Clinical Study Protocol

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

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:	236073
Sponsor Study Number:	TM003
EudraCT Number:	2017-003339-13
IMP Name:	Tesofensine, metoprolol
Development Phase:	Phase 1, pharmacokinetics, relative bioavailability
Version (Date) of Final Protocol:	Final 1.0 (15 September 2017)

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

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SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

Protocol Title: A randomized, open-label, single-dose, parallel-arm, Phase 1 study to investigate the pharmacokinetic profile of a fixed-dose combination tablet of tesofensine and metoprolol (Tesomet) and co-administration of tesofensine plus commercial metoprolol in adult healthy subjects

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

18/9 - 2017

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Declaration of the Principal Investigator and Deputy Principal Investigator

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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 randomized, open-label, single-dose, parallel-arm, Phase 1 study to investigate the pharmacokinetic profile of a fixed-dose combination tablet of tesofensine and metoprolol (Tesomet) and co-administration of tesofensine plus commercial metoprolol in adult healthy subjects
Study Numbers	PAREXEL Study No.: 236073 Sponsor Protocol No.: TM003
Development Phase	Phase 1, pharmacokinetics (PK), relative bioavailability
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 The study will be conducted at a single center (PAREXEL International GmbH, Early Phase Clinical Unit Berlin).
Study Objectives	**Primary objective** To evaluate the PK profile and relative bioavailability of a single dose of the Tesomet fixed-dose combination (FDC) tablet and co-administration of tesofensine plus commercial metoprolol. **Secondary objectives** • To evaluate the PK profile and relative bioavailability of a single dose of the Tesomet FDC tablet in fed state • To evaluate the PK profile of a single dose of the high and low dose of the Tesomet FDC tablet • To evaluate overall safety and tolerability of the Tesomet FDC tablet and co-administration of tesofensine plus commercial metoprolol in adult healthy volunteers
Study Design	This is a randomized, open-label, parallel-arm study in 60 healthy male subjects who meet the inclusion and none of the exclusion criteria for the study. Each subject will participate in a screening period, a baseline period (the day preceding drug administration), and a single-dose treatment period with an on-site observation period of at least 48 hours after the dose. Subjects will be admitted to the study center at least 24 hours prior to dosing. Each subject will then be randomized to one of the 4 treatment groups and receive one of the following treatments: **Treatment A (Test 1)**: A Tesomet FDC tablet (20 mg immediate release [IR] metoprolol, 1 mg tesofensine, 80 mg extended release [ER] metoprolol) in fasted condition ("High" dose) **Treatment B (Test 2)**: A Tesomet FDC tablet (5 mg IR metoprolol, 0.2 mg tesofensine, 20 mg ER metoprolol) in fasted condition ("Low" dose) **Treatment C (Comparator)**: 1 mg tesofensine (2 tablets of 0.5 mg), 25 mg commercial IR metoprolol (1 tablet of 25 mg), 75 mg commercial ER metoprolol (1 ER tablet of 25 mg and 1 ER tablet of 50 mg), fasted condition **Treatment D (Test 3)**: A Tesomet FDC tablet (20 mg IR metoprolol, 1 mg tesofensine, 80 mg ER metoprolol in fed condition ("High" dose)

