products with similar chemical structures. 24. Any contraindication for metoprolol, e.g. severe peripheral arterial disease, untreated pheochromocytoma, concomitant intravenous administration of calcium antagonists of verapamil and diltiazem, due to the risk of hypotension, AV conduction disturbances, or left ventricular insufficiency. 25. Subject has lactose intolerance or a rare hereditary problem of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency. 26. Subject is unable to understand and communicate in German language or to understand the protocol requirements, instructions and study-related restrictions, the nature, scope and possible consequences of the clinical study or is unlikely to comply with the study requirements; e.g., uncooperative attitude and improbability of completing the clinical study. 27. Subject has previously been enrolled in this clinical study. 28. Vulnerable subjects defined as individuals whose willingness to volunteer in a clinical study may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate (e.g., persons in detention, minors and those incapable of giving consent). 29. Subject is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study or employee of the Sponsor or PAREXEL. 30. Poor or ultrarapid CYP2D6 metabolizer.
Criteria for Evaluation	**Primary Endpoint** The dose of metoprolol which will result in no change in M24HR for each respective dose of tesofensine – this will be calculated from a dose-response relationship with the dose of metoprolol as independent variable and change in M24HR induced by various doses of metoprolol given to patients on steady-state dose of tesofensine as the dependent variable. The dose for no change in M24HR derived from above calculation and the corresponding 95% CI will be calculated for each dose of tesofensine. **Secondary Endpoints** • The difference in increase in M24HR caused by tesofensine alone (calculated as the difference between the M24HR at pre-tesofensine baseline and the mean of M24HR on Days 14, 17, 20 and 23) and the reduction in M24HR following each of the 3 metoprolol doses (M24HR on Day 15, 18 or 21) • Mean and absolute change in M24HR between pre-tesofensine baseline (Day -1) and after tesofensine alone (Day 14, Day 17, Day 20 and Day 23) • Mean and absolute change in M24HR after tesofensine co-administered with metoprolol (Day 15, Day 18 and Day 21)

	• Maximum and minimum HR24 (HRmax and HRmin) values after tesofensine alone (Day 14, Day 17, Day 20, and Day 23) • HRmax and HRmin values after tesofensine co-administered with metoprolol (Day 15, Day 18 and Day 21) • Time of HRmin and HRmax after tesofensine alone (Day 14, Day 17, Day 20 and Day 23) • Time of HRmin and HRmax after tesofensine co-administered with metoprolol (Day 15, Day 18 and Day 21) • Mean HR during a designated quiet hour and a designated period after tesofensine alone (Day 14, Day 17, Day 20 and Day 23) • Mean HR during a designated quiet hour and a designated period after tesofensine co-administered with metoprolol (Day 15, Day 18 and Day 21) • HR after at least 10 minutes rest before each PK sampling time point or the corresponding time point (Day -1, Day 13 [pre-dose only], Day 14, Day 15, Day 17, Day 18, Day 20, Day 21 and Day 23) • SBP and DBP values after at least 10 minutes rest before each PK sampling time point or the corresponding time point (Day -1, Day 13 [pre-dose only], Day 14, Day 15, Day 17, Day 18, Day 20, Day 21 and Day 23) The following PK parameters will be determined: • C_{trough} of tesofensine on Day 13, Day 14, Day 15, Day 18, Day 21 and Day 23 • C_{max} of metoprolol on Day 15, Day 18, and Day 21 • T_{max} of metoprolol on Day 15, Day 18, and Day 21 • AUC_{0-24} of metoprolol on Day 15, Day 18, and Day 21 • Relation between metoprolol concentration and HR will be explored by tesofensine dose • A PK-PD curve for each dose of tesofensine will be generated with PK parameters (AUC_{0-24} and C_{max}) of metoprolol on the X-axis and change in M24HR on the y-axis. The X-axis intercept and the corresponding 95% CI will be calculated for each dose of tesofensine **Safety Endpoints** The following safety variables will be recorded at specified time points during the study: • Vital signs (supine BP, pulse and body temperature) • Twelve-lead electrocardiogram (ECG) • Clinical laboratory tests (hematology, clinical chemistry and urinalysis) • Adverse event assessments • Concomitant medication assessments • Physical examinations
Statistical Methods	*Sample Size Considerations* No formal sample size calculation has been performed. With a sample size of N=20 with 80% power assuming the same within-subject variability in HR as observed in the study TM001 (within-subject variability = 5%) a mean difference of 3.3 beats per minute can be detected within a tesofensine cohort. This detectable difference is smaller than the increase in HR induced by all 3 studied doses of tesofensine in the study TIPO-1; thus, 20 subjects per cohort should provide adequate sample size for the purpose of

this Phase 1 study.

Data Presentation/Statistics

- The mean and absolute change in M24HR after tesofensine alone will be calculated as the difference between the mean of the 3 pre-administration measurements on Day 14, Day 17 and Day 20 and the post-administration measurement on Day 23 and pre-tesofensine baseline (Day -1) and summarized descriptively by treatment.
- The mean and absolute change in M24HR after tesofensine co-administered with 3 different doses of metoprolol will be calculated as the difference between each mean of the 3 metoprolol doses on Days 15, 18 and 21, and pre-tesofensine baseline (Day -1) and summarized descriptively by treatment.
- The mean maximum and minimum HR24 values after tesofensine alone and when co-administered with 3 different doses of metoprolol will be summarized descriptively by treatment.
- The time of minimum heart rate (HRmin) and maximum heart rate (HRmax) after tesofensine alone and when co-administered with 3 different doses of metoprolol will be summarized descriptively by treatment.
- Mean SBP and DBP values after tesofensine alone and when co-administered with 3 different doses of metoprolol will be summarized descriptively by treatment.
- Mean HR during a designated quite hour and a designated period will be summarized descriptively by treatment.
- M24HR on Days 14, 17, 20 and 23 will be compared by means of analysis of variance (ANOVA) with random subjects nested under sequence. In this analysis there will be no period effect and treatment effect (such as metoprolol dose) other than the fixed days.
- Change from pre-tesofensine baseline (Day -1) of M24HR on Days 15, 18 and 21 will be compared by means of ANOVA with random subjects nested under sequence and fixed Day (Day 15, 18 and 21 will play the role of period in a conventional cross-over) and treatments. In this analysis the metoprolol dose will be distinguishing between treatments.
- Boxplots will be made on M24HR for Days -1, 14, 15, 17, 18, 20, 21 and 23 and will be displayed using treatment and treatment plus visit (for tesofensine days).

A cross-over ANOVA model will be used to reduce change from baseline M24HR data to mean levels for each dose (adjusting for subject, day and treatment effects). A straight line linear regression will be used to fit the means to log dose. Based on the regression equation a dose for no effect will be estimated. Confidence intervals will be determined using a bootstrap method.

Details of the modelling will be provided in the statistical analysis plan (SAP).

In case the linear model linking M24HR to log dose is clearly not satisfactory, an alternative strategy may be employed, for instance, by interpolation between 2 adjacent doses. The need and approaches for such analysis will be discussed after the initial analysis is finished.

The relation between metoprolol concentration and HR will be explored using plots of HR or time-matched change from baseline HR against concentration by tesofensine dose. The plots will possibly be augmented with local regression lines and confidence intervals.

A straight line regression will be used to fit change from baseline M24HR against PK parameters (AUC_{0-24} and C_{max}) of metoprolol for each tesofensine

	dose. Based on the regression equation a parameter value for no effect will be estimated. Confidence intervals will be determined using a bootstrap method. Details of the analysis and/or additional approaches will be provided in the SAP. A population PK-PD model may be developed if deemed appropriate on the data from this study with the final objective of describing relative contribution to the final effect of plasma exposure to tesofensine and metoprolol, simulating optimal dose regimen for multiple administration and evaluate effect of covariates (e.g., polymorphism of PK, body weight, gender) on the overall effect. Details of the analysis will be in case included in a separate Data Analysis Plan and outcome of the modelling will be reported separately. All demographic, safety, PD and PK data will be listed and summarized in tabular format by descriptive statistics as appropriate. Descriptive statistics will be applied and presented by treatment group. No imputation of missing data will be performed but for PK the trapezoidal method will handle missing data by interpolation over a single time point where PK is missing. Summary statistics of the PK parameters will be presented by treatment and dose-normalized when relevant. Pharmacokinetics data may also be displayed graphically as appropriate. A SAP will be issued as a separate document, providing detailed methods for the analyses.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-24}	Area under the concentration-time curve from pre-dose (time 0) until 24 hours post-dose
AV	Atrioventricular
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CL/F	Total body clearance
C_{max}	Maximum plasma concentration
CPK	Creatine phosphokinase
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome P450
DAT	Dementia of Alzheimer type
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DMP	Data management plan
ECG	Electrocardiogram
EoS	End-of-study
ER	Extended release
eSDR	Electronic source data report
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle-stimulating hormone

Abbreviation	Definition
GAD-7	Generalized Anxiety Disorder-7
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
HRmin	Minimum heart rate in 24 hours
HRmax	Maximum heart rate in 24 hours
i.v.	Intravenous
IB	Investigator's Brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IR	Immediate release
IUD	Intrauterine device
LDH	Lactate dehydrogenase
M24HR	Mean heart rate of 24 hours
MAO	Monoamine oxidase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-the-counter
PD	Pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic(s)

Abbreviation	Definition
PT	Preferred Term
QP	Qualified Person
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
RA	Regulatory authority
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SMP	Safety management plan
SNRI	Serotonin and norepinephrine reuptake inhibitor
SOC	System organ class
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SSRI	Selective serotonin reuptake inhibitor
$t_{½}$	Terminal elimination half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment emergent adverse event
T_{max}	Time of maximum plasma concentration
TSH	Thyroid-stimulating hormone
TZD	Thiazolidinediones
ULN	Upper limit of normal
USA	United States of America
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
λ_z	The terminal elimination rate constant

1. INTRODUCTION

Tesofensine was initially noted to cause a marked weight loss in overweight patients with Parkinson's disease and dementia of Alzheimer type (DAT), even though no attempts to promote weight control were included in the study. The weight reducing effect was confirmed in a subsequent Phase 2 clinical study in obese subjects (TIPO-1), exceeding benchmarks set by the regulatory agencies for approval of weight loss agents [1]. Although tesofensine was generally well tolerated in these studies, an increase of blood pressure (BP) of 1–5 mmHg and an increase of heart rate (HR) up to 8 beats per minute (bpm) were observed in patients dosed with 0.25 to 1.0 mg of tesofensine once daily.

Historically, cardiovascular (CV) safety and the need for a favorable CV safety profile has been a critical requirement and hurdle for approval in the area of endocrine and metabolic, thus, it has been concluded that any increase in HR and/or BP constitutes an unacceptable safety risk and significantly impacts the overall benefit/risk profile of tesofensine. Consequently, it has been decided by Saniona not to develop tesofensine as a stand-alone therapy. Instead, Saniona decided to develop combination product (Tesomet): tesofensine combined with metoprolol, a β1-(cardio-selective) selective adrenoceptor-blocking agent, in order to mitigate the increase in BP and HR.

To date, co-administration of tesofensine and metoprolol to human has been investigated in 3 clinical studies of which 2 have been completed. First, a Phase 1 drug-drug interaction study (Q-21125) where a single dose of metoprolol was added to tesofensine administered for 14 days to study pharmacokinetics (PK) of both when administered together. Second, a Phase 2 study in obese and overweight patients with type 2 diabetes mellitus (T2DM) (TM001) designed to provide the proof-of-concept data that addition of metoprolol mitigates the tesofensine-induced increase in HR and BP. In both studies, the co-administration of the drugs was generally well tolerated and the collected data have provided good base for future investigation of a fixed combination of tesofensine and metoprolol (Tesomet) for various indications. Third, the clinical part of a Phase 1 study with the new fixed-dose combination multi-layer tablet Tesomet (TM003) has just been completed.
Currently, there is an ongoing Phase 2 study in patients with Prader-Willi syndrome (TM002).

In addition, the clinical development program of Tesomet draws heavily on a substantial body of data available for tesofensine, for which - despite not being approved or developed as a stand-alone agent - there is a complete pre-clinical efficacy and safety data package available and

has been to date studied in more than 1300 subjects. Also, metoprolol was approved in the United States of America (USA) in 1978 and has since become one of the most widely used drugs ever with millions of patient-years of safety data available.

Given the mechanism of action, available pre-clinical and clinical data, it is anticipated that Tesomet could be developed for a variety of indications such as treatment of obesity, T2DM, pre-diabetes, Prader-Willi syndrome, binge eating disorder, etc.

For more information please see the Tesomet Investigator's Brochure (IB) [2] and Tesofensine IB [3].

1.1. Pharmacokinetics

1.1.1. Tesofensine

In man the clearance after oral administration was low (total body clearance [CL/F] 30 to 40 mL/min) and tesofensine was shown to have a long half-life ($t_{1/2}$) of about 9 days (220 hours). In all species including man the volume of distribution exceeded the total volume of body water, indicating that tesofensine was extensively distributed into the tissues. The protein binding was about 91%.

Tesofensine was mainly metabolized to the N-desmethyl-metabolite (NS2360), which was the only metabolite found in human plasma. NS2360 was shown to have a longer half-life than tesofensine, i.e., approximately 16 days (374 hours) in man and have an exposure of 31 to 34% of the parent compound at steady state. *In vivo* data indicated that NS2360 was responsible for approximately 6% of the activity. Similarly to animals, the kidney in man seems to play only a minor role in the clearance of tesofensine in man (about 15 to 20%).

The PK profile in man was linear after single and multiple doses over all doses tested. No relevant differences in the PK of healthy elderly subjects, patients with mild DAT or Parkinson's disease were observed. Similarly, no differences were observed between Japanese and Caucasians or between recreational drug abusers and non-abusers. No relevant changes of the PK in subjects with mild renal impairment were observed, but an increase in exposure (of about 30%) occurred in subjects with moderate and severe renal impairment. Steady state plasma concentrations in the target population (obese patients) did not differ significantly from that in healthy volunteers. The relative bioavailability of tesofensine was not significantly affected by food intake. Based on cross-study comparison with intravenous (i.v.) data the absolute bioavailability after oral administration was estimated to be > 90%. Investigation of cytochrome

P450 2D6 (CYP2D6) and CYP3A4 interaction in man did not indicate clinically relevant PK interactions.

For further details refer to the IB of tesofensine [3].

1.1.2. Metoprolol

Adults: In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the cerebrospinal fluid in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma $t_{1/2}$ ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in metoprolol succinate dosage is usually needed in patients with chronic renal failure.

Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and in about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Poor metabolizers and extensive metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity [4].

