

## **CLINICAL STUDY PROTOCOL**

### **A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTIPLE-DOSE, TWO-CENTRE, SAFETY AND EFFICACY STUDY OF CO-ADMINISTRATION OF TESOFENSINE/METOPROLOL TREATMENT IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS**

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Protocol number: TM001  
EudraCT number: 2015-005522-19



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## CLINICAL STUDY PROTOCOL SYNOPSIS

<b>Study Title</b>	A double-blind, randomized, placebo-controlled, multiple-dose, two-center, safety and efficacy study of co-administration of tesofensine/metoprolol treatment in subjects with type 2 diabetes mellitus (T2DM)
<b>Study Sponsor</b>	Saniona, A/S Baltorpvej 154 DK2750 Ballerup Denmark
<b>Phase</b>	2a
<b>Number of sites</b>	2 sites (Units) in Germany
<b>Sample size</b>	60, 30 per treatment group (2 groups)
<b>Study design</b>	Two-center, double-blind, placebo-controlled, randomized, and multiple-dose clinical study
<b>Study timelines</b>	January 2016 – December 2016
<b>IMP and Dosing schedule</b>	<p>Arm 1) tesofensine 0.5 mg + metoprolol 100 mg administered once a day, in the morning with a meal (the first 2 days a loading dose of 1.0 mg/d of tesofensine will be given) or</p> <p>Arm 2) Placebo tablets matching oral tesofensine + metoprolol administered once a day, in the morning with meal (the first 2 days a loading dose of 1.0 mg/d of placebo tesofensine will be given)</p> <p>Each tablet will be formulated separately; a currently available commercial formulation of metoprolol, MetoHEXAL® 100 mg retard, will be used.</p>
<b>Study objectives</b>	<p><u>Primary objective:</u></p> <ul style="list-style-type: none"> <li>To compare the effects of co-administration of tesofensine/ metoprolol treatment vs. placebo on 24-hour mean heart rate</li> </ul> <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none"> <li>To compare the effects of co-administration of tesofensine/ metoprolol treatment vs. placebo on systolic and diastolic blood pressure</li> <li>To demonstrate a positive effect of co-administration of tesofensine/ metoprolol treatment on: <ul style="list-style-type: none"> <li>body weight</li> <li>glycaemic endpoints</li> <li>body composition (liver fat)</li> </ul> </li> <li>To evaluate overall safety and tolerability of co-administration of tesofensine/metoprolol treatment</li> </ul>
<b>Study population (inclusion/exclusion criteria)</b>	60 males and females subjects with confirmed diagnosis of T2DM between 18-70 years
<b>Inclusion criteria</b>	1. Males and females

	<ol style="list-style-type: none"> <li>2. Confirmed diagnosis of T2DM (either by being on anti-diabetic medication or by confirmed or repeated laboratory findings)</li> <li>3. 18-70 years of age</li> <li>4. Normal BP or well managed hypertension (only if dose of BP medication(s) has been stable for at least two months)</li> <li>5. Normal lipid profile or well managed dyslipidemia (only if dose of lipid-lowering medication(s) has been stable for at least 2 months)</li> <li>6. No history of CV or any other major disease</li> <li>7. On any dose of metformin stable for at least two months, or</li> <li>8. On any dose of metformin plus one other oral antidiabetic agent (except TZDs); the other oral agent will be washed out prior to randomization</li> <li>9. HbA1c <math>\geq 7.0\%</math></li> </ol>
<b><i>Exclusion criteria</i></b>	<ol style="list-style-type: none"> <li>1. BP &gt;140/90 (excluding white-coat hypertension; therefore, if a repeated measurement shows values within the range, the subject can be included in the trial)</li> <li>2. HbA1c &gt; 8.5%</li> <li>3. Fasting plasma glucose &gt; 200 mg/dl at screening</li> <li>4. HR <math>\geq 90</math>, &lt;50 bpm</li> <li>5. BMI &lt; 27 kg/m<sup>2</sup></li> <li>6. Hypersensitivity to tesofensine/metoprolol</li> <li>7. Heart failure class II or greater according to the New York Heart Association (NYHA) or decompensated heart failure</li> <li>8. History of myocardial infarction or stroke within 12 months prior to enrolment</li> <li>9. History of coronary revascularization or angioplasty in the last 12 months prior to enrolment</li> <li>10. Patients reporting angina in the last 6 months prior to enrolment</li> <li>11. Treatment with insulin and/or other injectable anti-diabetic medications, or TZDs</li> <li>12. Any clinically significant cardiac arrhythmia</li> <li>13. Treatment with calcium channel blockers or beta blockers or their combination</li> <li>14. Current treatment with medications which should not be co-administered according to the excluded medications list (Appendix I)</li> <li>15. Concomitant use of monoaminoxidase inhibitors</li> <li>16. Bulimia or anorexia nervosa</li> <li>17. Any agent used for weight loss within the last 3 months</li> </ol>