	Subjects assigned to Treatments A, B and C will be required to remain fasted from at least 10 hours before dosing and until 4 hours post-dose. At 4 hours after dosing a light standardized meal will be served. The Investigator or a designee will administer the appropriate treatment with 240 mL water to the subjects as per randomization schedule. Subjects assigned to Treatment D will be required to eat a Food and Drug Administration (FDA) standardized high-fat breakfast within a period of 30 minutes before dosing. The Investigator or a designee will administer the treatment to the subjects 30 minutes after start of the breakfast and within 5 minutes of completing the meal. For each of the treatment groups, blood samples will be collected pre-dose and at designated time points post dosing. Subjects will be discharged after the 48 hours post-dose assessments have been completed. The end-of-study (EoS) safety evaluation will be performed 7 days (i.e., on Day 8) after dosing over the phone. Subjects will be asked regarding adverse events (AE), and concomitant medications. The total duration for each subject will be up to 38 days, including Screening.
Investigational Medicinal Products	• Tesomet "high" dose: An FDC tablet with 20 mg IR metoprolol, 1 mg tesofensine, 80 mg ER metoprolol, single oral dose, Treatment Group A and D only • Tesomet "low" dose: An FDC tablet with 5 mg IR metoprolol, 0.2 mg tesofensine, 20 mg ER metoprolol, single oral dose, Treatment Group B only • Tesofensine, film-coated tablet, 0.5 mg, single oral dose of 2 tablets, Treatment Group C only • Metoprolol, 25 mg IR tablet, single oral dose, Treatment Group C only Egilok 25 mg - EGIS Pharmaceuticals PLC (Hungary) • Metoprolol, 25 mg ER tablet, single oral dose of 1 tablet, Treatment Group C only Metoprolol-ratiopharm® Succinat 23,75 mg Retardtabletten – ratiopharm GmbH (Germany) (corresponding to 25 mg metoprolol tartrate) • Metoprolol, 50 mg ER tablet, single oral dose of 1 tablet, Treatment Group C only Metoprolol-ratiopharm® Succinat 47,5 mg Retardtabletten - ratiopharm GmbH (Germany) (corresponding to 50 mg metoprolol tartrate)
Number of Subjects	A total of 60 subjects is planned for enrollment. The subjects will be randomly assigned to one of the 4 treatment groups with 15 subjects per group.
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 Visit procedures. 2. Males between 18 to 55 years of age, inclusive, at the Screening Visit. 3. Nonsmokers (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 the Screening Visit and admission. 4. Body mass index (BMI) between 18.5 and 30.0 kg/m^2, inclusive, at the Screening Visit. 5. Healthy, determined by pre-study medical evaluation (medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory

	evaluations). **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, urologic, pulmonary, 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. 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 at the Screening Visit or admission. One re-test is allowed, if (a) test result(s) is outside these limits. 5. Subject has a corrected QT interval using Fridericia's formula (QTcF) interval > 450 msec at Screening. If the mean QTcF exceeds the limits above, an additional ECG may be taken. If this also gives an abnormal result, the subject will be excluded. 6. 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. 7. 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 study drug administration, except for the occasional use of paracetamol (up to 2 g/day) or other non-steroidal anti-inflammatory drugs (NSAIDs). 8. Subject has history of alcohol and/or illicit drug abuse within 2 years of entry. 9. Subject has positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids) or alcohol test at the Screening Visit or admission. 10. History of drinking more than 21 units of alcohol per week (1 unit = 10 g pure alcohol = 250 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. 11. Subject is unwilling to avoid consumption of coffee and caffeine-containing beverages within 48 hours prior to admission until discharge from the clinical site. 12. Subject is unwilling to avoid use of alcohol or alcohol-containing foods, medications or beverages, within 48 hours prior to admission until discharge from the clinical site. 13. 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. 14. Participation in any clinical study within 3 months prior to the expected date of investigational medicinal product (IMP) administration, provided that the clinical study did not entail a biological compound with a long t1/2 or

	participation in more than 3 clinical studies within 12 months. 15. History of any clinically significant cardiac arrhythmia. 16. History of bulimia or anorexia nervosa. 17. Use of any agent used for weight loss within the last 3 months. 18. More than 5% weight loss within the last 3 months. 19. Hypo- or hyperthyroidism. 20. Subject is unwilling to abstain from vigorous exercise from 48 hours prior to admission until discharge. 21. Subject has a history of hypersensitivity to the study drugs or any of the excipients or to medicinal products with similar chemical structures. 22. Subject has lactose intolerance. 23. 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. 24. Subject has previously been enrolled in this clinical study. 25. 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). 26. 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.
Criteria for Evaluation	**Pharmacokinetics Endpoints** The following PK parameters for tesofensine and metoprolol will be determined after dosing for all 4 treatments, as appropriate: • C_{max}: Maximum tesofensine and metoprolol concentrations determined directly from the concentration-time profile • AUC_{0-48}: Area under the concentration-time curve from pre-dose (time 0) to 48 hours post-dose calculated using the linear-log trapezoidal rule • T_{max}: Time of maximum tesofensine and metoprolol concentrations determined directly from the concentration-time profile • λ_z: The terminal elimination rate constant determined by selection of at least 3 data points on the terminal phase of the concentration-time curves • $t_{½}$: Terminal elimination half-life calculated as: $\ln 2/\lambda_z$ **Safety Endpoints** The following safety variables will be recorded at regular intervals during the study: • Vital signs (supine blood pressure [BP], pulse, body temperature and respiratory rate) • Twelve-lead electrocardiogram (ECG) • Clinical laboratory tests (hematology, clinical chemistry and urinalysis) • Adverse event assessments • Concomitant medication assessments • Physical examinations