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of MetoHEXAL® 100 mg (metoprolol succinate extended release [ER] tablets) are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once daily administration of MetoHEXAL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the

average bioavailability of metoprolol following administration of MetoHEXAL, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24-hour dosing interval, β1-blockade is comparable and dose-related (see Section Clinical Pharmacology of Tesomet IB [2]). The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following MetoHEXAL administration.

1.1.3. Co-administration of Tesofensine and Metoprolol

PK data when tesofensine and metoprolol were co-administered chronically are available from the study TM001. Tesofensine, its N-desmethyl-metabolite (NS2360) and metoprolol concentrations in plasma were measured pre-dose at baseline and at the end of treatment. The tesofensine PK results obtained in this study are in line with the PK data obtained in the study TIPO-1 where tesofensine was administered in similar population of patients for 24 weeks. The exposures of metoprolol are also in line with those previously published.

For further details refer to the Tesomet IB [2], Tesofensine IB [3] and Summary of Product Characteristics (SPC) of metoprolol ER tablets [4].

1.2. Rationale for the Clinical Study

It has been decided to develop a fixed-dose combination tablets with tesofensine and metoprolol, with metoprolol mitigating the increases in BP and HR caused by tesofensine. In this study, the dose-response relationship between tesofensine and metoprolol will be examined and thus the optimal dose of metoprolol to mitigate the effects of tesofensine on HR will be determined. HR is the primary endpoint because in the previous studies it has been shown to be the most affected safety endpoint by the effects of tesofensine.

1.2.1. Safety in Previous Clinical Studies with Tesofensine

Sixteen Phase 1 studies with 339 healthy volunteers have been completed, with 289 subjects being exposed to tesofensine. Tesofensine was well tolerated up to and including single oral doses of 6.75 mg. Multiple daily doses up to 1.0 mg and loading doses up to 2.0 mg in Phase 1 studies were considered to be well tolerated. In all single and multiple dose Phase 1 studies in healthy volunteers, including a study with intravenous infusion up to 1.2 mg in volunteers, no changes in vital signs, electrocardiogram (ECG) or laboratory parameters assessed as clinically significant by the Investigator were observed, and no serious adverse events (SAEs) occurred.

Seven Phase 2 studies have been completed in patients with neurodegenerative diseases and one Phase 2 study in patients with obesity (NS2330-001, "TIPO-1"). In obese patients, one dose ranging study of 24 weeks' duration was conducted including 203 obese patients, with 151 of them exposed to 0.25 to 1.0 mg tesofensine. The most frequent adverse events (AEs) in this study were insomnia, dry mouth, dizziness, and constipation. These events were dose-dependent and categorized as expected for drugs belonging to the same pharmacological class. Three 4-week studies used forced-titration and included 62 patients (60 to 80 years) with possible DAT and 9 patients with advanced Parkinson's disease. A total of 53 of them were exposed to tesofensine. Tesofensine was well tolerated at all doses, i.e., daily doses up to 2.0 mg for the first 3 days (loading doses) followed by daily doses up to 1.0 mg for up to 25 consecutive days. In 4 dose finding studies of 14 weeks' duration, 1036 DAT and Parkinson's disease patients were included and 796 of them were exposed to doses of 0.125-1.0 mg of tesofensine.

Also a long-term study, TIPO-4 (an extension study of the "TIPO-1"-study with patients with uncomplicated obesity), over 48 weeks has been completed. In this study all patients started on 0.5 mg tesofensine for the first 24 weeks and could be uptitrated to 1.0 mg. The last 24 weeks all patients received 0.5 mg. Pooled data from these studies did not indicate increased incidence of cardiovascular events or reveal an increased incidence in any of the psychiatric AEs.

In conclusion, tesofensine has shown a robust, dose-dependent effect on weight loss in the target population of obese patients and a benign safety profile in toxicological and clinical studies compatible with its pharmacological profile. The emerging efficacy and safety profile of tesofensine from the studies in obese patients has identified a clinically relevant, safe and well tolerated dose range of 0.25 mg up to 6.75 mg.

Tesofensine has been evaluated in approximately 170 subjects in studies examining the metabolic and weight loss effects in overweight and obese patients and in approximately 900 patients in other indications.

Based on the pharmacological profile it can be assumed that tesofensine causes dopaminergic side effects such as insomnia, agitation, hallucinations, psychoses including delusion, paranoid ideation and depression.

The AEs which were commonly reported in all investigated populations were insomnia, dry mouth, dizziness, and constipation, which also expressed dose-dependency. In obese patients the most frequent AEs were dry mouth, headache, nasopharyngitis, nausea, influenza, insomnia, diarrhea, constipation, and back pain. Psychiatric side effects were more frequently reported in the elderly population (patients with Parkinson's disease or DAT). Psychotic events, such as

hallucinations, were also observed in this elderly population, mostly with high doses (> 0.75 mg/day).

Undesired effects which have been observed up to now comprise:

- Very frequently (> 10%): headache, insomnia, dizziness, somnolence, loss of appetite, lack of energy, dry mouth, attention disturbances, cold-like symptoms, diarrhea, constipation
- Frequently (< 10%): nausea, vomiting, fast pulse, muscle spasms, sweating, palpitations, vertigo, blurry vision, flatulence, abdominal pain or discomfort, tooth pain, fatigue
- Rarely (< 0.1%): altered state of consciousness, sensory disturbance, agitation and persecutory delusion were found in a subject with high doses of tesofensine.

Overdose

Clinical experience with tesofensine in overdose is limited. Exaggerated dopaminergic action should be anticipated with risk of psychotic behavior, cardiac symptoms (tachycardia, palpitations, atrial extrasystolia), orthostatic hypotension, and gastrointestinal symptoms (nausea, emesis, diarrhea).

For further details refer to the Tesomet IB [2] and Tesofensine IB [3].

1.2.2. Safety of Metoprolol

Metoprolol is a selective β_1 receptor blocker, used in the treatment of, e.g., hypertension, angina pectoris, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure and prevention of migraine headaches.

Metoprolol is available as IR and ER tablets and as solution for i.v. injection.

For further details refer to the SPC of metoprolol [4].

1.2.3. Safety of Co-administration of Tesofensine and Metoprolol

To date, tesofensine tablet and metoprolol tablet have been co-administered to humans in 4 clinical studies. Firstly, a Phase 1 drug-drug interaction (DDI) study (Q-21125) where a single dose of metoprolol was added to tesofensine administered for 2 weeks to study PK of both drugs when administered together. Secondly, a 90 days Phase 2 study in obese and overweight patients with T2DM (TM001) designed to provide the proof-of-concept data that addition of metoprolol mitigates the tesofensine-induced increase in HR and BP. In both studies (both completed), the co-administration of the drugs was generally well tolerated. No new or unexpected safety

findings have been observed in the study compared to previous studies with tesofensine alone. Third, the clinical part of a Phase 1 study (TM003) with the new fixed-dose combination multi-layer tablet of Tesomet has just been completed. Currently, there is an ongoing Phase 2 study in patients with Prader-Willi syndrome (TM002).

1.3. Risk-benefit Assessment

For details regarding safety data of tesofensine refer to the IB [3]. For details regarding safety data of metoprolol refer to SPC of metoprolol ER tablets [4].

Most probably, there will be no direct health benefit for the subjects from receipt of the Investigational medicinal product (IMP). Only subjects with overweight will be included and a decrease in body weight may occur after tesofensine treatment. However, due short duration of tesofensine dosing, more than slight to moderate decreases in body weight are unlikely to occur.

The protocol has been designed to minimize the risk to participating subjects: strict in- and exclusion criteria are implemented to minimize potential risks and subjects will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs. Metoprolol has already been approved for years, therefore side effects are well known. Obese but otherwise healthy subjects will be eligible for the study only, if they do not meet any contraindications or the listed special warnings from metoprolol SPC. Additionally, subjects will only be eligible to participate if they don't have comorbidities typical for obesity such as hypertension, diabetes or any cardiovascular conditions. Therefore it is acceptable to also include subjects with Grade 2 obesity who are otherwise healthy.

Tesofensine and metoprolol have been co-administered in 2 completed clinical studies: in the DDI study as well as in the study with T2DM. In both studies, the co-administration of the drugs was generally well tolerated. Steady state levels of tesofensine had no major influence on the PK of metoprolol (Study Q-21125). Increases in HR and BP may occur due to tesofensine dosing and decreases in HR and BP may occur due metoprolol dosing. Subjects with hyper- or hypotension will not be eligible for the study and vital signs will be measured at all visits. Subjects will be in-house on all metoprolol dosing days and on the days of the administration of the loading doses of tesofensine and they will be closely monitored. If needed remedial therapy would be immediately available. Specific stopping criteria have been employed.

Psychiatric AEs appeared to be associated with high single doses or forced titration of tesofensine and, importantly, in an age group (elderly) and populations (patients with Parkinson´s or Alzheimer´s disease) different from the population of this study. Insomnia

occurred as most prominent psychiatric event but only at higher loading doses. Psychotic events seen in healthy volunteers were associated either with a single dose treatment with more than > 6 mg of tesofensine, or with multiple doses of more than 2 mg/day of tesofensine. The maintenance doses planned for this study will be below these higher doses and the loading doses chosen will not exceed 2 mg/day.

In obese patients (TIPO-1), 1 dose ranging study of 24 weeks' duration was conducted including 203 obese patients, with 151 of them exposed to 0.25 to 1.0 mg tesofensine. The most frequent AEs in these studies were insomnia, dry mouth, dizziness, and constipation. These events were dose-dependent and categorized as expected for drugs belonging to same pharmacological class.

Cardiovascular AEs were most frequently reported in the elderly population, which was characterized by significant comorbidities, including cardiovascular conditions. Serious cardiovascular AEs were reported only in PD/DAT patients, in 2% of the subjects in the tesofensine group and in 4% in the placebo group. No clear dose-dependency was observed for any of the cardiovascular events reported in any target population. No serious or severe cardiovascular AEs have been reported to date.

Psychiatric tests (Patient Health Questionnaire-9 [PHQ-9] and Generalized Anxiety Disorder Assessment [GAD-7]) will be performed at Screening to exclude subjects with any psychiatric conditions or history of psychiatric conditions like anxiety disorders and or depression.

Taken together, data from the clinical studies do not suggest that tesofensine 0.25 mg and 0.5 mg once daily in obese patients or up to 2 mg/day (for 7 days) in healthy volunteers will be associated with a clinically significant undesirable psychiatric adverse effect profile.

Also, no additional risks are expected by the co-administration compared to those known for dosing of tesofensine and metoprolol alone.

Please refer to the IB of Tesofensine [3] for further details.

2. STUDY OBJECTIVES

The objectives of this study are as follows:

2.1. Primary Objective

- To determine the optimal dose of metoprolol to mitigate the effect of tesofensine on HR

2.2. Secondary Objectives

- To confirm that addition of metoprolol mitigates the effect of tesofensine on HR
- To examine the concentration-response relationship between tesofensine and metoprolol on HR and BP
- Assess the time dependence of tesofensine effect on HR by comparing HR data under tesofensine alone
- Safety and tolerability of tesofensine alone and co-administration of tesofensine and metoprolol

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1. Overview

This is a randomized, open-label for tesofensine and single-blind for metoprolol, parallel-arm study in 60 male and female subjects who meet the inclusion and none of the exclusion criteria for the study.

Each subject will participate in a Screening Period (Day -28 to Day -3), a Baseline Period (Day -2 to Day -1) and a Treatment Period (Day 1 to Day 24) and will have 2 Follow-up phone calls (Day 30 and Day 50).

The Treatment Period will comprise:

- In Cohorts 1 and 2, an initial in-house stay (Day -2 to Day 3) until the last loading dose of tesofensine has been administered on Day 3
  or
  In Cohort 3, an initial in-house stay until the third loading dose tesofensine has been administered on Day 3
- In Cohorts 1 and 2, a home-dosing period (Day 4 to Day 12, once daily dosing to achieve steady state of tesofensine with an ambulatory visit in the clinical unit on Day 7)
  or
  In Cohort 3, 2 ambulatory visits on Days 4 and 5 with administration of the 4th and 5th loading dose, followed by a home-dosing period (Day 6 to Day 12, once daily dosing to achieve steady state of tesofensine with an ambulatory visit in the clinical unit on Day 7)
  and
- A second in-house stay (Day 13 to Day 24). Safety evaluations will be performed on Day 30 and Day 50 (end-of-study [EoS]) after last dosing over the phone. A study overview is provided in Figure 1 and Figure 2.

A total of 60 subjects will be randomly assigned to one of the following treatment cohorts:

- **Cohort 1** (20 subjects): tesofensine 0.25 mg once daily for 23 days (loading dose of 1.0 mg for the first 3 days)
- **Cohort 2** (20 subjects): tesofensine 0.50 mg once daily for 23 days (loading dose of 2.0 mg for the first 3 days)

- **Cohort 3** (20 subjects): tesofensine 0.75 mg (0.25 mg + 0.50 mg) once daily for 23 days (loading dose of 2.0 mg [4 tablets of 0.50 mg] for the first 5 days)

Dosing of tesofensine will be performed approximately 30 minutes after start of breakfast. Timing and quantity of meals will be consistent on PK and pharmacodynamic (PD) days, i.e., on Day -1, Day 13, Day 14, Day 15, Day 17, Day 18, Day 20, Day 21 and Day 23.

In addition, each subject will receive a single dose of 25 mg, 50 mg or 100 mg metoprolol ER in random order in the morning of Day 15, Day 18 and Day 21, respectively, approximately 30 minutes after start of a standard breakfast and together with the tesofensine dose.

For each subject assessments (24-hour ECG, blood sampling for PK of metoprolol and tesofensine [Day 15, Day 18 and Day 21 only], blood sampling for PK of tesofensine [Day 13, Day 14 and Day 23 only] and 12-lead ECG, BP and pulse before each blood sampling for PK) will be performed to examine the dose-response relationship in combination of tesofensine and metoprolol:

- On the day before start of IMP dosing (on Day -1); Holter-ECG recording will be checked prior to dosing on Day 1 to confirm that at least 22 hours are evaluable for HR. If the Day - 1 Holter-ECG is not fully evaluable, it can be repeated (and the subject would be dosed later)

At tesofensine steady state

- On Day 14 and 15 (before and after the 1st metoprolol dose)
- On Day 17 and 18 (before and after the 2nd metoprolol dose)
- On Day 20 and 21 (before and after the 3rd metoprolol dose)
- And on Day 23 (tesofensine alone)

In addition, safety assessments will be performed throughout the study. Day 16, Day 19 and Day 22 will be wash-out days for metoprolol.

At each dosing of metoprolol, a metoprolol placebo tablet will be administered in addition to the metoprolol tablet in order to mask the dose level of metoprolol.