	<ol style="list-style-type: none"> <li>18. Patients with history of major depressive disorder or any history of suicide attempt/ideation</li> <li>19. Patients with family history of severe psychiatric diseases</li> <li>20. Patients using selective serotonin reuptake inhibitors (SSRIs), antidepressants or anxiolytics.</li> <li>21. PHQ-9 (Patient Health Questionnaire) score <math>\geq 10</math> or any score <math>&gt; 0</math> on question 9</li> <li>22. Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using highly effective contraceptive methods or postmenopausal women being amenorrheic for less than 1 year and not using highly effective contraceptive methods</li> <li>23. Contraindications to administration of metoprolol per current summary of product characteristics</li> <li>24. Untreated hypo- or hyperthyroidism</li> <li>25. Clinically significant liver (<math>&gt;3 \times \text{ULN}</math>) and/or kidney impairment (<math>\text{GFR} &lt; 45 \text{ ml/min}</math>)</li> <li>26. More than 5% weight loss within the last 3 months</li> <li>27. Any clinically significant history of hypotension</li> <li>28. Any other clinically meaningful condition, in the opinion of the investigator, which would make participation potentially unsafe</li> <li>29. Inability to undergo a MRS scan for any reason</li> </ol>
<b>Study procedures</b>	<p>Following screening, eligible subjects will be instructed to maintain their diet, metformin treatment, anti-hypertensive and dyslipidemic management, if any. Any other anti-diabetic treatments will be washed out.</p> <p>Within three to 28 days following the screening, the subjects will be admitted to the Unit in the evening (Day -2) and undergo all the baseline assessments, including the 24-h endpoint assessments, starting the following morning (Day -1). The next morning (Day 1) randomization will be performed and the first dose of study medication will be administered, lifestyle (dietary) counselling will be performed and subjects will receive medication supply for up to 8 days.</p> <p>On Days 7, 14, 21, 28, 42, 56, and 70 the subjects will come back to the Unit for basic safety evaluations and medication supply.</p> <p>Dispense of study medication will be done for either for 8 days (visits 2, 3, 4, 5), 15 days (visits 6, 7, 8) or 20 days (visit 9).</p> <p>Visits on days 28 and 56 will also include some additional assessments (see the schedule of events for details).</p> <p>On Day 89 the subjects will come in for the final admission. Final 24-h endpoint assessments will be initiated on Day 90, which will also be the last day the subjects receive the study</p>