Statistical Methods	*Sample Size Considerations* Formal sample size calculations were not performed. The number of subjects was chosen based on literature and experience from similar studies and is considered sufficient to meet the study objectives. No formal statistical test will be performed. Only descriptive statistics for PK and safety data by treatment group will be presented. The sample size chosen is therefore judged reasonable to gain knowledge regarding key parameters in each of the treatment groups. *Data Presentation/Descriptive Statistics* All demographic, safety and PK data will be listed and summarized in tabular format by descriptive statistics as appropriate. Only 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, e.g., AUC_{0-48}, C_{max}, T_{max}, $t_{½}$, etc. will be presented by treatment and dose-normalized when relevant. Pharmacokinetics data may also be displayed graphically as appropriate. A statistical analysis plan (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
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-48}	Area under the concentration-time curve from pre-dose (time 0) until 48 hours post-dose
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
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
Hb	Hemoglobin

Abbreviation	Definition
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
i.v.	Intravenous
IB	Investigator's Brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IR	Immediate release
LDH	Lactate dehydrogenase
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	Parkinson's disease
PK	Pharmacokinetic(s)
PT	Preferred Term
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

Abbreviation	Definition
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

Tesomet is a fixed-dose combination (FDC) product with 2 active ingredients – tesofensine (NS2330) – a serotonin, norepinephrine and dopamine reuptake inhibitor and metoprolol – a β1-(cardio-selective) selective adrenoceptor-blocking agent.

Tesofensine was initially noted to cause a marked weight loss in overweight patients with Parkinson's disease (PD) and dementia of Alzheimer type (DAT), even though no attempts to promote weight control was 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 impact the overall benefit/risk profile of tesofensine. Consequently, it has been decided by Saniona not to develop tesofensine as a stand-alone therapy. Instead, tesofensine has been combined with the beta-blocker metoprolol in order to mitigate the increase in BP and HR and ensure a favorable risk/benefit profile for the combination product Tesomet.

To date, co-administration of tesofensine and metoprolol to human has been investigated in 2 completed clinical studies. 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 drugs were generally well tolerated and the collected data have provided solid base for future investigation of Tesomet for various indications. 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].

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 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 PD 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 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, 5, 6].

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 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. Tesomet (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 IB [2] and Summaries of Product Characteristics (SPCs) of metoprolol immediate release (IR) and ER tablets [4, 5, 6].

1.2. Rationale for the Clinical Study

It has been decided to develop combination tablets with tesofensine and metoprolol, with metoprolol mitigating the increases in BP and HR caused by tesofensine. In this study, the release characteristics of the multi-layer tablet will be investigated in an exploratory manner. The PK profiles will be compared to those of mono-components administered to a parallel group.

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 clinically significant changes in vital signs, electrocardiogram (ECG) or laboratory parameters 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. Three 4-week studies used forced-titration and included 62 patients (60 to 80 years) with possible DAT and 9 patients with advanced PD. 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 PD patients were included and 796 of them were exposed to doses of 0.125-1.0 mg of tesofensine.

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 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.

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 800 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 PD 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 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 the different metoprolol formulations [4, 5, 6].

1.2.3. Safety of Tesomet (Co-administration of Tesofensine and Metoprolol)

To date, Tesomet (as co-administration of tesofensine tablet and metoprolol tablet) has been administered to humans in 2 completed 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, 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. 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 Tesomet and tesofensine tablets refer to the IBs [2, 3]. For details regarding safety data of metoprolol refer to SPCs of metoprolol IR and ER tablets [4, 5, 6].

There will be no direct health benefit for healthy subjects from receipt of the study drug. The protocol has been designed to minimize the risk to research participants. Subjects will be

monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs.

Tesofensine and metoprolol have been co-administered in a previous clinical study and were well tolerated. Steady state levels of tesofensine had no major influence on the PK of metoprolol (Study Q-21125). No additional risks are expected by the co-administration compared to those known for single dosing of tesofensine and metoprolol alone.