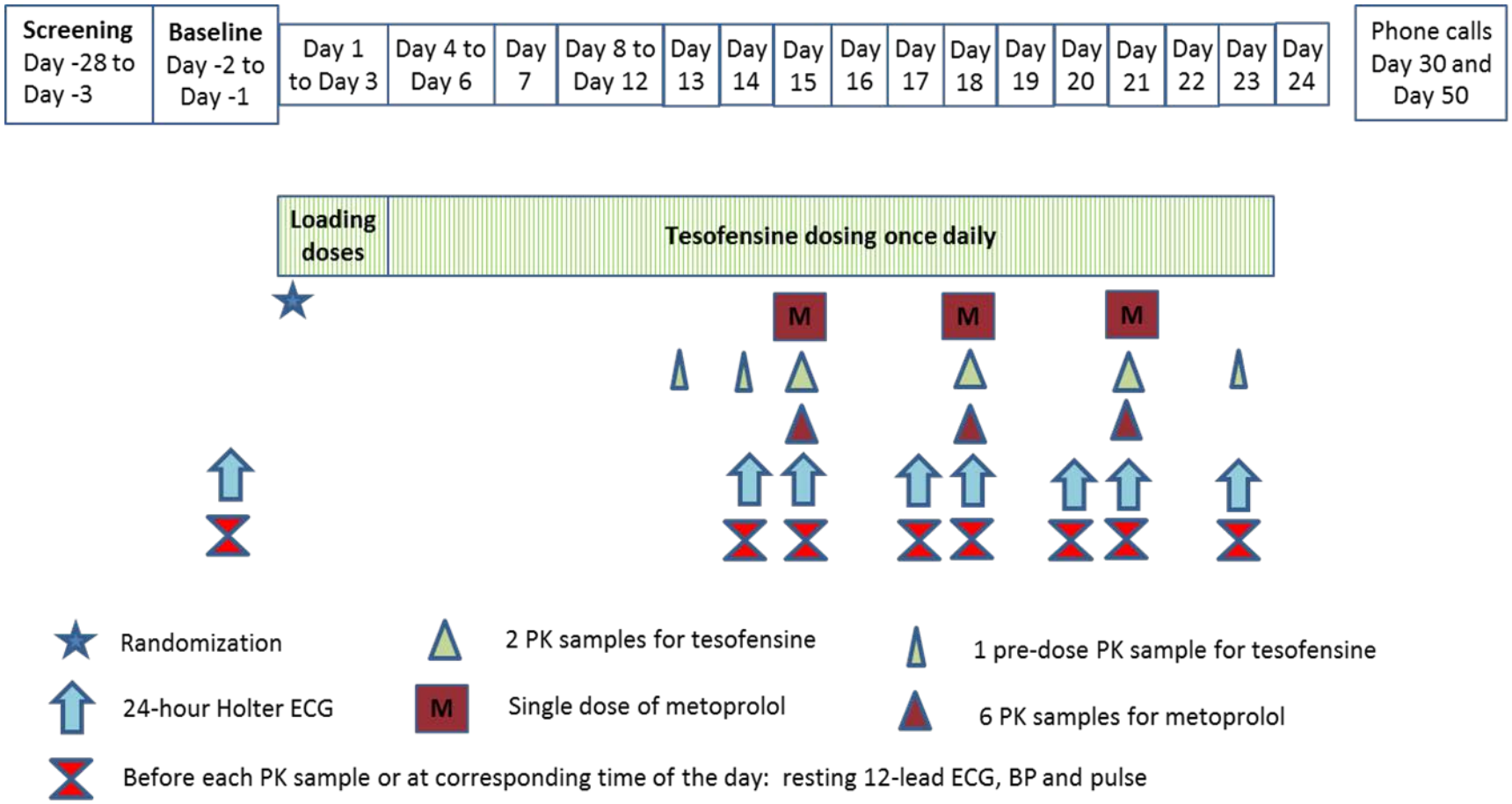
On in-house days (i.e., Day 1 to Day 3, Day 7 and Day 13 to Day 23 and, in addition in Cohort 3, Day 4 and Day 5), the Investigator or a designee will administer the IMP(s), i.e., tesofensine, metoprolol and placebo, to the subjects approximately 30 minutes after start of the breakfast. From Day 4 to Day 6 (Cohorts 1 and 2) or on Day 6 (Cohort 3) and from Day 8 to Day 12 (all

cohorts), subject will self-administer a single dose of tesofensine approximately 30 minutes after start of breakfast.

For each of the treatment groups, blood samples will be collected pre-dose and at designated time points post dosing. PD assessments (24-hour Holter-ECG, 12-lead ECG, BP and pulse) will be performed pre-dose and at designated time points post dosing. Subjects will be discharged from the clinical unit after the 48 hours post-dose assessments have been completed on Day 3. Subjects will have a home-dosing period (from Day 4 to Day 6 [Cohorts 1 and 2] or on Day 6 [Cohort 3] and from Day 8 to Day 12 [all cohorts]) with once daily dosing to achieve steady state of tesofensine with an ambulatory visit in the clinical unit (on Day 7) and a second in-house stay (Day 13 to Day 24). At the Safety Follow-up phone calls (on Day 30 and Day 50), subjects will be asked regarding AE, and concomitant medications.

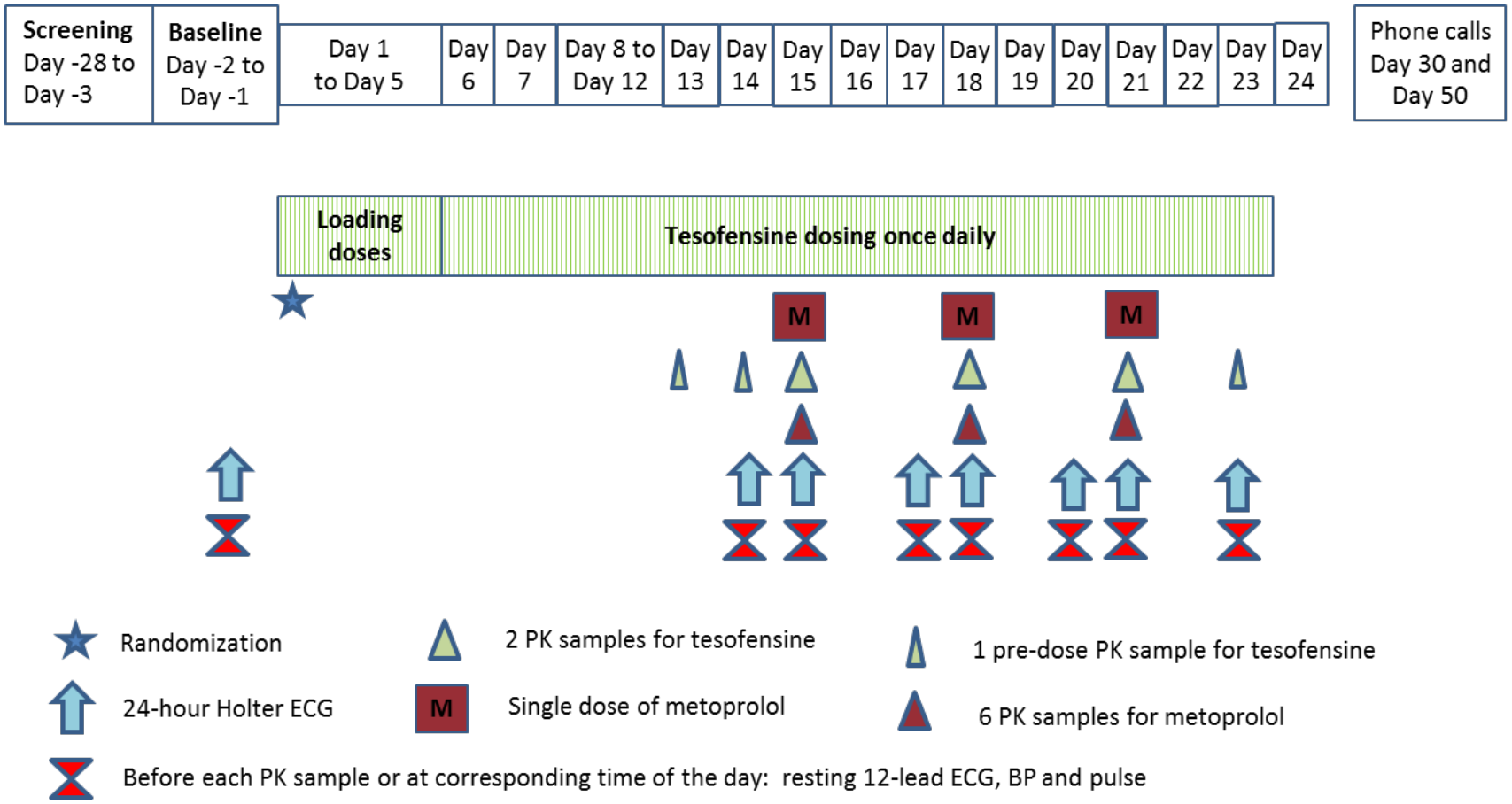
The total duration for each subject will be up to 78 days, including Screening and Follow-up period.

Figure 1 Study Flow Overview – Cohort 1 and Cohort 2



BP = blood pressure; ECG = electrocardiogram, PK = pharmacokinetic

Figure 2 Study Flow Overview – Cohort 3



BP = blood pressure; ECG = electrocardiogram, PK = pharmacokinetic

Please refer to Table 5 and Table 6 for detailed lists of procedures performed on each study day and visit.

3.2. Endpoints

3.2.1. Primary Endpoint

The dose of metoprolol which will result in no change in M24HR for each respective dose of tesofensine – this will be calculated from a dose-response relationship with the dose of metoprolol as independent variable and change in M24HR induced by various doses of metoprolol given to patients on steady-state dose of tesofensine as the dependent variable. The dose for no change in M24HR derived from above calculation and the corresponding 95% CI will be calculated for each dose of tesofensine.

3.2.2. Secondary Endpoints

- The difference in increase in M24HR caused by tesofensine alone (calculated as the difference between the M24HR at pre-tesofensine baseline and the mean of M24HR on Days 14, 17, 20 and 23) and the reduction in M24HR following each of the 3 metoprolol doses (M24HR on Day 15, 18 or 21)
- Mean and absolute change in M24HR between pre-tesofensine baseline (Day -1) and after tesofensine alone (Day 14, Day 17, Day 20 and Day 23)
- Mean and absolute change in M24HR after tesofensine co-administered with metoprolol (Day 15, Day 18 and Day 21)
- Maximum and minimum HR24 (HRmax and HRmin) values after tesofensine alone (Day 14, Day 17, Day 20 and Day 23)
- HRmax and HRmin values after tesofensine co-administered with metoprolol (Day 15, Day 18 and Day 21)
- Time of HRmin and HRmax after tesofensine alone (Day 14, Day 17, Day 20 and Day 23)
- Time of HRmin and HRmax after tesofensine co-administered with metoprolol (Day 15, Day 18 and Day 21)
- Mean HR during a designated quiet hour and a designated period after tesofensine alone (Day 14, Day 17, Day 20 and Day 23)
- Mean HR during a designated quiet hour and a designated period after tesofensine co-administered with metoprolol (Day 15, Day 18 and Day 21)

- HR after at least 10 minutes rest before each PK sampling time point or the corresponding time point (Day -1, Day 13 [pre-dose only], Day 14, Day 15, Day 17, Day 18, Day 20, Day 21 and Day 23)
- Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values after at least 10 minutes rest before each PK sampling time point or the corresponding time point (Day -1, Day 13 [pre-dose only], Day 14, Day 15, Day 17, Day 18, Day 20, Day 21 and Day 23)

The following PK parameters will be determined:

- C_{trough} of tesofensine on Day 13, Day 14, Day 15, Day 18, Day 21 and Day 23
- C_{max} of metoprolol on Day 15, Day 18, and Day 21
- T_{max} of metoprolol on Day 15, Day 18, and Day 21
- AUC_{0-24} of metoprolol on Day 15, Day 18, and Day 21
- Relation between metoprolol concentration and HR will be explored by tesofensine dose
- A PK-PD curve for each dose of tesofensine will be generated with PK parameters (AUC_{0-24} and C_{max}) of metoprolol on the X-axis and change in M24HR on the y-axis. The X-axis intercept and the corresponding 95% CI will be calculated for each dose of tesofensine

3.2.3. Safety Endpoints

The following safety variables will be recorded at specified time points during the study:

- Vital signs (supine BP, pulse and body temperature)
- Twelve-lead ECG: 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

3.3. Justification of the Study Design

The safety assessments included in the study are accepted measures for ensuring safety of subjects during a clinical study.

The PK sampling schedule is considered appropriate given the information available and the goals of this study. This study evaluates the PK profiles of 3 different doses of tesofensine and 3 different doses of metoprolol administered orally. Safety and PK of tesofensine have already been evaluated in many other studies and, therefore, it is not considered necessary to investigate the PK profiles in more detail. The proposed sampling time points are deemed satisfactory to investigate the PK/PD correlation within a dosing interval.

A cross-over approach with intra-individual comparison of the PD and PK profiles of 3 different metoprolol doses was chosen to cover a broad range of HR response. A wash-out period of 48 hours between the metoprolol doses has been chosen because of the continuous release of metoprolol from the ER tablets for about 20 hours and the mean half-life of metoprolol of about 3.5 hours. This shall ensure that HR values return to baseline before the next dose of metoprolol is given and to avoid continuous stimulus on the adrenergic receptors which could potentially lead to a change in receptor expression and presentation over time.

A parallel-group design was chosen for the tesofensine doses due to the long half-life of tesofensine.

The major metabolic pathway of metoprolol is via CYP2D6, therefore poor and ultrarapid CYP2D6 metabolizers are excluded to reduce variability in metoprolol PK and PD data.

Overweight and obese subjects up to a BMI of <40 kg/m^2 will be included in order to investigate the effects in the target population. This "real-life approach" is deemed more appropriate to meet the objectives of the study and in order to better plan future projects than using a purely mechanistic approach in a different population where the results would need to be adapted or extrapolated to the target population. The next (Phase 2) study is planned in obese subjects and the data collected in this study will guide the metoprolol dose for that planned study.

The rationale for dose selection is discussed in Section 5.2.

3.4. Stopping Criteria and Termination of the Clinical Study

The following event shall result in an immediate stop to dosing of all subjects and a re-evaluation of the risk-benefit profile:

- A serious adverse reaction (i.e., an SAE considered at least possibly related to the IMP administration) in one subject.

In the event of an SAE, in which a relation to the IMPs cannot be excluded, the study may be restarted only after review and approval by Independent Ethics Committee (IEC) and Competent Authority.