	<p>medication.</p> <p>On Day 91 the subjects will be released. In order to gradually reduce the dose of metoprolol and avoid potential undesirable fluctuation in blood pressure, the subjects will be given two dosages of half-dose of metoprolol to be taken at home, one dosage each day over the next two days.</p> <p>Subjects in study arm 1) will receive the active medication, subjects in arm 2) will receive placebo.</p> <p>On Day 98 a phone call visit for a safety check will be performed and will be followed by a final visit at the Unit on Day 110 for a final efficacy and safety assessments. This will conclude subjects' participation in the study.</p> <p>Subjects who during the study (throughout the whole trial) exceed predefined values of FPG &gt;220 mg/dl (12.2 mmol/l) on two consecutive mornings, should contact the investigator to have the FPG checked at the unit. If FPG is still &gt;220 mg/dl (12.2 mmol/l) or if HbA1c is <math>\geq 9\%</math> during an on-site measurement, the subject should be withdrawn from the study and will be referred to his/her personal physician for further treatment. Subjects who during the treatment period exceed BP systolic values &gt;160, &lt;100 mmHg, or diastolic &gt;100, &lt;60 mmHg on two consecutive mornings and confirmed at the investigational site will be withdrawn from the study.</p>
<b>Statistics</b>	<p>The primary endpoint will be compared between treatment arms by means of an ANCOVA model including treatment as fixed factor and baseline value as covariate. Least square means and 95% confidence of treatment differences will be estimated. Analysis will be based on the Per Protocol Population.</p> <p>Analysis of safety endpoints will include all subjects of the Safety Analysis Set. Continuous data will be summarized using non-missing counts, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using counts and percentages. Frequencies of AEs will be analyzed using a logistic regression model. Odds ratios, p-values, and 95% confidence intervals for the comparisons between treatments will be estimated. Other secondary and exploratory endpoints will be analyzed using the same procedure as described for the primary endpoint.</p> <p>As this is an explorative study no formal sample size calculation was done. The chosen sample size is a balance between exposing the lowest possible number of patients to the study medications, while still being able to compare the effects of co-administration of tesofensine/metoprolol treatment vs. placebo.</p>

## INVESTIGATOR STATEMENT

TM001: A double-blind, randomized, placebo-controlled, multiple-dose, two-center, safety and efficacy study of co-administration of tesofensine/metoprolol treatment in subjects with type 2 diabetes mellitus (T2DM).

I understand that this Clinical Study Protocol contains information that is confidential and proprietary to Saniona A/S. I hereby declare, that I will keep all information obtained from my participation in this Clinical Study confidential unless otherwise agreed in writing.

I have read the Clinical Study Protocol and I understand the information. With my signature, I agree to conduct this Study in accordance with the protocol, ICH-GCP guidelines, Declaration of Helsinki and with all applicable local law and regulatory requirements.

I will discuss the contents of this Clinical Study Protocol to all those authorized study staff, which will assist me in conducting this study in order to ensure that they are fully informed about the Investigational Medicinal Product (IMP) and the course of the Study.

If required, I will also provide necessary protocol information to the responsible Ethics Committee (EC) and/or to the Regulatory Authorities (BfArM) under the following condition: the contents of this Clinical Study Protocol will not be used in any other clinical study and may not be disclosed to any other person or entity without prior written permission of Saniona A/S.

Any supplemental information that may be added to this document is also confidential and proprietary to Saniona A/S and must be kept in confidence in the same manner as the contents of this Clinical Study Protocol.

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Signature:

Date:

## SIGNATURE PAGE

TM001: A double-blind, randomized, placebo-controlled, multiple-dose, two-center, safety and efficacy study of co-administration of tesofensine/metoprolol treatment in subjects with type 2 diabetes mellitus (T2DM).

We hereby declare that this Clinical Study Protocol was prepared scientifically accurately and in full compliance with the current regulatory guidelines.

With our signatures, we agree to conduct the Study in accordance with the protocol, ICH-GCP guidelines, Declaration of Helsinki and with all applicable local law and regulatory requirements. Moreover, we will keep all information obtained in this Study confidential unless otherwise agreed in writing.