2. STUDY OBJECTIVES

The objectives of this study are as follows:

2.1. Primary Objective

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

2.2. Secondary Objectives

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

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1. Overview

This is a randomized, open-label, parallel-arm study in 60 healthy male subjects who meet the inclusion and none of the exclusion criteria for the study. Each subject will participate in a screening period, a baseline period (the day preceding drug administration), and a single-dose treatment period with an on-site observation period of at least 48 hours after the dose. A study flow chart is provided in Figure 1.

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

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

An overview is provided in Figure 2. Subjects assigned to Treatments A, B and C will be required to remain fasted from at least 10 hours before dosing and until 4 hours post-dose. At 4 hours after dosing a light standardized meal will be served. The Investigator or a designee will administer the appropriate treatment with 240 mL water to the subjects as per randomization schedule. Subjects assigned to Treatment D will be required to eat a Food and Drug Administration (FDA) standardized high-fat breakfast within a period of 30 minutes before dosing. The Investigator or a designee will administer the treatment to the subjects 30 minutes after start of the breakfast and within 5 minutes of completing the meal.

For each of the treatment groups, blood samples will be collected pre-dose and at designated time points post dosing. Subjects will be discharged after the 48 hours post-dose assessments have been completed. The end-of-study (EoS) safety evaluation will be performed 7 days (i.e., on Day 8) after dosing over the phone. Subjects will be asked regarding AEs, and concomitant medications. The total duration for each subject will be up to 38 days, including Screening.

Figure 1 Study Flow Chart

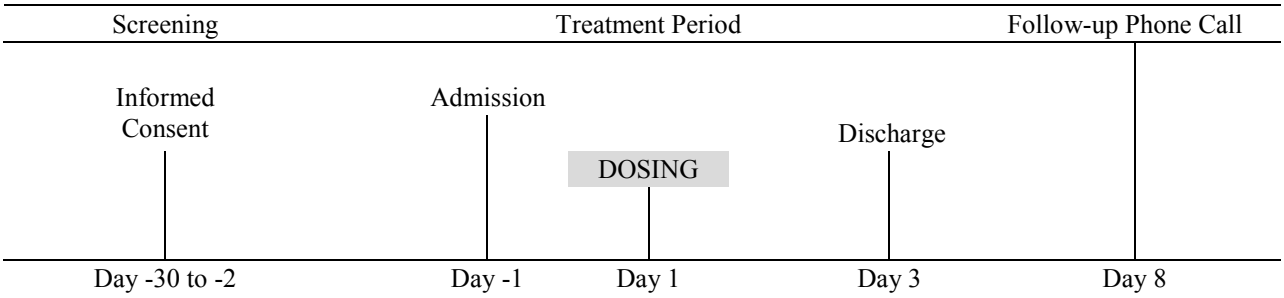
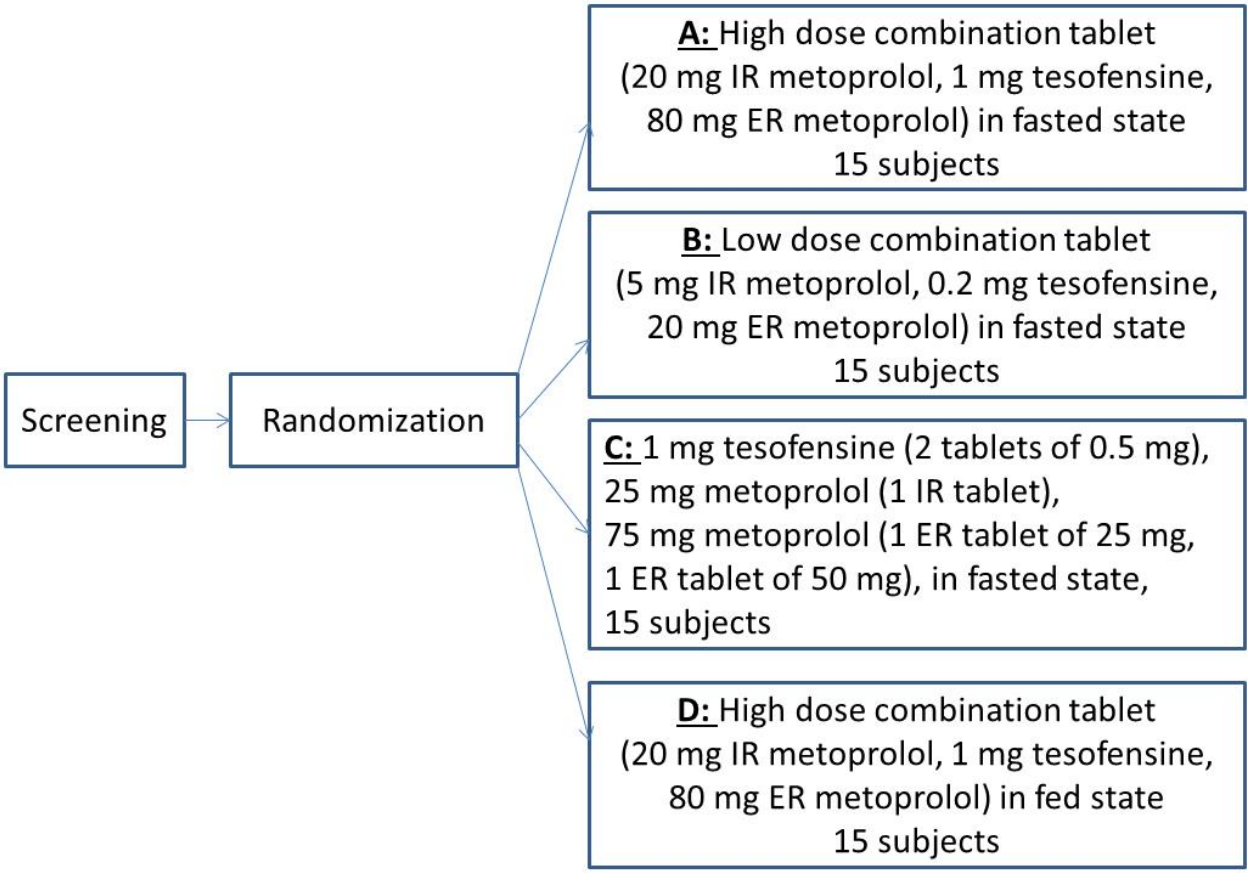