Based on safety criteria, the study will be stopped in case of any of the following:

- Adverse event stopping criteria:
  - 3 or more subjects experience a severe AE of related causality
  - The Principal Investigator (or his deputy) and the Sponsor consider that the number and/or severity of AEs justify discontinuation of the study

Based on safety criteria, the study will be stopped, if 2 or more subjects in a cohort experience the same stopping criterion of the following:

- Psychiatric stopping criteria:
  - Severe AE related to any classified psychiatric disorder.
- Vital signs stopping criteria:
  - Symptomatic hypotension (SBP < 85 mmHg). If symptomatic hypotension is observed during the study, then a minimum of 2 repeat BP measurements should be obtained within 30 minutes. The mean of the 3 SBP measurements will be used to determine stopping criteria.
  - Tachycardia defined as HR > 120 bpm lasting longer than 30 minutes or with impaired consciousness.
- Electrocardiogram stopping criteria:
  - QTcB or QTcF interval > 500 msec or increase of QTc interval > 60 msec compared to pre-tesofensine baseline (If a prolonged QTc interval is observed during the study, then a minimum of 2 repeat ECGs should be obtained within 30 minutes. The mean of the 3 ECGs will be used to determine stopping criteria.)
- Clinical laboratory stopping criteria:
  - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 3 times the upper limit of normal (ULN, confirmed by repeat)
    with
    a) bilirubin ≥ 2 times the ULN (confirmed by repeat) without simultaneous alkaline phosphatase (ALP) ≥ 2 times the ULN (confirmed by repeat)

or

b) international normalized ratio (INR; will be assessed, if the above criteria are reached) > 1.5 times the ULN without simultaneous alkaline phosphatase (ALP) ≥ 2 times the ULN (confirmed by repeat)

or

c) the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic inflammation, e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia in 2 consecutive measurements within 24 hours.

If the Principal Investigator or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study will be terminated after appropriate consultation among the involved parties. The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant or unacceptable risk to the subjects enrolled in the clinical study;
- Failure to enroll subjects at the required rate;
- A decision of the Sponsor to suspend or discontinue development of the IMP.

Should the study be terminated and/or the site closed for whatever reason, all documentation pertaining to the study and IMPs must be returned to the Sponsor. Any actions of PAREXEL required for assessing or maintaining subject safety will continue as required, despite termination of the study by the Sponsor.

Subject withdrawal criteria for the individual are provided in Section 4.4.

For definition of EoS refer to Section 7.4.

4. STUDY POPULATION

The study population will consist of male and female volunteers. Subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria. In addition to subjects with overweight, subjects with obesity type I and II have been selected as an appropriate study population in order to translate the results to the intended target patient population. Two long-term studies (12 weeks on tesofensine/metoprolol; up to 24 weeks (TIPO-1) and an additional 48 weeks (TIPO-4) on tesofensine) have been already conducted in individuals within BMI ranges up to 40 mg/kg^2 with no major safety issues. Strict inclusion and exclusion criteria applied in this study ensure that obese subjects do not suffer from comorbidities which could affect a subjects' safety.

4.1. Number of Subjects

A total of 60 subjects are planned for enrollment in the clinical study (N=20 will be randomly assigned to each of the 3 cohorts) according to the inclusion/exclusion criteria. Reasonable efforts will be made to achieve gender balance; at least 8 subjects of each gender will be included into each cohort. Subjects withdrawn due to other reasons than IMP-related AEs may be replaced (up to 25% in the study) after mutual agreement between Principal Investigator and Sponsor. Overweight and obese subjects, who are otherwise healthy, will be included in order to investigate the effects in the target population.

4.2. Inclusion Criteria

Subjects who meet the following criteria will be considered eligible to participate in the clinical study:

1. Subject voluntarily agrees to participate in this study and signs an IEC-approved informed consent prior to performing any of the Screening procedures.
2. Male and female subjects between 18 to 60 years of age, inclusive, at Screening.
3. Overweight and obese subjects with a body mass index (BMI) between ≥ 27 and < 40 kg/m^2 at Screening but otherwise healthy.
4. Non-smokers (or other nicotine use) as determined by history (no nicotine use over the past 6 months) and by urine cotinine concentration (< 500 ng/mL) at Screening and admission.
5. No clinically relevant deviation or finding in pre-study medical evaluation (medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory evaluations).

6. HbA1c < 6.5% at Screening.
7. Subject is willing to adhere to the contraception requirements details in Section 7.5.2.

4.3. Exclusion Criteria

Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. Subject has history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic (e.g., diabetes, metabolic acidosis), urologic, pulmonary (e.g., asthma or chronic obstructive pulmonary disease), neurologic, dermatologic, psychiatric, renal, and/or other major disease or malignancy as judged by the Investigator.
2. Subject has any disorder that would interfere with the absorption, distribution, metabolism or excretion of drugs.
3. Subject has a clinically significant abnormality following the Investigator's review of the physical examination, ECG and clinical study protocol-defined clinical laboratory tests at Screening or admission to the clinical unit or has any concurrent disease or condition that, in the opinion of the Investigator, would make the subject unsuitable for participation in the clinical study. One re-test is allowed, if (a) test result(s) is outside the limits.
4. History or presence of liver disease or liver injury, as indicated by abnormal liver function tests including:
    - AST > 1.2 x ULN
    - ALT > 1.1 x ULN
5. Subject has a pulse < 50 or > 90 bpm; SBP < 90 mmHg or > 140 mmHg; DBP < 50 mmHg or > 90 mmHg (using the mean of triplicate measurements) at Screening or admission. One re-test is allowed, if (a) test result(s) is outside these limits.
6. History of any clinically significant cardiac arrhythmia. Subject has a corrected QT interval using Fridericia's formula (QTcF) interval > 450 msec or 2nd or 3rd degree atrioventricular (AV) block, high-grade sinoatrial block or PQ interval > 0.24 seconds at Screening (using the mean of triplicate measurements). If a mean ECG parameter of a triplicate ECG exceeds the limits above, an additional triplicate ECG may be taken. If this also gives an abnormal result, the subject will be excluded. Also the following cardiac conditions will lead to exclusion of the subjects: Untreated heart failure (pulmonary oedema, impaired blood flow or

hypotension) and continuous or intermittent treatment leading to an increased contractility of the heart muscle (beta-receptor agonism); Sick sinus syndrome; cardiogenic shock; severe peripheral arterial circulatory disturbances.

7. Has a creatinine value exceeding the ULN.
8. Subject has positive test for hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (indicative of active hepatitis B), hepatitis A virus antibodies (immunoglobulin M), hepatitis C virus (HCV) antibodies or human immunodeficiency virus (HIV) 1 and/or -2 antibodies.
9. Use of any prescribed or non-prescribed drugs (including vitamins, natural and herbal remedies, e.g., St. John's Wort) in the 2 weeks prior to admission or 5 half-lives of the drug, whichever is longer, except for the occasional use of paracetamol (up to 2 g/day) or other non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraception for female subjects.
10. Subject has history of alcohol and/or illicit drug abuse within 2 years of entry.
11. Subject has positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids) or alcohol test at Screening or at admission.
12. History of drinking > 168 g (males) and > 84 g (females) pure alcohol per week (10 g pure alcohol = 259 mL of beer [5%] or 35 mL of spirits [35%] or 100 mL of wine [12%] within 3 months prior to admission to the clinical unit.
13. Subject consumes more than 600 mg caffeine per day (e.g., more than 3 cups of coffee containing 200 mg caffeine per cup) within the 4 weeks before admission or the subject is unwilling to avoid consumption of coffee and caffeine-containing beverages within 48 hours prior to admission until discharge from the clinical unit.
14. Subject is unwilling to avoid use of alcohol or alcohol-containing foods, medications or beverages, within 48 hours prior to Screening and from admission until discharge from the clinical unit.
15. Any significant blood loss, donated one unit (450 mL) of blood or more, or received a transfusion of any blood or blood products within 60 days, or donated plasma within 7 days prior to the admission to the clinical unit.
16. Participation in any clinical study within 3 months or 5 half-lives of the drug, whichever is longer, prior to the expected date of IMP administration, or participation in more than 3 clinical studies within 12 months.

17. Subject with a relevant history or with a present psychiatric disorder, including depression, suicidal ideation, or eating disorders (e.g., bulimia or anorexia nervosa). Subjects with a medical history of relevant psychiatric disorders or known and relevant family history or evidence of anxiety disorders or depression as judged by the Investigator using the Generalized Anxiety Disorder Assessment (GAD-7) and Patient Health Questionnaire-9 (PHQ-9) at Screening. Any of the following will lead to exclusion of the subject:
    - Subject has a GAD-7 mood scale score ≥ 10
    - Subject has a score ≥ 10 on the PHQ-9 questionnaire
    - Subject selects a response of "1, 2 or 3" to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9).
18. Use of any agent used for weight loss within the last 3 months.
19. More than 5% weight loss within the last 3 months.
20. Hypo- or hyperthyroidism.
21. Subject is pregnant or lactating.
22. Subject is unwilling to abstain from vigorous exercise from 48 hours prior to admission until discharge.
23. Subject has a history of hypersensitivity to the IMPs or any of the excipients or to medicinal products with similar chemical structures.
24. Any contraindication for metoprolol, e.g. severe peripheral arterial disease, untreated pheochromocytoma, concomitant intravenous administration of calcium antagonists of verapamil and diltiazem, due to the risk of hypotension, AV conduction disturbances, or left ventricular insufficiency.
25. Subject has lactose intolerance or a rare hereditary problem of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency.
26. Subject is unable to understand and communicate in German language or to understand the protocol requirements, instructions and study-related restrictions, the nature, scope and possible consequences of the clinical study or is unlikely to comply with the study requirements; e.g., uncooperative attitude and improbability of completing the clinical study.
27. Subject has previously been enrolled in this clinical study.

28. Vulnerable subjects defined as individuals whose willingness to volunteer in a clinical study may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate (e.g., persons in detention, minors and those incapable of giving consent).
29. Subject is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study or employee of the Sponsor or PAREXEL.
30. Poor or ultrarapid CYP2D6 metabolizer.

4.4. Subject Withdrawal and Replacement

The Sponsor reserves the right to request the withdrawal of a subject due to protocol deviation, administrative or any other valid and ethical reason. If an Investigator judges a subject to be at medical risk by complying with the protocol, he or she will discontinue the participation of the subject. The circumstances surrounding the decision must be discussed with the Sponsor and recorded in the subject's source documents and electronic source data report (eSDR).

Subjects must be withdrawn by the Investigator under the following circumstances:

- SAE
- AE that is unacceptable for the subject or the Investigator
- Protocol violation affecting subject safety or evaluability of the study data
- The subject withdraws consent
- Pregnancy or breastfeeding
- Study discontinuation by the Sponsor
- At the discretion of Investigator
- Subject shows a hypertension with resting supine SBP above 200 mmHg and persisting for at least 10 minutes, confirmed by a repeat measurement
- Subject shows an increase in BP (confirmed SBP >160 mmHg and/or DBP >100 mmHg) for ≥ 3 consecutive days
- Subject may not be dosed with metoprolol if pre-dose resting supine SBP < 90 mmHg), confirmed by a repeat measurement. However, the subjects does not have to discontinue, if SBP < 90 mmHg after metoprolol administration without symptoms

- Subject shows a 2nd or 3rd degree AV block, high-grade sinoatrial block, significant cardiac arrhythmias related to the IMP intake, e.g., atrial fibrillation or confirmed significant tachycardia >120 bpm. Subject may not be dosed with metoprolol if pre-dose resting supine HR < 45 bpm. However, the subjects does not have to discontinue, if HR < 45 bpm after metoprolol administration without symptoms
- Subject shows an absolute QTcF of > 500 msec or QTcF change from pre-tesofensine baseline > 60 msec in 3 repeated measurements within at least a 1 hour interval
- Subject has ALT or AST ≥ 3 × ULN (confirmed by repeat) with

  a) Total bilirubin ≥ 2 × ULN without simultaneous ALP ≥ 2 times the ULN (confirmed by repeat)
  or
  b) INR (will be assessed, if the above criteria are reached) > 1.5 times the ULN without simultaneous ALP ≥ 2 times the ULN (confirmed by repeat)
  or
  c) the appearance or worsening of symptoms potentially related to hepatic inflammation, e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia in 2 consecutive measurements within 24 hours.

- Subject shows dopaminergic side effects such as agitation, hallucinations, psychoses including delusion, paranoid ideation and depression of moderate to severe intensity, jeopardizing subject safety and requiring medical intervention and supervision

The reason(s) for withdrawal will be recorded in ClinBase™.

If a subject is withdrawn, or chooses to withdraw, from the clinical study for any reason, the Investigator must make every possible effort to perform the evaluations described for Day 24.

A genuine effort must be made to determine the reason(s) why a subject fails to return for the necessary visits (if needed) or is discontinued from the study. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent to the subject requesting him/her to contact the clinic.

While subjects are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Reasonable effort will be made to determine why any subject withdraws from the study prematurely. All subjects who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical

unit should be collected at the time of premature discontinuation or at the scheduled discharge (see also Section 7.3).

Enrollment will continue until a total of 60 subjects are randomized. Subjects withdrawn due to other reasons than IMP-related AEs may be replaced (up to 25% in the study) after mutual agreement between Principal Investigator and Sponsor.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. Identity of the Investigational Medicinal Products

The products that will be used in this study are outlined in Table 1.

Table 1 Identity of Investigational Products

Drug Name	Formulation	Strength	Route	Manufacturer
Tesofensine	Film-coated tablet	0.25 mg tesofensine	Oral	Sponsor
Tesofensine	Film-coated tablet	0.50 mg tesofensine	Oral	Sponsor
Metoprololsuccinat "Orion", depottabletter[1]	ER tablet	25 mg metoprolol	Oral	Orion Corporation (Finland)
Metoprololsuccinat "Orion", depottabletter[2]	ER tablet	50 mg metoprolol	Oral	Orion Corporation (Finland)
Metoprololsuccinat "Orion", depottabletter[3]	ER tablet	100 mg metoprolol	Oral	Orion Corporation (Finland)
Metoprolol placebo tablet	Film-coated tablet	Not applicable	Oral	Solural Pharma ApS (Denmark)

ER = extended release

1 contains 23.75 mg metoprolol succinate corresponding to 25 mg metoprolol tartrate

2 contains 47.5 mg metoprolol succinate corresponding to 50 mg metoprolol tartrate

3 contains 95 mg metoprolol succinate corresponding to 100 mg metoprolol tartrate

5.2. Dose Rationale Including Time of Dosing

The doses of tesofensine selected for this study are based on the previous clinical experience, particularly the tesofensine alone study TIPO-1 (0.25 to 1.0 mg of tesofensine once daily for up to 24 weeks) as well as the recently completed Phase 2 study with Tesomet TM001 (0.5 mg of tesofensine co-administered with 100 mg of metoprolol ER for 12 weeks). In addition, tesofensine alone was administered to more than 1300 patients at doses up to 1.0 mg for up to 48 weeks. Tesofensine was well tolerated up to and including single oral doses of 6.75 mg. Based on the available data it is anticipated that the range of doses of tesofensine co-administered with metoprolol might be between 0.25 to 0.75 mg once daily. On the other side of the dose range, doses < 0.2 mg of tesofensine are unlikely to produce clinically meaningful efficacy. For more information please see the Tesomet IB [2].