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# 1 LIST OF ABBREVIATIONS

AE	Adverse Event	ICH	International Conference on Harmonization
ADR	Adverse Drug Reaction	IEC	Independent Ethics Committee
ALT	Alanine Aminotransferase	IMP	Investigation Medicinal Product
ANCOVA	Analysis of co-variance	IP	In-patient
AST	Aspartate Aminotransferase	RA	Regulatory Authority
ATC	Anatomical Therapeutic Chemical Classification	IP	In-person
AUC	Area Under the Plasma Concentration	kg	Kilogram
A/S	Aktieselskab	l	Liter
BMI	Body Mass Index	LDL	Low-density lipoprotein
BP	Blood Pressure	LPLV	Last Patient Last Visit
Bpm	Beats per minute	MedDRA	Medical Dictionary for Regulatory Activities
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte	mg	Milligram
BMI	Body Mass Index	mL	Milliliter
CI	Confidence Interval	mmHg	Millimeter of mercury
Cm	Centimeter	mmol	Millimol
Cmax	Maximum measured plasma concentration	MRS	Magnetic Resonance Spectroscopy
CRF	Case Report Form	N (No)	Number
CRO	Contract Research Organization	ng	Nanogram
CYP	Cytochrome P450	NYHA	New York Heart Association
CV	Coefficient of Variation	OP	Out-patient
CV	Cardio Vascular	OTC	Over the Counter
CVD	Cardio Vascular Disease	Ph	Phone
°C	Degrees Celsius	PHQ	Patient Health Questionnaire
DBP	Diastolic Blood Pressure	PK	Pharmacokinetic
DCCT	Diabetes Control and Complications Trial	PK/DM	Pharmacokinetics/Drug Metabolism
DDI	Drug-drug Interaction	PPP	Per-Protocol Population
dl	Deciliter	Q	Quarter
DMP	Data Management Plan	QA	Quality Assurance
ECG	Electrocardiogram	QC	Quality Control
EC	Ethic Committee	SAE	Serious Adverse Event
eCRF	Electronic Case Report Form	SAP	Statistical Analysis Plan
EMA	European Agency for the Evaluation of Medical Products	SBP	Systolic Blood Pressure
EU	European Union	SD	Standard Deviation
FPG	Fasting Plasma Glucose	SOP	Standard Operating Procedure
GCP	Good Clinical Practice	SUSAR	Suspected Unexpected Serious Adverse Reactions
HDL	High-density lipoprotein	Tmax	Time of the maximum
HbA1c	Hemoglobin A1c	TZD	Thiazolidinediones
HR	Heart Rate	T2MD	Type 2 diabetes mellitus
IB	Investigator Brochures	ULN	Upper Limit of Normal range
ICF	Informed Consent Form	USA	United States of America
		WHO DD	World Health Organisation Drug Dictionnaire

## 2 GENERAL INFORMATION

### 2.1 INTRODUCTION

#### Etiology and treatment of diabetes mellitus

There are about 280 million people worldwide suffering from Type 2 diabetes (T2DM) and this number is increasing every year. T2DM is the most common form of diabetes, which is caused by a combination of factors, including insulin resistance, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. There is now undisputable body of evidence linking the increasing incidence and prevalence of T2DM with obesity (1), more specifically excessive accumulation of body fat in certain compartments, particularly the liver (2). The presence of obesity, visceral and hepatic adiposity leads to cellular and systemic dysfunction at many levels – dysregulated glucose production and release by the liver, altered response to insulin signalling, impaired glucose uptake by insulin responsive tissues, pancreatic beta cell dysfunction, release of inflammatory and pro-coagulant factors, altered metabolism on insulin itself, and many others (3).

Lifestyle changes, particularly those aimed at reducing body fat are a staple of treatment of all subjects with T2DM worldwide. Indeed, weight loss of 5-10% of bodyweight, irrespective of how it is achieved, is associated with improvements in cardiovascular risk profiles and reduce incidence of type 2 diabetes. The Diabetes Prevention Program proved that people with pre-diabetes at high risk of developing type 2 diabetes could sharply lower their risk by losing weight through regular physical activity and a diet low in fat and calories (4). In 2009, a follow-up study of Diabetes Prevention Program Outcomes Study showed that the benefits of weight loss lasted for at least 10 years after the original study began (5). This benefit of weight loss has been repeatedly proven with other means of inducing weight loss (6,7). Overall, it is now clear that reduction in body weight (fat) has direct benefits on both developing T2DM and improving glycaemic control in those with overt T2DM.