Figure 2 Study Overview



ER = extended release; IR = immediate release

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

3.2. Endpoints

3.2.1. Pharmacokinetics Endpoints

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

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

3.2.2. Safety Endpoints

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

- Vital signs (supine BP, pulse, body temperature and respiratory rate)
- 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 tesofensine and metoprolol administered orally as single doses in fasted and fed condition. The design is considered

appropriate to meet the exploratory (i.e., non-confirmatory) objectives of the study. Safety and PK of tesofensine have already been evaluated in many other studies and, therefore, it is not considered necessary to investigate the PK profile of tesofensine until a full half-life period or a multiple thereof has been completed, which would mean blood sampling for PK for at least 10 days. The proposed sampling period was deemed satisfactory given the exploratory nature of this study and because:

- Metoprolol's plasma profile is fully covered within 48 hours sampling - both as IR and ER formulation.
- Tesofensine's plasma distribution phase into the elimination phase has a duration of approximately 24 hours, i.e., within 48 hours the known (and established) elimination phase constant has been reached meaning that the rest of the plasma profile can be simulated and predicted. This means that there is no real scientific rationale for performing more sampling. If one would like to add more sampling points then this should be done in an a) outpatient basis (subjects to come to the unit for blood sampling) and b) sampling every 5 to 7 days to ensure an array of data points making the estimated area under the curve (AUC) more qualified than just one final sampling point.

Due to the very long half-life of tesofensine of about 9 days, a cross-over approach with intra-individual comparison of the PK profiles of 2 or more treatments is not considered feasible, because the wash-out period would have to be too long. Therefore, a parallel-group design was chosen.

The rationale for dose selection is discussed in Section 5.2.

3.4. Stopping Criteria for the Clinical Study

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

- Adverse event stopping criteria:
  - More than 25% of subjects experience a severe AE of related causality
  - Any SAE of related causality

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

- Vital signs stopping criteria:
  - Symptomatic hypotension (systolic blood pressure [SBP] < 85 mmHg). If symptomatic hypotension is observed during the study, then a minimum of 2 repeat BP measurements should be obtained over a brief period. 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 baseline (If a prolonged QTc interval is observed during the study, then a minimum of 2 repeat ECGs should be obtained over a brief period. 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)
    with
    bilirubin ≥ 2 times the ULN
  - Creatine phosphokinase (CPK) ≥ 3 times the ULN (that cannot be attributed to causes other than the study drug; i.e., vigorous exercise)

4. STUDY POPULATION

The study population will consist of healthy male volunteers. Subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

4.1. Number of Subjects

A total of 60 subjects is planned for enrollment in the clinical study (N=15 will be randomly assigned to one of the 4 treatment treatment groups) according to the inclusion/exclusion criteria.