The doses of metoprolol selected for this study are based on the study TM001 mentioned above and also the vast amount of clinical experience with metoprolol and its SPCs [4]. From the results of TM001, it seems that the required doses of metoprolol to be used in Tesomet are ≤100 mg ER. On the low side, metoprolol ER is usually prescribed as 50 mg once daily, but it is possible that for the low end of tesofensine dose range 25 mg of metoprolol may be enough to

mitigate the effects of tesofensine on HR. For more information please the Tesomet IB [2] and metoprolol SPCs [4].

It is important to note that the doses for both compounds proposed for administration in this study have been extensively studied and have a solid tolerability and safety track record.

Timing of dosing will be as follows:

- Tesofensine, film-coated tablet, 0.25 mg:
  - Oral dose of 4 tablets once daily from Day 1 to Day 3, Cohort 1 only (loading dose of 1.0 mg)
  - Oral dose of 1 tablet once daily from Day 4 to Day 23, Cohort 1only
  - Oral dose of 1 tablet once daily from Day 6 to Day 23, Cohort 3 only
- Tesofensine, film-coated tablet, 0.50 mg:
  - Oral dose of 4 tablets once daily from Day 1 to Day 3, Cohort 2 only (loading dose of 2.0 mg)
  - Oral dose of 4 tablets once daily from Day 1 to Day 5, Cohort 3 only (loading dose of 2.0 mg)
  - Oral dose of 1 tablet once daily from Day 4 to Day 23, Cohort 2 only
  - Oral dose of 1 tablet once daily from Day 6 to Day 23, Cohort 3 only
- Metoprolol, 25 mg ER tablet (Metoprololsuccinat "Orion" 25 mg, depottabletter; each tablet contains 23.75 mg metoprolol succinate equivalent to 25 mg metoprolol tartrate; manufacturer: Orion Corporation, [Finland])
  - Single oral dose of 1 tablet in each subject of Cohort 1, Cohort 2 and Cohort 3, on Day 15, Day 18 or Day 21
- Metoprolol, 50 mg ER tablet (Metoprololsuccinat "Orion" 50 mg, depottabletter; each tablet contains 47.5 mg metoprolol succinate equivalent to 50 mg metoprolol tartrate; manufacturer: Orion Corporation, [Finland])
  - Single oral dose of 1 tablet in each subject of Cohort 1, Cohort 2 and Cohort 3, on Day 15, Day 18 or Day 21

- Metoprolol, 100 mg ER tablet (Metoprololsuccinat "Orion" 100 mg, depottabletter; each tablet contains 95 mg metoprolol succinate equivalent to 100 mg metoprolol tartrate; manufacturer: Orion Corporation, [Finland])
  - Single oral dose of 1 tablet in each subject of Cohort 1, Cohort 2 and Cohort 3, on Day 15, Day 18 or Day 21
- Metoprolol placebo film-coated tablet; manufacturer: Solural Pharma ApS (Denmark)
  - Single oral dose of 1 tablet in each subject at each metoprolol dosing i.e., on Day 15, Day 18 and Day 21

Each subject will receive tablets for all days with self-administration of tesofensine. Subjects in Cohort 1 will receive 0.25 mg tablets, subjects in Cohort 2 will receive 0.50 mg tablets and subjects in Cohort 3 will receive 2 containers: one with 0.25 mg tablets and one with 0.50 mg tablets.

5.3. Supply, Packaging, Labeling and Storage

Investigational medicinal products will be supplied by a third party (KLIFO A/S, Smedeland 36, Glostrup, 2600, Denmark) contracted by Saniona A/S. Tesofensine tablets will be packaged, labeled and Qualified Person (QP)-certified according to applicable local and regulatory requirements by KLIFO A/S. ClinBase™ barcode will be added by contract pharmacy Hubertus to the subject-specific tesofensine containers provided by KLIFO A/S. Metoprolol and placebo tablets will be packaged and labeled according to applicable local and regulatory requirements by contract pharmacy Hubertus.

All supplies of IMPs must be stored in accordance with the manufacturer's instructions. The IMPs will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Tesofensine for home-dosing days will be dispenses to the subjects in appropriately labeled containers together with instructions of use.

5.4. Drug Accountability, Dispensing and Destruction

The Investigator or designee is responsible for maintaining accurate accountability records of the IMPs throughout the clinical study. The drug accountability log includes information such as, random number, amount dispensed and amount returned to the pharmacy (if any). Products returned to the Hubertus pharmacy will be stored under the same conditions as products not yet

dispensed. The returned products should be marked as 'returned' and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. When the Study Monitor visits PAREXEL, he/she will reconcile the drug accountability log with the products stored in the contract pharmacy (Hubertus).

The pharmacist (or designee under the direction of the pharmacist) will prepare the IMPs for each subject according to the randomization list and will ship the IMPs to the site.

After receiving Sponsor approval in writing, PAREXEL is responsible for returning all unused or partially used IMPs to the Sponsor or designated third party or for preparing the IMPs for destruction via incineration by the contract pharmacy.

5.5. Subject Identification and Randomization

5.5.1. Screening Numbers

Subjects will be assigned a RunIn number after the subject has signed the informed consent document (ICD). A subject who was screened for the study on a previous occasion but who was not enrolled may be re-screened for eligibility again, if he/she was eligible but could not be enrolled due to logistical reasons or due to transient reasons for ineligibility (e.g., too short wash-out of previous medication). The re-screened subject will then be assigned a new RunIn number after signing a new ICD.

5.5.2. Randomization Numbers

Prior to first dosing, 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 from the beginning of the list with 101 for male subjects and starting from the end of the list (number 160) for female subjects.

Once a randomization number has been allocated to one subject, it may not be assigned to another subject. 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. For example, if Subject 145 withdraws and is replaced, then the randomization number for the replacement subject will be 1145.

5.5.3. Randomization

There will be 20 subjects in each of the 3 cohorts. Subjects will be randomly assigned to a cohort. Within each cohort the subjects will be randomized to different sequences of metoprolol doses. For 18 of the subjects within each cohort a 3 treatment Williams design will be used to determine the sequences. The final 2 subjects will be randomized according to an incomplete 3 treatment Latin Square. Each metoprolol sequence will have at least one subject of each gender. An additional 2 sequences will randomly be assigned to 2 sequences. Thus there will be at least 8 subjects of each gender within each cohort.

5.6. Administration of Investigational Medicinal Products

On in-house dosing days (i.e., Day 1 to Day 3 [Cohort 1 and Cohort 2], Day 1 to Day 5 [Cohort 3], Day 7 and Day 13 to Day 23), the Investigator or a designee will administer the IMP(s), i.e., tesofensine, metoprolol and placebo, with 240 mL water to the subjects as per randomization schedule approximately 30 minutes after start of a standard breakfast (all IMPs at the same time). From Day 4 to Day 6 (Cohort 1 and 2) or on Day 6 (Cohort 3) and from Day 8 to Day 12, subject will self-administer a single dose of tesofensine approximately 30 minutes after start of breakfast. If more water is needed for the intake of the tablets, up to further 200 mL water may be taken. All IMPs should be swallowed whole with water.

A mouth check will be performed to ensure the entire dose was swallowed by the subject.

5.7. Compliance

When subjects are at the site, dosing will be performed by trained, qualified personnel designated by the Investigator. The date and time of dosing will be documented. On outpatient days, date and time of dosing will be documented in a diary. Comments will be recorded if there are any deviations from the planned dosing procedures.

5.8. Blinding and Breaking the Blind

Tesofensine dosing will be performed open-label.

Metoprolol dosing will be performed “single-blind”, i.e., subjects will be blinded, Investigator(s), designee(s) and Sponsor will be unblinded. Since the 3 dose strengths of metoprolol tablets used in this study have different sizes, to mask the metoprolol dose level, a placebo tablet similar to the 50 mg metoprolol Orion tablet will be administered simultaneously at the time of each metoprolol dosing.

During the administration itself, subjects' eyes will be covered as each IMP would otherwise be visually distinguishable from the others due to having a different size.

All tablets of metoprolol are of the same shape, just the size differs. Therefore, a placebo tablet of the same shape and color but of different size will be added to avoid unblinding of the subjects. With these procedures in place, it is very unlikely that subjects would be able to tell which dose they were administered.

Single blinding procedures for metoprolol dosing:

Single blinding will be achieved by the following procedures:

- The ICD will be carefully worded so as not to associate any metoprolol dose with a particular tablet size and will not mention how many of each will be administered. It will only list the dosage for each of the study drugs.
- The randomization list will be prepared by a statistician.
- Randomization list will be provided to the pharmacist, the pharmacovigilance group the clinical team, data management and statistician. A copy will be available at the site in the emergency binder.
- The individual subject doses will be prepared for administration at the pharmacy and put into hard, non-transparent containers. On metoprolol dosing days, the labels on the subject-specific containers and the documentation in ClinBase™ will contain all possible dose strengths of metoprolol, i.e., 25 mg, 50 mg or 100 mg, but not the allocated dose for the specific day.
- Dose administrators will perform only visual cross-checking of the number of tablets against ClinBase™ (verbal readout of the metoprolol will include all possible dose strengths, i.e., 25 mg, 50 mg or 100 mg).
- Subjects will have their eyes covered by blindfolds at time of administration.
- The study drugs will be administered by the site staff and maximum care will be taken so that the subjects never actually see or touch the study drugs.
- The study drugs will be given to subjects with a glass of water (240 mL) and they will be instructed to swallow them immediately. If more water is needed for the intake of the tablets, up to further 200 mL water may be taken.

After removing of blindfold from subject, they will be given instructions to avoid discussion surrounding dosing procedures and study drug (i.e., taste, texture, number, etc.).

5.9. Prior and Concomitant Medications

Any medicinal product, prescribed or over-the-counter (OTC), including herbal and other nontraditional remedies, is considered a concomitant medication. Prior and concomitant medication use will be recorded for the 30 days prior to Screening until the Safety Follow-up phone call. Prior and concomitant medication use is not permitted from 2 weeks before admission until discharge (occasional use of paracetamol up to 2 g/day or other NSAIDs and hormonal contraception is permitted). However, concomitant medication use may be warranted for the treatment of AEs, a list of prohibited medication is provided in Appendix 11.1, with emergencies being the exemption.

5.10. Treatment of Overdose

Overdose is unlikely to occur in this study. Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available. At intoxication, symptomatic treatment with dopamine D2-receptor antagonist haloperidol should be considered.

An overdose of tesofensine is defined in this study as 6 times of single dose and metoprolol as 4 times of a daily dose with or without occurrence of clinical symptoms. If a subject or any unintended other person not part of the study has an accidental or intentional overdose of the IMP, even if the consequences are not serious, the overdose must be reported to the Sponsor immediately (within 24 hours). The procedure for reporting SAEs should be followed.

6. MEASUREMENTS AND METHODS OF ASSESSMENT

For timing of assessments, refer to the Schedules of Assessments (Table 5 and Table 6).

A Safety management plan (SMP) will be signed between the Sponsor and PAREXEL.

6.1. Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Medication history
- Family history of psychiatric disorders (focusing on psychosis, depression, suicidality or suicide)

The following demographic information will be recorded:

- Age
- 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, without shoes (kg), waist circumference
- BMI (kg/m^2)

Other baseline characteristics will be recorded as follows:

- History of drug abuse
- History of alcohol abuse
- Smoking history
- History of caffeine use (or other stimulating beverages)
- Special diet (vegetarian)
- History of blood or plasma donation

6.2. Safety Variables

6.2.1. Adverse Events

Adverse event reporting will begin for each subject from the date the ICD is signed and will continue until the final Safety Follow-up phone call (EoS).

6.2.1.1. Definitions

6.2.1.1.1. Definition of Adverse Event

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.

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.

6.2.1.1.2. Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening; this means that the subject was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation in existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect, or
- Is another important medical event (see below)

Important medical events that do not result in death, are not life-threatening or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

6.2.1.2. Recording of Adverse Events

Adverse events should be collected and recorded for each subject from the date the ICD is signed until the end of their participation in the study, i.e., the subject has discontinued or completed the study.

Adverse events may be volunteered spontaneously by the subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity and action taken of the AE will be documented together with the Investigator's assessment of the seriousness of the AE and causal relationship to IMP (with causality being assessed separately for tesofensine and metoprolol) and/or study procedure.

All AEs should be recorded individually unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

6.2.1.3. Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the categories discussed in the following sections.

6.2.1.3.1. Intensity

The Principal Investigator or designee will assess all AEs for severity in accordance with the following standard ratings.

- Mild: Ordinarily transient symptoms, does not influence performance of subject's daily activities. Treatment is not ordinarily indicated.
- Moderate: Marked symptoms, sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment may be necessary.
- Severe: Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue in the study and treatment may be necessary.

When changes in the intensity of an AE occur, the maximum intensity for the event will be noted.

6.2.1.3.2. Causality

The Investigator will assess the causality/relationship between the IMPs and the AE. The causality will be assessed separately for tesofensine and metoprolol. One of the categories described in Table 2 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 2 Assessment of Relationship of Adverse Events to Investigational Product

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain.
Not related	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration or confirmed other cause (e.g., other medical condition).

6.2.1.3.3. Seriousness

Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2.1.1.2.

6.2.1.4. Reporting of Serious Adverse Events

The Investigator will review each SAE and evaluate the intensity and the causal relationship of the event to IMP. All SAEs will be recorded from signing of the ICD until the EoS, i.e., the final Safety Follow-up phone call. Serious AEs occurring after the EoS and coming to the attention of the Investigator must be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the IMP.

An SAE Report Form has to be completed and sent by email to:

pharmacovigilance@klifo.com

or

fax: +45 39 209 045

The Investigator is responsible for providing notification to the KLIFO Pharmacovigilance Service of any SAE, whether deemed IMP-related or not, that a subject experiences during their participation in study within 24 hours of becoming aware of the event.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Subject number
- Sex
- Age
- Name of Principal Investigator and full clinical unit address
- Details of SAE
- Criterion for classification as 'serious'
- IMP name, or code and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification)

KLIFO will send a receipt confirmation to the Site (PAREXEL) within 1 working day, with a copy to the Sponsor. If required, KLIFO will request follow-up using a data clarification form. Request for follow-up will be sent to the Site/PAREXEL. The Principal Investigator or an

authorized delegate is responsible for sending the requested information to KLIFO within 24 hours of the Sponsor's request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports), with the subject's personal identifiers removed. All relevant information obtained by the Principal Investigator through review of these documents will be recorded and sent to the KLIFO within 24 hours of receipt of the information. If a new SAE Report Form is sent, then the Investigator must sign and date the form. KLIFO may also request additional information on the SAE, which the Principal Investigator or an authorized delegate must send to the KLIFO within 24 hours of the request.