#### Current treatment strategies

Lifestyle changes, particularly improved diet and increased physical activity remain a cornerstone of modern management of subjects with T2DM. However, only very motivated individuals can achieve adequate, long-term, glycaemic control with lifestyle intervention only. Thus, almost all subjects with the disease require pharmacological therapy very soon and many of them ultimately need some form of insulin replacement. Pharmacologic therapy of T2DM has changed dramatically in the last 10 years, with new drugs and drug classes becoming available. Availability of variety of drugs with different mechanisms of action allowed the use of combination therapy, often with improvement in glycaemic control, which was previously beyond the reach of medical therapy. More importantly, combination therapy can significantly delay need for insulin replacement.

Despite all of these advances treatment of T2DM remains an area of unmet medical need as none of the therapies actually treats the underlying pathology: they are all symptomatic and the disease invariably progresses with many deleterious consequences. Thus, novel therapies are needed, particularly those able to directly address the underlying causes of the diseases.

#### Overview of tesofensine

Tesofensine was initially studied for the treatment of Parkinson and Alzheimer's diseases.

However, clinical studies showed only a limited efficacy of tesofensine, but weight loss was noted in majority of participants, despite the fact that they did not attempt to lose weight. Tesofensine is an inhibitor of monoamine presynaptic reuptake of the neurotransmitters noradrenaline, dopamine and serotonin. This means it influences these chemicals in the brain to suppress appetite. Tesofensine demonstrated strong weight reducing effects in Phase 2 clinical studies in obese subjects, exceeding benchmarks set by the regulatory agencies for approval of weight loss agents (8). Also, post-hoc analysis of the data from the Phase 2 obesity study showed that individuals with pre-diabetes in these studies experienced a favorable reduction in body weight and glycaemic endpoints while on tesofensine.

In general, tesofensine was well tolerated in humans. However, blood pressure and heart rate increase observed with the therapeutically relevant doses of tesofensine (0.25 mg and 0.5 mg) were 1–3 mmHg and up to 8 bpm, respectively (8). These increases could potentially have an adverse impact on the cardiovascular safety in the target subject population. This led to the addition of metoprolol to mitigate these effects and provide a favorable benefit/risk profile. For more information on tesofensine please see the Investigators' Brochure (Version 12).

#### Overview of metoprolol

Metoprolol is a beta<sub>1</sub>-selective (cardio selective) adrenoceptor blocking agent, for oral administration, which has been approved in the 70's and has been one of the most widely prescribed medicines to date. It is indicated for hypertension, angina pectoris and heart failure. It is now available as extended-release tablets. MetoHEXAL® 100 mg retard, containing 100 mg of metoprolol tartrate, has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. This is also the formulation selected for this study (for more information please see the Summary of Product Characteristics of MetoHEXAL® 100 mg retard ).

#### Overview of tesofensine/metoprolol

In a pre-clinical study in rats the co-administration of tesofensine+metoprolol showed a HR and BP profile similar to placebo (vehicle) while the weight-reducing efficacy was maintained (9). In addition, in a drug-drug interaction study in healthy male subjects addition of short acting metoprolol on the background of chronic dosing with tesofensine showed a short term, but substantial, reduction in HR previously increased by tesofensine. Taken together, the available data support the concomitant use of tesofensine and a beta-blocker such as metoprolol as an investigational agent for the proposed indication of treatment of T2DM.

#### Purpose of the Comparison to Placebo

Double blind, placebo-controlled design is the gold standard in evaluation of efficacy and safety of new drugs. It provides the most rigorous and unbiased evaluation of the true effects of an intervention. This design was chosen because it is critical to thoroughly assess whether the addition of metoprolol truly mitigates the elevation in HR and BP observed with tesofensine monotherapy as well as the efficacy of co-administration of tesofensine/metoprolol in the treatment of T2DM.