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 Independent Ethics Committee (IEC)-approved informed consent prior to performing any of the Screening Visit procedures.
2. Males between 18 to 55 years of age, inclusive, at the Screening Visit.
3. Nonsmokers (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 the Screening Visit and admission.
4. Body mass index (BMI) between 18.5 and 30.0 kg/m^2, inclusive, at the Screening Visit.
5. Healthy, determined by pre-study medical evaluation (medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory evaluations).

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, urologic, pulmonary, 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. Subject has a pulse < 50 or > 90 bpm; SBP < 90 mmHg or > 140 mmHg; diastolic blood pressure (DBP) < 50 mmHg or > 90 mmHg at the Screening Visit or admission. One re-test is allowed, if (a) test result(s) is outside these limits.
5. Subject has a corrected QTcF interval > 450 msec at Screening. If the mean QTcF exceeds the limits above, an additional ECG may be taken. If this also gives an abnormal result, the subject will be excluded.
6. 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.
7. 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 study drug administration, except for the occasional use of paracetamol (up to 2 g/day) or other non-steroidal anti-inflammatory drugs (NSAIDs).
8. Subject has history of alcohol and/or illicit drug abuse within 2 years of entry.
9. Subject has positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids) or alcohol test at the Screening Visit or admission.
10. History of drinking more than 21 units of alcohol per week (1 unit = 10 g pure alcohol = 250 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.
11. Subject is unwilling to avoid consumption of coffee and caffeine-containing beverages within 48 hours prior to admission until discharge from the clinical site.
12. Subject is unwilling to avoid use of alcohol or alcohol-containing foods, medications or beverages, within 48 hours prior to admission until discharge from the clinical site.
13. 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.

14. Participation in any clinical study within 3 months prior to the expected date of investigational medicinal product (IMP) administration, provided that the clinical study did not entail a biological compound with a long $t_{1/2}$ or participation in more than 3 clinical studies within 12 months.
15. History of any clinically significant cardiac arrhythmia.
16. History of bulimia or anorexia nervosa.
17. Use of any agent used for weight loss within the last 3 months.
18. More than 5% weight loss within the last 3 months.
19. Hypo- or hyperthyroidism.
20. Subject is unwilling to abstain from vigorous exercise from 48 hours prior to admission until discharge.
21. Subject has a history of hypersensitivity to the study drugs or any of the excipients or to medicinal products with similar chemical structures.
22. Subject has lactose intolerance.
23. 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.
24. Subject has previously been enrolled in this clinical study.
25. 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).
26. 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.

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 may 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).

For this study with single dosing safety related individual withdrawal criteria are not applicable, as no further doses will be given. Therefore, mainly withdrawal criteria are applicable that limit the validity of the data:

- Incompliance with required procedures
- Intake of not-allowed medication
- Study procedures pose a medical risk to the subject

Subject participation may be terminated prior to completing the study and the reason recorded as follows:

1. Adverse event
2. Protocol violation
3. Loss to follow-up
4. Subject withdrew consent at own request
5. Other

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

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 to contact the clinic.

Enrollment will continue until a total of 60 subjects are randomized. Withdrawn subjects may be replaced after mutual agreement between Principal Investigator and Sponsor.

4.5. Termination of the Clinical Study

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 study drug.

Should the study be terminated and/or the site closed for whatever reason, all documentation pertaining to the study and study drugs 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.

Study-specific stopping criteria are listed in Section 3.4.

For definition of EoS refer to Section 7.4.