Details can be found in the SMP.

6.2.1.5. Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Principal Investigator, until there is a satisfactory explanation for the changes observed or until the subject is lost to follow-up.

6.2.1.6. Pregnancy

Any pregnancy that occurs in a female subject or the female partner of a male subject during trial participation until at least 8 weeks after the last administration of IMP must be reported on a pregnancy report form in the same manner as an SAE to KLIFO Pharmacovigilance Service (Section 6.2.1.4).

The Investigator will arrange for the pregnant person to be counselled by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the pregnant person should continue until the outcome of the pregnancy is known.

The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the trial.

All data related to pregnancy, pregnancy outcome, and SAE associated with pregnancy will also be recorded in a safety database maintained by KLIFO Pharmacovigilance Service.

Consent to report information regarding pregnancy outcomes has to be obtained from the mother and the (where possible) father.

6.2.2. Clinical Laboratory Assessments

Samples for clinical laboratory assessments will be collected at the time points detailed in the Schedules of Assessments (Table 5 and Table 6).

Clinical laboratory tests will be performed by the laboratories mentioned in the List of Study Staff of this clinical study protocol. Samples will be collected in appropriate tubes and handled according to standard procedures of the applicable laboratory.

Clinical laboratory variables will be determined as outlined in Table 3.

Table 3 Clinical Laboratory Assessments

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
	HbA1c (at Screening only)
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)	Follicle-stimulating hormone (female subjects only, at Screening only)
Urinalysis	
Bilirubin	Blood
Glucose	pH and specific gravity
Ketones	Protein
Leukocytes	Urobilinogen
Nitrite	
Upon a positive urine test from leucocytes, blood or protein, the Investigator may require further urine analysis, such as flow cytometry. Results of additional urine analyses will be included in the database. If the flow cytometry examination shows a different result than the urine stix, it will be checked by microscopy or full automated digital imaging, (e.g., leukocytes, erythrocytes, casts in urine will be analyzed).	
Viral Serology	
Hepatitis B core antibody (anti-HBc)	Human immunodeficiency virus (HIV) (Types 1 and 2) antibodies
Hepatitis B surface antigen (HBsAg)	
Hepatitis A virus antibodies (immunoglobulin M)	Hepatitis C virus antibody (anti-HCV)
Pregnancy Tests (in Female Subjects)	
β-human chorionic gonadotropin in serum (at Screening)	β-human chorionic gonadotropin in urine (on each admission)
Urine Drug Screening, Cotinine and Alcohol Test	
Amphetamines	Cocaine
Barbiturates	Opiates
Benzodiazepines	Phencyclidine
Cannabinoids	Cotinine
Alcohol	Urinary creatinine (to exclude dilution effect)

Any value outside the normal range will be flagged for the attention of the Principal Investigator or designee at the site. The Principal Investigator or designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during the Screening Period is indicated as clinically significant, the subject will not be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at discharge, it should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized, at the discretion of the Principal Investigator.

6.2.3. Vital Signs

Vital signs will be assessed at the time points detailed in the Schedules of Assessments (Table 5 and Table 6). The following vital signs will be measured in triplicates (i.e., 3 measurements at least 1 minute apart) with an appropriate cuff always at the same arm:

- Blood pressure (systolic and diastolic [mmHg])
- Pulse (bpm)

Recordings will be made after the subject has been supine and at rest ≥ 10 minutes. At Screening and first admission the mean of the 3 measurements will be used to check eligibility.

In addition, oral body temperature (°C) will be measured.

6.2.4. Standard 12-lead Electrocardiograms

Standard safety 12-lead ECGs will be performed at the time points detailed in the Schedules of Assessments (Table 5 and Table 6).

The12-lead ECGs will be performed in triplicates (i.e., 3 recordings of 10 seconds each at least 60 seconds apart) after the subject has been resting supine for ≥ 10 minutes. The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be collected: HR, PR interval, QRS interval, RR interval, QT interval and QTc interval (QTcB and QTcF) (QTcF will be used for clinical decisions). The mean ECG parameters of the triplet will be used to determine subject eligibility.

All ECGs must be evaluated by a qualified physician for the presence of abnormalities.

6.2.5. Physical Examinations

Physical examinations will be performed at the time points detailed in the Schedules of Assessments (Table 5 and Table 6).

Physical examination:

An assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal), including orientating neurologic examination.

Other evaluations may be performed as deemed necessary by the Investigator. This will be commented upon in the clinical study report (CSR), if performed.

6.2.6. Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder Assessment (GAD-7)

The Patient Health Questionnaire (PHQ) was developed and validated as a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD). The PHQ in general and the PHQ-9 depression scale in particular have gained increasing use in both research and practice for assessing and monitoring depression severity. Though originally developed and validated to diagnose generalized anxiety disorder, the GAD-7 also proved to have good sensitivity and specificity as a screener for panic, social anxiety, and post-traumatic stress disorder.

Each PHQ module can be used alone (e.g. the PHQ-9 if depression is the condition of interest), together with other modules, or as part of the full PHQ.

Question No. 9 of the PHQ-9 serves as screener for suicidal ideation and self-harm. A final decision about the actual risk of self-harm requires a clinical interview.

The final question on the PHQ addresses patient-rated difficulty (“How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?”). It is not used in calculating any PHQ score or diagnosis but rather represents the patient‘s global impression of symptom-related impairment. It may be useful in decisions to be made by a health care professional or an Investigator in a clinical study.

The severity scores are now used much more commonly than the provisional diagnoses. A cutpoint of 10 or greater is considered a "yellow flag" on both measures (i.e., drawing attention

to a possible clinically significant condition), while a cutpoint of 15 is a "red flag" on all 3 measures (i.e., targeting individuals in whom active treatment is probably warranted).

PHQ-9 Depression Severity. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all", "several days," "more than half the days", and "nearly every day", respectively. PHQ-9 total score for the 9 items ranges from 0 to 27. Scores of 5, 10, 15, and 20 represent cutpoints for mild, moderate, moderately severe and severe depression, respectively [5]. Sensitivity to change has also been confirmed.

GAD-7 Anxiety Severity. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all", "several days", "more than half the days", and "nearly every day", respectively. GAD-7 total score for the 7 items ranges from 0 to 21. Scores of 5, 10, and 15 represent cutpoints for mild, moderate, and severe anxiety, respectively. Though designed primarily as a screening and severity measure for generalized anxiety disorder, the GAD-7 also has moderately good operating characteristics for 3 other common anxiety disorders – panic disorder, social anxiety disorder, and post-traumatic stress disorder. When screening for anxiety disorders, a recommended cutpoint for further evaluation is a score of 10 or greater.

Subjects rating ≥ 1 on the suicidal ideation question of the PHQ-9 or whose ratings of ≥ 10 in PHQ-9 or GAD-7 indicate moderate or worse depressive or anxiety symptomatology, respectively, will not be included in the study.

Please refer to the Instruction Manual [6] and the questionnaires [7] for further details.

Severity of psychiatric AEs will be assessed by the Investigator. Life-threatening events should be reported as SAEs. The subject must be referred to a mental health care professional for further assessment and/or treatment in case of psychiatric SAEs. The decision on whether the study treatment should be discontinued is to be taken by the Investigator in consultation with the mental health professional to whom the subject is referred.

6.3. Pharmacokinetics Variables

6.3.1. Blood Sample Collection

Blood for the analysis of tesofensine and metoprolol will be collected at the time points detailed in the Schedules of Assessments (Table 5 and Table 6). Analysis of tesofensine's active metabolite will not be performed.

Blood sample collection, processing and shipping details will be outlined in a separate laboratory manual. In brief, blood will be processed and plasma analyzed using validated assays.

6.4. Pharmacodynamic Variables

A 2-lead Holter-ECG device will be used for recording of 24-hour HR at the time periods detailed in the Schedules of Assessments (Table 5 and Table 6).

With regard to HRmin and HRmax the minute in which the minimum and the minute in which the maximum HR occurred will be determined over the 24 hour period.

In addition, the mean HR from a designated period (from 3 to 16 hours post-dose) and in a quiet hour (from 12 to 13 hours post-dose) will be extracted from the Holter-ECG. During the quiet hour, subjects will have to rest, i.e., each subject will be asked to find a personally comfortable supine position with the head and whole body firmly supported. The subjects will not be permitted to watch television or to listen to radio or music player. They will not be permitted to read, to sleep or converse, and will be kept free from any external disturbance (e.g., personal media). No electric equipment including mobile phones may be switched on in the room.

In addition, 12-lead ECG, BP and pulse will be assessed after a rest of at least 10 minutes as detailed in the Schedules of Assessments (Table 5 and Table 6), in Section 6.2.3 and Section 6.2.4.

6.5. Total Amount of Blood

Each subject will have less than 500 mL of blood collected over the course of the entire study (from Screening to discharge, but not including repeat or additional tests ordered by the Investigator), which presents no undue risk to the subjects (see Table 4).

Table 4 Approximate Total Amount of Blood for Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Blood Volume (mL)
Pharmacokinetics (tesofensine, metoprolol or both)	7.5	21	157.5
Hematology and clinical chemistry[1]	10.2	4	40.8
Cytochrome (CYP)2D6	2.7	1	2.7
Total Blood Volume[2] per Subject			**201.0**

[1] Viral serology and pregnancy test will be performed on the sample collected for hematology and clinical chemistry at Screening, as applicable.

[2] Excluding repeat laboratory investigations.

7. STUDY CONDUCT

7.1. Schedule of Assessments

The study consists of a Screening Visit (Day –28 to Day –3), admission (Day –2), a Baseline Period (Day -2 to Day -1) and a Treatment Period (Day 1 to Day 24) and will have 2 Follow-up phone calls (Day 30 and Day 50). The Treatment Period will comprise an initial in-house stay (Day -2 to Day 3) until the last loading dose of tesofensine has been administered on Day 3 (see below), a home-dosing period (Day 4 to Day 12, once daily dosing to achieve steady state of tesofensine with an ambulatory visit in the clinical unit on Day 7) and a second in-house stay (Day 13 to Day 24). Safety evaluations will be performed on Day 30 and Day 50 (EoS) after last dosing over the phone.

Therefore, the maximal study duration for an individual subject will be up to 78 days, including Screening.

Please see Table 5 and Table 6 for the Schedules of Assessments.

Table 5 Schedule of Assessments for Cohort 1 and Cohort 2

Evaluation	Screening	Base-line		Treatment Period															Safety FU Phone Calls	
Day	**-28 to -3**	**-2**	**-1[a]**	**1**	**2**	**3**	**7**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**30**	**50**
Admission		X						X													
Discharge						X													X		
In-house stay[b]		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		
Ambulatory visits	X						X														
Phone call																				X	X
Informed consent	X																				
Medical history	X																				
Demographics	X																				
Inclusion/exclusion criteria	X																				
Physical examination	X																		X		
Body weight	X	X							X			X			X				X		
Waist circumference	X	X							X			X			X				X		
Height, calculation of BMI	X																				
Blood sampling for CYP2D6	X																				
Viral serology	X																				
Clinical laboratory tests (clinical chemistry, hematology and urinalysis) in fasted state	X	X					X												X		
HBA1c	X																				
Serum pregnancy test[m]	X																		X		
Urine pregnancy test[m]		X						X													X[n]
Psychodiagnostic self-rating instruments (PHQ-9 and GAD-7)	X																				
Urine drug screen, cotinine and alcohol test	X	X						X													
24-hours Holter ECG[c]			X[a]						X	X		X	X		X	X		X			
12-lead ECG[d,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Evaluation	Screening	Base-line		Treatment Period																Safety FU Phone Calls	
Day	**-28 to -3**	**-2**	**-1[a]**	**1**	**2**	**3**	**7**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**30**	**50**
Supine blood pressure and pulse[e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body temperature[g]	X	X	X						X	X		X	X		X	X		X			
A designated period from 3 to 16 hours post-dose and a quiet hour from 12 to 13 hours post-dose[f]			X						X	X		X	X		X	X		X			
Randomization[h]				X																	
Dosing of tesofensine[i]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dosing of metoprolol[j]										X			X			X					
Blood sampling for PK[k]								X	X	X			X			X		X			
Dispense of tesofensine container						X															
Subject returns tesofensine container to the clinical unit								X													
Dispense of the diary and instructions[l]					X																
Collection of the diary								X													
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; BMI = Body Mass Index; ECG = electrocardiogram; FU = Follow-up; PK = pharmacokinetics; GAD-7 = Generalized Anxiety Disorder Assessment; PHQ-9 = Patient Health Questionnaire-9

a The 24-hours ECG recording at pre-tesofensine baseline may be repeated, if less recording time than 22 hours for comparison of the data is available for evaluation due to technical issues. Then dosing and all subsequent assessments will be postponed by 1 day.

b Subjects will be admitted in the morning of Day -2 and will leave the study center in the morning of Day 3 after dosing of the last loading dose and after completion of all study-related assessments.
Subject will take tesofensine at home once daily from Day 4 to Day 6 and from Day 8 to Day 12.
On Day 7, subject will come to the study center for an ambulatory visit (including dosing).
Subjects will be admitted in the morning of Day 13 and will leave the study center on Day 24 after completion of all study-related assessments.

c 2-lead Holter-ECG recordings will start in the morning before dosing (or at corresponding time at pre-tesofensine baseline) and will end approximately 24 hours after respective dose.

d On Days -1, 14, 15, 17, 18, 20, 21 and Day 23: Triplicate measurement (i.e., 3 recordings of 10 seconds each, at least 60 seconds apart) within 10 minutes before each PK sampling and at corresponding time points (pre-dose and at 2, 4, 8, 12 and 24 hours post-dose).
On other days and at Screening, also in triplicates: once daily in the morning (pre-dose on dosing days).

e On Days -1, 14, 15, 17, 18, 20, 21 and Day 23: Triplicate measurement within 10 minutes before each PK sampling and at corresponding time points (pre-dose and at 2, 4, 8, 12 and 24 hours post-dose).
On other days and at Screening, also in triplicates: once daily in the morning (pre-dose on dosing days).

f Subjects will have to rest during the quiet hour and for at least 10 minutes before 12-lead ECG recording and blood pressure and pulse measurements, i.e., each subject will be asked to find a personally comfortable supine position with the head and whole body firmly supported. The subjects will not be permitted to watch television or to listen to radio or music player. They will not be permitted to read, to sleep or converse, and will be kept free from any external disturbance (e.g., personal media). No electric equipment including mobile phones may be switched on in the room.

g Once daily, on in-house days in the morning.

h Randomization will be performed pre-dose on Day 1.

i Dosing of tesofensine will start in the morning of Day 1 and will be continued until the morning of Day 23, when the last dose of tesofensine will be given; subjects will be randomly assigned to any of the 3 tesofensine dose cohorts (Cohort 1, Cohort 2, Cohort 3).
Cohort 1: 1.0 mg once daily for the first 3 days (loading dose), then 0.25 mg once daily.
Cohort 2: 2.0 mg once daily for the first 3 days (loading dose), then 0.50 mg once daily.

j Dosing of extended release metoprolol will be performed in the morning of Day 15, Day 18 and Day 21 approximately 30 minutes after start of a breakfast.
Administration of single doses of 25 mg, 50 mg and 100 mg in random order.

k Blood sampling for metoprolol: at pre-dose and at 2, 4, 8, 12 and 24 hours post-dose on Day 15, Day 18 and Day 21.
Blood sampling for tesofensine: at pre-dose on Day 13, Day 14 and Day 15 to confirm steady state, at pre-dose on Day 18, Day 21 and Day 23 and at 8 hours post-dose on Day 15, Day 18 and Day 21.

l On outpatient days, date and time of dosing, adverse events (if any) and use of concomitant medication (if any) will be documented in a diary.

m Pregnancy tests will be performed whenever deemed necessary.

n The pregnancy test on Day 50 will be performed at home and the result will be communicated during the safety FU phone call.

Table 6 Schedule of Assessments for Cohort 3

Evaluation	Scree-ning	Base-line		Treatment Period																		Safety FU Phone Calls	
Day	**-28 to -3**	**-2**	**-1[a]**	**1**	**2**	**3**	**4**	**5**	**7**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**30**	**50**
Admission		X								X													
Discharge						X															X		
In-house stay[b]		X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X		
Ambulatory visits	X						X	X	X														
Phone call																						X	X
Informed consent	X																						
Medical history	X																						
Demographics	X																						
Inclusion/exclusion criteria	X																						
Physical examination	X																				X		
Body weight	X	X									X			X			X				X		
Waist circumference	X	X									X			X			X				X		
Height, calculation of BMI	X																						
Blood sampling for CYP2D6	X																						
Viral serology	X																						
HBA1c	X																						
Clinical laboratory tests (clinical chemistry, hematology and urinalysis) in fasted state	X	X							X												X		
Serum pregnancy test[m]	X																				X		
Urine pregnancy test[m]		X								X													X[n]
Psychodiagnostic self-rating instruments (PHQ-9 and GAD-7)	X																						
Urine drug screen, cotinine and alcohol test	X	X								X													
24-hours Holter ECG[c]			X[a]								X	X		X	X		X	X		X			
12-lead ECG[d,f]	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X		

Evaluation	Scree-ning	Base-line		Treatment Period																		Safety FU Phone Calls	
Day	**-28 to -3**	**-2**	**-1[a]**	**1**	**2**	**3**	**4**	**5**	**7**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**30**	**50**
Supine blood pressure and pulse[e,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body temperature[g]	X	X	X								X	X		X	X		X	X		X			
A designated period from 3 to 16 hours post-dose and a quiet hour from 12 to 13 hours post-dose[f]			X								X	X		X	X		X	X		X			
Randomization[h]				X																			
Dosing of tesofensine[i]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dosing of metoprolol[j]												X			X			X					
Blood sampling for PK[k]										X	X	X			X			X		X			
Dispense of tesofensine containers								X															
Subject returns tesofensine containers to the clinical unit										X													
Dispense of the diary and instructions[l]					X																		
Collection of the diary										X													
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; BMI = Body Mass Index; ECG = electrocardiogram; FU = Follow-up; PK = pharmacokinetics; GAD-7 = Generalized Anxiety Disorder Assessment; PHQ-9 = Patient Health Questionnaire-9

a The 24-hours ECG recording at pre-tesofensine baseline may be repeated, if less recording time than 22 hours for comparison of the data is available for evaluation due to technical issues. Then dosing and all subsequent assessments will be postponed by 1 day.

b Subjects will be admitted in the morning of Day -2 and will leave the study center in the morning of Day 3 after dosing of the last loading dose and after completion of all study-related assessments.
Subjects will come to the study center for ambulatory visits and dosing of tesofensine on Days 4 and 5.
Subjects will take tesofensine at home once daily on Day 6 and from Day 8 to Day 12.
On Day 7, subject will come to the study center for an ambulatory visit (including dosing).
Subjects will be admitted in the morning of Day 13 and will leave the study center on Day 24 after completion of all study-related assessments.

c 2-lead Holter-ECG recordings will start in the morning before dosing (or at corresponding time at pre-tesofensine baseline) and will end approximately 24 hours after respective dose.

d On Days -1, 14, 15, 17, 18, 20, 21 and Day 23: Triplicate measurement (i.e., 3 recordings of 10 seconds each, at least 60 seconds apart) within 10 minutes before each PK sampling and at corresponding time points (pre-dose and at 2, 4, 8, 12 and 24 hours post-dose).
On other days and at Screening, also in triplicates: once daily in the morning (pre-dose on dosing days).

e On Days -1, 14, 15, 17, 18, 20, 21 and Day 23: Triplicate measurement within 10 minutes before each PK sampling and at corresponding time points (pre-dose and at 2, 4, 8, 12 and 24 hours post-dose).
On other days and at Screening, also in triplicates: once daily in the morning (pre-dose on dosing days).

f Subjects will have to rest during the quiet hour and for at least 10 minutes before 12-lead ECG recording and blood pressure and pulse measurements, i.e., each subject will be asked to find a personally comfortable supine position with the head and whole body firmly supported. The subjects will not be permitted to watch television or to listen to radio or music player. They will not be permitted to read, to sleep or converse, and will be kept free from any external disturbance (e.g., personal media). No electric equipment including mobile phones may be switched on in the room.

g Once daily, on in-house days in the morning.

h Randomization will be performed pre-dose on Day 1.

i Dosing of tesofensine will start in the morning of Day 1 and will be continued until the morning of Day 23, when the last dose of tesofensine will be given; subjects will be randomly assigned to any of the 3 tesofensine dose cohorts (Cohort 1, Cohort 2, Cohort 3).
Cohort 3: 2.0 mg once daily for the first 5 days (loading dose), then 0.75 mg once daily.

j Dosing of extended release metoprolol will be performed in the morning of Day 15, Day 18 and Day 21 approximately 30 minutes after start of a breakfast.
Administration of single doses of 25 mg, 50 mg and 100 mg in random order.

k Blood sampling for metoprolol: at pre-dose and at 2, 4, 8, 12 and 24 hours post-dose on Day 15, Day 18 and Day 21.
Blood sampling for tesofensine: at pre-dose on Day 13, Day 14 and Day 15 to confirm steady state, at pre-dose on Day 18, Day 21 and Day 23 and at 8 hours post-dose on Day 15, Day 18 and Day 21.

l On outpatient days, date and time of dosing, adverse events (if any) and use of concomitant medication (if any) will be documented in a diary.

m Pregnancy tests will be performed whenever deemed necessary.

n The pregnancy test on Day 50 will be performed at home and the result will be communicated during the safety FU phone call.

7.2. Order of Assessments

The following order will be in effect when more than one assessment is required at a pre-dose (except for Screening and on admission) and post-dose time point, with PK blood sampling being performed nearest to the specified time:

1. 12-lead ECG
2. Vital signs
3. PK blood sampling
4. Blood sampling for safety assessments

7.3. Early Termination

If a subject withdraws prematurely after dosing, all data normally collected at discharge from the clinical unit should be collected at the time of premature discontinuation or at the scheduled discharge. The subjects will have Safety Follow-up phone calls. If deemed necessary by the Principal Investigator, the subject will be asked to return for a Follow-up visit.

7.4. End-of-Study

End-of-study is defined as completion of the final Follow-up phone call. For those subjects that withdraw prematurely, EoS is defined as the time of the subject's last data collection.

7.5. Restrictions

7.5.1. Dietary and Fluid Restrictions

Caffeine: Xanthine containing products (coffee, tea, chocolate, cola, energy drinks) are prohibited from 48 hours before each admission until discharges from the clinical unit.

Alcohol: Alcohol use is prohibited 48 hours prior to the Screening Visit. Alcohol use is prohibited from 48 hours prior to first admission until discharge.
Subjects may not drink > 168 g (males) and > 84 g (females) pure alcohol per week (10 g pure alcohol = 259 mL of beer [5%] or 35 mL of spirits [35%] or 100 mL of wine [12%] within 3 months prior to first admission.

Meals: No outside food or drink is permitted at the clinical unit. All meals and snacks will be provided. Subjects will receive standard meals and snacks at regimented times on PK and PD days.

7.5.2. Contraception Requirements

Subjects should be informed of the potential risks associated with becoming pregnant or fathering a child while enrolled in the trial.

Female subjects

Women of childbearing potential must be using highly effective methods of birth control† (failure rate < 1% per year when used consistently and correctly) starting at least 4 weeks prior to Screening and continued until at least 8 weeks after the last administration of IMP. The subjects should be using the same method for 3 months prior to the first dose of tesofensine. In addition, a barrier method‡ must always be used concomitantly to the highly effective method. Double-barrier is not considered a highly effective method.

Abstinence is acceptable, if it is the subject's usual lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) is not an acceptable means of contraception.

Female subjects are considered to be of non-childbearing potential, when they are either

- surgically sterile (hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy and/or bilateral tubal ligation), or
- post-menopausal, i.e., 12 months of amenorrhoea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or for women < 60 years the follicle-stimulating hormone (FSH) level is > 40 mIU/mL.

†Highly effective methods of birth control are implants, injectables, combined oral contraceptives, and some intrauterine devices (Note: The intrauterine device (IUD) must have a failure rate < 1%).

‡ Barrier methods of contraception include:

- Condom (without spermicidal foam/gel/film/cream/suppository or fat- or oil-containing lubricants)
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository

Please note: The combination of a condom together with diaphragm/cervical cap with spermicidal foam/gel/film/cream/suppository is not considered as highly effective contraceptive method.

Male subjects

Male subjects must use a condom without spermicide or oil-containing products (e.g., lubricants) during sexual activity with female partners of childbearing potential throughout the trial until at least 8 weeks after the last administration of IMP. Female sexual partners of male subjects should be willing to avoid pregnancy according to the above described methods.

7.5.3. Other Restrictions

Nicotine: Smoking and other nicotine containing products are prohibited. The study must enroll nonsmoking subjects.

Activity: Strenuous physical activity is prohibited from 48 hours prior to first admission until Day 24. After discharge, mild physical activity can be resumed. Subjects will be required to rest at the times specified in Table 5 and Table 6.

Medications: Use of prescription, herbal, OTC medication(s) or dietary supplements is prohibited within the 2 weeks prior to study Day -2 until the Safety Follow-up phone call. Concomitant medication use is permitted if indicated by the Investigator for treatment of an AE. Occasional use of paracetamol (up to 2 g/day) or other NSAIDs and the use of hormonal contraceptives are permitted. A list of prohibited medication is provided in Appendix 11.1.

Blood donation: Donation of one unit (450 mL) of blood or more is prohibited during the study and until 3 months after discharge.

8. STATISTICAL METHODS

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described in an SAP addendum and described and justified in the CSR.

8.1. Study Population

8.1.1. Analysis Populations

Safety population: All subjects who received at least one dose of IMP. Subjects will be included in the analysis according to the dose and IMP received. The safety population will be used for all safety analysis and to list PK concentrations.

PK population: All randomized subjects with at least one quantifiable tesofensine or metoprolol concentration and without major protocol deviations which could influence the PK. Subjects will be included in the analysis according to the dose and IMP received. The PK population will be used for all PK analysis.

PD population: All randomized subjects with at least HR assessments on at least 2 days out of Baseline (Day -2 to -1), Day 15, Day 18 and Day 21 without any major protocol deviations which could influence the PD parameters. Subjects will be included in the analysis according to the dose and IMP received. The PD population will be used for all PD analysis.

8.2. General Considerations

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, standard deviation [SD], minimum, median and maximum). Categorical data will be summarized by treatment group using frequency tables (number and percentage).

The individual subject concentration-time data will be listed and displayed graphically on the linear and log scales by analyte, treatment and overall, as applicable. The concentration-time data will be summarized descriptively by analyte, treatment and overall in tabular and graphical formats (linear and log scales). The non-compartmental PK parameters named in Section 3.2.2 will be listed and summarized descriptively by analyte and treatment in tabular format. Summary statistics of the PK parameters will be presented by treatment and dose-normalized when relevant.

If needed, selected individual vital signs and ECG parameters may be plotted against concentration data of tesofensine and/or metoprolol.

An SAP will be issued as a separate document, providing detailed methods for the analyses.

8.3. Protocol Deviations

Important protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with PAREXEL standard operating procedures (SOPs).

8.4. Subject Disposition

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

Subjects excluded from the safety, PK and PD analysis sets and data excluded from the PK and PD analysis sets will be listed including the reason for exclusion. Subject disposition will be summarized and will include the following information: number of subjects randomized and dosed, 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.

8.5. Demographic and Anthropometric Information and Baseline Characteristics

Demographic and anthropometric variables (age, gender, ethnicity, race, height, weight and BMI) will be listed by subject. Demographic characteristics (age, gender, ethnicity and race) and anthropometric characteristics (height, weight and BMI) will be summarized by treatment and for all subjects in the safety analysis set. The denominator for percentages will be the number of subjects in the safety analysis set for each treatment or for all subjects as applicable.

Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA system organ class (SOC), MedDRA preferred term (PT), start date, and stop date (or ongoing, if applicable).

8.6. Prior and Concomitant Medication and Drug Administration

Prior medications are those that started and stopped prior to the first dose of 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, PT, the route of administration, dose, frequency, start date/time, duration and indication.

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO-DD) latest version.

Drug administration dates and times will be listed for each subject.

8.7. Exposure

A listing of drug administration will be created and will include the date and time of administration.

8.8. Safety Analyses

8.8.1. Adverse Events

All AEs will be listed. The number and percent of subjects experiencing a treatment emergent AE (TEAE) will be tabulated by treatment for each SOC and PT. The TEAEs will also be tabulated according to intensity and causality.

Serious AEs will be listed separately.

8.8.2. Clinical Laboratory Tests

Individual data listings of laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listings.

Clinical laboratory tests (observed values) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters.

8.8.3. Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Individual clinically significant vital signs findings that were considered AEs by the Principal Investigator will be presented in the AE listings.

Observed values as well as change from baseline data will be summarized descriptively in tabular format. Graphical displays over time may be presented for individual and summarized data.