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
Tesomet "high" dose	Tablet	20 mg IR metoprolol 1 mg tesofensine 80 mg ER metoprolol	Oral	Sponsor
Tesomet "low" dose	Tablet	5 mg IR metoprolol 0.2 mg tesofensine 20 mg ER metoprolol	Oral	Sponsor
Tesofensine	Film-coated tablet	0.5 mg tesofensine	Oral	Sponsor
Egilok 25 mg	IR tablet	25 mg metoprolol	Oral	EGIS Pharmaceuticals PLC (Hungary)
Metoprolol-ratiopharm® Succinat 23,75 mg Retardtabletten[1]	ER tablet	25 mg metoprolol	Oral	ratiopharm GmbH (Germany)
Metoprolol-ratiopharm® Succinat 47,5 mg Retardtabletten[2]	ER tablet	50 mg metoprolol	Oral	ratiopharm GmbH (Germany)

ER = extended release; IR = immediate release

1 corresponding to 25 mg metoprolol tartrate

2 corresponding to 50 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 highest clinical dose of tesofensine co-administered with metoprolol might be 1.0 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, 5, 6]. 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. For more information please the Tesomet IB [2] and metoprolol SPCs [4, 5, 6].

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.

5.3. Supply, Packaging, Labeling and Storage

Investigational medicinal products will be supplied by Saniona A/S or a third party contracted by PAREXEL. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

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

5.4. Drug Accountability, Dispensing and Destruction

The Investigator or designee is responsible for maintaining accurate accountability records of the study drugs 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 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.

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 study drugs to the Sponsor or designated third party or for preparing the study drugs 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. The re-screened subject will then be assigned a new RunIn number after signing a new informed consent form.

5.5.2. Randomization Numbers

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

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 202 withdraws and is replaced, then the randomization number for the replacement subject will be 1202.

5.6. Administration of Investigational Medicinal Products

Subjects assigned to Treatments A, B and C will be required to remain fasted from at least 10 hours before dosing. At 4 hours after dosing a light standardized meal will be served. The Investigator or a designee will administer the appropriate treatment with 240 mL water to the subjects as per randomization schedule. If more water is needed for the intake of the 5 tablets in Group C, up to further 200 mL water may be taken. All IMPs should be swallowed whole with water.

For subjects assigned to Treatment D, dosing will be performed in fed state as detailed in Section 3.1. All IMPs should be swallowed whole with water.

A mouth check will be performed to ensure the entire dose was swallowed by the subject. Subjects must remain in an upright position for at least 2 hours after dosing. Subjects should not drink anything within 1 hour before and after dosing (except for water with IMP administration

and high-fat breakfast for Treatment D). Subjects must remain fasting from food and drink other than water for at least 4 hours after dosing.

5.7. Compliance

Dosing will be performed by trained, qualified personnel designated by the Investigator. The date and time of dosing will be documented. For Treatment Group D, the date and time of breakfast will also be documented. Comments will be recorded if there are any deviations from the planned dosing procedures.

5.8. Blinding and Breaking the Blind

Not applicable in this open-label study.

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 the Screening Visit until the Safety Follow-up phone call. Prior and concomitant medication use is not permitted from 2 weeks before Day 1 until discharge (occasional use of paracetamol up to 2 g/day or other NSAIDs 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 very unlikely to occur in this single-dose 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 Schedule of Assessments (Table 5).

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

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)
- 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 Safety Follow-up phone call.

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 study drug 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 study drugs (overall relationship to IMP) and the AE. 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 study drug. All SAEs will be recorded from signing of the ICD until the EoS, i.e., the 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 study drug.

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

Berlin_Medical@parexel.com

The Investigator is responsible for providing notification to the Sponsor 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
- Year of birth
- Name of Principal Investigator and full clinical site address
- Details of SAE
- Criterion for classification as 'serious'
- Study drug name, or code and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification)

The Sponsor will request clarification of omitted or discrepant information from the initial notification. The Principal Investigator or an authorized delegate is responsible for sending the requested information to the Sponsor 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 Sponsor 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. The Sponsor may also request additional information on the SAE, which the Principal Investigator or an authorized delegate must send to the Sponsor within 24 hours of the request.

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.

6.2.2. Clinical Laboratory Assessments

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

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
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)	
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, (e.g., leukocytes, erythrocytes, casts in urine will be analyzed).	
Viral Serology	
Hepatitis B core antibody (anti-HBc) Hepatitis B surface antigen (HBsAg)	Human immunodeficiency virus (HIV) (Types 1 and 2) antibodies
Hepatitis A virus antibodies (immunoglobulin M)	Hepatitis C virus antibody (anti-HCV)
Urine Drug Screening and Cotinine Test	
Amphetamines	Cocaine
Barbiturates	Opiates
Benzodiazepines	Phencyclidine
Cannabinoids	Cotinine
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 Schedule of Assessments (Table 5). The following vital signs will be measured with an appropriate cuff always at the same arm:

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

In addition, body temperature (°C) and respiratory rate (breaths per minute) will be measured. Recordings will be made after the subject has been supine and at rest ≥ 5 minutes.

6.2.4. Standard 12-lead Electrocardiograms

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

The12-lead ECGs will be performed after the subject has been resting supine for ≥ 5 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).

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 Schedule of Assessments (Table 5).

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.

6.3. 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 Schedule of Assessments (Table 5). 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. Total Amount of Blood

Each subject will have less than 500 mL of blood collected over the course of the entire study (from the Screening Visit 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	7.5	15	112.5
Hematology and clinical chemistry[1]	10.2	3	30.6
Total Blood Volume[2] per Subject			**143.1**

[1] Viral serology 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 –30 to Day –2, admission (Day –1), an in-house dosing, safety and PK visit (Day 1 to Day 3) and a Safety Follow-up phone call on Day 8. Therefore, the maximal study duration for an individual subject will be up to 38 days.

Please see (Table 5) for the Schedule of Assessments.

Table 5 Schedule of Assessments

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

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

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

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

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

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

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

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

7.2. Order of Assessments

The following priority order will be in effect when more than one assessment is required at a pre-dose (except for Screening and Day -1) 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 site should be collected at the time of premature discontinuation or at the scheduled discharge. 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 (EoS) 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 admission until discharge.

Alcohol: Alcohol use is prohibited 48 hours prior to the Screening Visit. Alcohol use is prohibited from 48 hours prior to admission until discharge from the clinical site.

Meals: No outside food or drink is permitted at the clinical site. All meals and snacks will be provided. Subjects will receive standard meals and snacks at regimented times during confinement.

Beverages: Subjects should not drink anything within 1 hour before and after dosing (except for water with IMP administration and high-fat breakfast for Treatment D).

Fasting: Dosing in Treatment Groups A, B and C will take place after a minimum 10-hour overnight fast. Fasting restrictions will continue (no food or drink other than water) for at least 4 hours post-dose.

Fed: For subjects assigned to the fed treatment (Treatment Group D), subjects must consume a high-fat content meal that consists of the following: 2 scrambled eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 120 g of fried potatoes and 240 mL of whole milk. This high-fat meal contains the equivalent of approximately 125 protein calories, 255 carbohydrate calories and 605 fat calories. Subjects should not eat or drink other than water for at least 4 hours post-dose.

7.5.2. Other Restrictions

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

Activity: Strenuous activity is prohibited from 48 hours prior to admission until discharge. After discharge, mild physical activity can be resumed. Following IMP administration subjects will be required to sit upright on the edge of their beds for 20 minutes and must not lie down during this time. Subjects will remain ambulatory or seated upright for at least 2 hours following dose administration with the exception of supine rest period prior to measurements. However, subjects may be placed in an appropriate position or permitted to lie down on their right side should AEs occur at any time (e.g., lightheadedness associated with a blood draw).

Medications: Use of prescription, herbal, OTC medication(s) or dietary supplements is prohibited within the 2 weeks prior to study Day 1 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 is 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 randomized subjects who received at least one dose of study drug. Subjects will be included in the analysis according to the dose and study drug received.

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

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).

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 and PK analysis sets and data excluded from the PK 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

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 listed in Section 3.2.1 will be calculated using WinNonlin version 6.3 or later. The PK parameter data will be listed and summarized descriptively by analyte and treatment in tabular format.

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.

8.10. Interim Analyses

No formal interim analysis will be performed.

8.11. Determination of Sample Size

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

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 site 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 utilised 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, initialled 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 studys. 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 study drug.

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 study drug. 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 PAREXEL.

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 13, Final, 15 November 2016
4. SPC of metoprolol 25 mg IR tablets. Egilok 25 mg, EGIS Pharmaceuticals PLC (Hungary), SPC dated 23.1.2017
5. SPC of metoprolol 25 mg ER tablets. Metoprolol-ratiopharm® Succinat 23,75 mg Retardtabletten, ratiopharm GmbH (Germany), SPC dated October 2013
6. SPC of metoprolol 50 mg ER tablets. Metoprolol-ratiopharm® Succinat 47,5 mg Retardtabletten, ratiopharm GmbH (Germany), SPC dated October 2013

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	