8.8.4. Standard 12-lead Electrocardiogram

Standard 12-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values will be summarized descriptively in tabular format. Change from baseline will be summarized descriptively for QTc data. A categorical QTc analysis will also be performed. Graphical displays over time may be presented for individual and summarized data.

8.8.5. Physical Examination

Abnormal physical examination findings will be listed.

8.9. Pharmacokinetic Analyses

PK parameters of metoprolol and tesofensine will be computed using standard non-compartmental methods using Phoenix®WinNonlin®6.3 (or higher) (Certara, L.P., 1699 South Hanley Road, St Louis, Missouri 63144, United States of America).

The PK parameters will be calculated using the actual sampling time relative to corresponding IMP administration for tesofensine and metoprolol.

PK parameters computed for metoprolol will be:

- Maximum observed plasma concentration (C_{max});
- Observed time at C_{max} (T_{max});
- Area under the plasma concentration-time curve from time zero to 24-hour post-administration of metoprolol (AUC_{0-24}).

PK parameters computed for tesofensine will be:

- Trough concentration in a dosing period (C_{trough})

Additional PK parameters may be calculated for exploratory purposes.

PK data will be listed and summarized in tabular format by descriptive statistics as appropriate. Descriptive statistics will be applied and presented by treatment group. No imputation of missing data will be performed. Summary statistics of the PK parameters will be presented by treatment and dose-normalized when relevant. PK data may also be displayed graphically as appropriate. An SAP will be written as a separate document, providing detailed methods for the analyses.

8.10. Pharmacodynamic Analyses

- The mean and absolute change in M24HR after tesofensine alone will be calculated as the difference between the mean of the 3 pre-administration measurements on Day 14, Day 17 and Day 20 and the post-administration measurement on Day 23 and pre-tesofensine baseline (Day -1) and summarized descriptively by treatment.
- The mean and absolute change in M24HR after tesofensine co-administered with 3 different doses of metoprolol will be calculated as the difference between each mean of the 3 metoprolol doses on Days 15, 18 and 21, and pre-tesofensine baseline (Day -1) and summarized descriptively by treatment.
- The mean and absolute change in M24HR after tesofensine co-administered with 3 different doses of metoprolol relative to tesofensine alone will be calculated as the difference between each mean of the 3 metoprolol doses on Days 15, 18 and 21 and the mean of the 3 pre-administration measurements on Day 14, Day 17 and Day 20 and the post-administration measurement on Day 23, and summarized descriptively by treatment.
- The mean maximum and minimum HR24 values after tesofensine alone and when co-administered with 3 different doses of metoprolol will be summarized descriptively by treatment.
- The time of minimum heart rate (HRmin) and maximum heart rate (HRmax) after tesofensine alone and when co-administered with 3 different doses of metoprolol will be summarized descriptively by treatment.
- Mean SBP and DBP values after tesofensine alone and when co-administered with 3 different doses of metoprolol will be summarized descriptively by treatment.
- Mean HR during a designated quite hour and a designated period will be summarized descriptively by treatment.

- M24HR on Days 14, 17, 20 and 23 will be compared by means of analysis of variance (ANOVA) with random subjects nested under sequence. In this analysis there will be no period effect and treatment effect (such as metoprolol dose) other than the fixed days.
- Change from pre-tesofensine baseline (Day -1) of M24HR on Days 15, 18 and 21 will be compared by means of ANOVA with random subjects nested under sequence and fixed Day (Day 15, 18 and 21 will play the role of period in a conventional cross-over) and treatments. In this analysis the metoprolol dose will be distinguishing between treatments.
- Boxplots will be made on M24HR for Days -1, 14, 15, 17, 18, 20, 21 and 23 and will be displayed using treatment and treatment plus visit (for tesofensine days).

8.10.1. Regression Analysis

A cross-over ANOVA model will be used to reduce change from baseline M24HR data to mean levels for each dose (adjusting for subject, day and treatment effects). A straight line linear regression will be used to fit the means to log dose. Based on the regression equation a dose for no effect will be estimated. Confidence intervals will be determined using a bootstrap method.

Details of the modelling will be provided in the SAP.

In case the linear model linking Mean M24HR to log dose is clearly not satisfactory, an alternative strategy may be employed, for instance, by interpolation between 2 adjacent doses. The need and approaches for such analysis will be discussed after the initial analysis is finished.

8.10.2. Pharmacokinetic-Pharmacodynamic Analysis

The relation between metoprolol concentration and HR will be explored using plots of HR or time-matched change from baseline HR against concentration by tesofensine dose. The plots will possibly be augmented with local regression lines and confidence intervals.

A straight line regression will be used to fit change from baseline M24HR against PK parameters (AUC_{0-24} and C_{max}) of metoprolol for each tesofensine dose. Based on the regression equation a parameter value for no effect will be estimated. Confidence intervals will be determined using a bootstrap method.

Details of the analysis and/or additional approaches will be provided in the SAP.

8.10.3. Pharmacokinetic-Pharmacodynamic Modelling

A population PK-PD model may be developed if deemed appropriate on the data from this study with the final objective of describing relative contribution to the final effect of plasma exposure

to tesofensine and metoprolol, simulating optimal dose regimen for multiple administration and evaluate effect of covariates (e.g., polymorphism of PK, body weight, gender) on the overall effect.

Details of the analysis will be in case included in a separate Data Analysis plan and outcome of the modelling will be reported separately.

8.11. Interim Analyses

No formal interim analysis will be performed.

However, after completion of approximately 20 evaluable subjects, M24HR obtained on Days 14, 17, 20, and 23 will be reviewed to confirm that the M24HR returned to steady state tesofensine conditions prior to each metoprolol dosing. Appropriate statistical methods such as regression analysis and/or ANOVA may be applied to compare HR24 values across study Days 14, 17, 20, 23. If similar pre-metoprolol dosing conditions cannot be confirmed the study may be stopped for ethical and futility reasons, or amended appropriately, e.g. by adjusting the metoprolol wash-out period. No other data will be evaluated during this interim look.

8.12. Determination of Sample Size

No formal sample size calculation has been performed.

With a sample size of N=20 with 80% power assuming the same within-subject variability in HR as observed in the study TM001 (within-subject variability = 5%) a mean difference of 3.3 beats per minute can be detected within a tesofensine cohort. This detectable difference is smaller than the increase in HR induced by all 3 studied doses of tesofensine in the study TIPO-1; thus, 20 subjects per cohort should provide adequate sample size for the purpose of this Phase 1 study.

9. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

9.1. Data Quality Assurance

The Sponsor will supervise a study initiation visit to verify the qualifications of the Principal Investigator, inspect the facilities and inform the Principal Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Principal Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical unit and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Principal Investigator will make all appropriate safety assessments on an ongoing basis.

All aspects of the study will be carefully monitored with respect to Good Clinical Practice (GCP) and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

9.1.1. Data Collection

PAREXEL's ClinBase™ system (a Clinical Study Management System for source data capture and process control) will be utilized in this study. Data from ClinBase™ can be exported to/prepared as an eSDR in PDF format. The eSDR will follow the same design as the empty eSDR that is used for the database setup approval.

PAREXEL ClinBase™ designer will design ClinBase™ to be completed for each subject who enters the study. The entries will be checked by trained personnel. Errors or inconsistencies will be corrected. Any changes or corrections to ClinBase™ will be dated, initialed and explained (if necessary). An explanation for the omission of any required data will appear on the appropriate page. The Investigator will sign the completed ClinBase™, thereby taking responsibility for the accuracy of the data in the entire ClinBase™. The Investigator will retain records of the changes and corrections.

Source data will be defined as such in the Source Document Agreement. The clinical unit's ClinBase™ system will be used to capture certain safety data - this will be indicated on the Source Document Agreement.

Paper-based data will be subject to data entry in ClinBase™. For electronic source data, no data entry will be performed.

The responsible Study Monitor will check data at the monitoring visits to the clinical unit. The Investigator will ensure that the data collected are accurate, complete and legible.

All clinical work conducted under this clinical study protocol is subjected to GCP regulations. This includes an inspection by the Sponsor and Competent Authority representatives at any time. The Investigator will agree to the inspection of study-related records by Competent Authority representatives and the audits of the Sponsor or third parties named by the Sponsor.

9.1.2. Data Management

Data management of all data documented will be performed under the responsibility of the Head of the Department of Data Management, PAREXEL Early Phase and in accordance with the SOPs for data management.

The Data management plan (DMP) will be provided to the Sponsor describing the work and data flow within this clinical study. Versions for the computer systems, coding and reconciliation of data will be defined in the DMP. The DMP will be sent to the Sponsor for review and approval. The DMP must be finalized in accordance with PAREXEL SOP.

9.2. Access to Source Data/Documents

PAREXEL will use an electronic data capture system to manage data collection during this study. The electronic data capture system (ClinBase™) is a software tool designed to ensure quality assurance and facilitate data capture during clinical studies. Through a system regulated workflow that includes barcode scanning and interfaces to medical equipment to avoid manual data entry, study operations performance is controlled and captured in real time. The system is fully Code of Federal Regulations (CFR) 21 part 11 compliant.

The Principal Investigator will ensure the accuracy, completeness and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability and consistency. A complete audit trail will be maintained of all data changes. The Principal Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Principal Investigator or designee will prepare and maintain adequate and accurate study documents (e.g., medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving IMP.

The Principal Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors and the IEC to have direct access to all documents pertaining to the study.

9.3. Archiving Study Documents

According to International Council for Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.4. Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Principal Investigator abide by the principles of the ICH guidelines on GCP. The clinical study also will be carried out in keeping with national and local legal requirements and with ethical principles that have their origins in the Declaration of Helsinki (Version 1996).

9.5. Informed Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country. As part of this procedure, the Principal Investigator must explain orally and in writing the nature, duration and purpose of the study and the action of the drug in such a manner that the subject is aware of the potential risks, inconveniences or AEs that may occur. The subject should be informed that he is free to withdraw from the study at any time. He will receive all information that is required by federal regulations and ICH guidelines. The Principal Investigator or

designee will provide the Sponsor with a copy of the IEC-approved ICD prior to the start of the study.

The ICD must be signed and dated; one copy will be handed to the subject, and the Principal Investigator will retain a copy as part of the clinical study records. The Principal Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the ICD may need to be revised to reflect the changes to the protocol. If the ICD is revised, it must be reviewed and approved by the responsible IEC, and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

9.6. Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the RA (regulatory authority) and IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the responsible staff and receive RA and IEC approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment, but will also be mentioned in the integrated CSR. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

9.7. Insurance and Indemnity

Every subject participating in the study is insured in accordance with local law against injuries to health, which may occur during the clinical study. Any injury to health, which might have occurred as a result of participating in the study, must be reported by the subject to the Investigator without delay. In all cases the Investigator is obliged to make a report to the Sponsor and the insurer. The Investigator is responsible for dispensing the study medication according to this protocol, and for its secure storage and safe handling throughout the study. Additional insurance details will be provided in the Insurance Policy. The subject insurance will be arranged by Saniona.

9.8. Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Principal Investigator and members of his/her research team (including the IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their randomization number, year of birth, not by name. Documents that identify the subject (e.g., the signed ICD) must be maintained in confidence by the Principal Investigator.

9.9. Publication Policy

By signing the clinical study protocol, the Principal Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the regulatory authorities will be notified of the Principal Investigator's name, address, qualifications and extent of involvement.

A Principal Investigator shall not publish any data (poster, abstract, paper, etc.) without obtaining prior written permission from the Sponsor.

PAREXEL will prepare a CSR after the completion of the study. The Sponsor representative will sign the final study report intended to be submitted to regulatory authorities.

The results of this study may be published or presented at scientific meetings. The Sponsor will be responsible for publication of all the data generated in this study.

10. REFERENCE LIST

1. Colman E. Food and Drug Administration's Obesity Drug Guidance Document: A Short History. Circulation 2012;125(17):2156-2164
2. Investigator's Brochure of Tesomet. Version 1.0, Final, 11 September 2017
3. Investigator's Brochure of tesofensine. Version 14.0, Final, 02 June 2018
4. SPC of metoprolol ER tablets. Metoprololsuccinat "Orion", depottabletter, Orion Corporation (Finland), SPC dated 16. November 2015
5. Spitzer RL, Kroenke K, Williams JB (1999). Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA. Nov 10; 282(18)*: 1737–44
6. INSTRUCTION MANUAL Instructions for Patient Health Questionnaire (PHQ) and GAD-7 Measures. https://phqscreeners.pfizer.edrupalgardens.com/sites/g/files/g10016261/f/201412/instructions.pdf
7. Patient Health Questionnaire (PHQ) Screeners: http://www.phqscreeners.com/select-screener/ [on-line; accessed 11 JUN 2018]

11. APPENDICES

11.1. Appendix 1 - List of Prohibited Medication

Drug Class	Episodic Use	Chronic Use	Comment
Antiarrhythmic (Amiodarone, quinidine)	N	N	Strong inhibitor of CYP2D6
Antiretroviral (Ritonavir)	N	N	Strong inhibitor of CYP2D6
Anorectic agents	N	N	
Antiandrogens (abiraterone, cyproterone acetate, finasteride)	N	N	
Antihistamines	Y	N	Topical antihistamines – always approved
Antiepileptic drugs	N	N	
Antidepressant drugs	N	N	
Anti-anxiety drugs	N	N	
Anti-Parkinsonian drugs	N	N	
Anti-Dementia drugs donepezil and galantamin	N	N	
Antifungal (terbinafine)	N	N	Moderate inhibitor of CYP2D6
Muscarinreceptor blocker darifenacin	N	N	Moderate inhibitor of CYP2D6
Barbiturates	N	N	
Benzodiazepines	N	N	
Beta- blockers	N	N	Per protocol
Buproprion (non-SSRI antidepressant)	N	N	Strong inhibitor of CYP2D6
Calcium channel blockers	N	N	Per protocol
Carbonic anhydrase inhibitors (e.g., acetazolamide, dichlorphenamide, dorzolamide, methazolamide)	N	N	
Cinacalcet (calcimimetic)	N	N	Strong inhibitor of CYP2D6
Dopamine reuptake inhibitors (e.g., bupropion)	N	N	
Glucocorticoids	Y	N	
Hypnotic sedative (glutethimide)	N	N	Strong inducer of CYP2D6
H_2-receptor antagonist (cimetidine)	N	N	Weak inhibitor of CYP2D6
Immunosuppressives	N	N	
Insulin and/or other injectable anti-diabetic medications, or thiazolidinediones (TZDs)	N	N	Per protocol
Lithium	N	N	
Monoamine oxidase (MAO) inhibitors	N	N	
Opioids, cannabinidiols	N	N	
Oral hypoglycemic	-	-	Per protocol
Orlistat	N	N	
Phenothiazines	N	N	
Selective serotonin reuptake inhibitors (SSRIs)	N	N	
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	N	N	