#### Purpose of this study

The purpose of this study is to investigate the safety and efficacy of co-administration of tesofensine/metoprolol treatment versus placebo.

### **3 STUDY OBJECTIVES AND ENDPOINTS**

#### **3.1 OBJECTIVES**

##### **Primary objective:**

- To compare the effects of co-administration of tesofensine/metoprolol treatment vs. placebo on 24-hour mean heart rate

##### **Secondary objectives:**

- To compare the effects of co-administration of tesofensine/metoprolol treatment vs. placebo on systolic and diastolic blood pressure
- To demonstrate a positive effect of co-administration of tesofensine/metoprolol treatment on:
  - body weight
  - glycaemic endpoints
  - body composition (liver fat)
- To evaluate overall safety and tolerability of co-administration of tesofensine/metoprolol treatment

#### **3.2 ENDPOINTS (Baseline = Day -1/1; End of treatment = Day 90/91)**

##### **Primary endpoint**

- Change from baseline to end of treatment in mean 24 hour HR

##### **Secondary endpoints**

- Change from baseline to end of treatment in mean SBP
- Change from baseline to end of treatment in mean DBP
- Change from baseline to end of treatment in body weight
- Change from baseline to end of treatment in HbA1c
- Change from baseline to end of treatment in FPG
- Change from baseline to end of treatment in 9-point blood glucose profile

##### **Other endpoints**

- Change from baseline to end of treatment in liver fat
- Change in fasting insulin from baseline to end of treatment
- Change in 1,5 anhydroglucitol from baseline to end of treatment
- Change from baseline to end of treatment in waist circumference
- Change from baseline to end of treatment in PHQ-9 score
- Safety: Adverse events (AEs), clinical laboratory findings, electrocardiogram (ECG)
- Number and severity of hypoglycaemic events

### **4 OVERALL STUDY DESCRIPTION**

This is a double-blind, randomized, placebo-controlled, multiple-dose, two-center, safety and efficacy study of co-administration of tesofensine/metoprolol treatment in subjects with T2DM. Study medication will be administered for ninety (90) days (+2 days after the final assessments with half-dose of metoprolol). Following all baseline assessments, eligible subjects will be randomly assigned to one of the two arms (1:1).

**Screening:** Subjects who give the written informed consent will be screened for the study. For subjects on any anti-diabetic medications, treatment with all anti-diabetic medications except metformin will be washed out. The subjects will return for a baseline visit at the end of the wash-out period (1-4 weeks). During the wash-out period the subjects will be asked to check the FPG every day. If during the wash-out period the FPG is  $>12.2$  mmol/l, it should be re-checked the next morning. Given the FPG is still  $>12.2$  mmol/l, the subjects should contact the investigator to have the FPG level checked at the Unit. If FPG is still  $>12.2$  mmol/l or if HbA1c is  $\geq 9\%$  during an on-site measurement, the subjects should be withdrawn from consideration for the study.

All subjects will be instructed to maintain their anti-hypertensive and dyslipidemic management, if any. Subjects who at screening are receiving diet treatment and/or metformin treatment only for their diabetes will be invited for the baseline visit after a minimum of 3 days (i.e. do not require a washout of other anti-diabetic medication). In addition, mood and suicidal ideation will be assessed using a validated PHQ-9 mood scale at screening, baseline and on subsequent visits.

**Baseline:** Subjects will be admitted to the Unit (investigational site) in the evening of Day -2 to undergo all baseline assessments. MRS assessment should be performed at Day -2 (in a sub-set). BP measurements will be initiated at Day -2 (six (6) BP measurements in total should be performed during the course of subject's admission, until Day 1 morning). The 24-h HR monitoring and 9-point glucose profile assessments will start in the morning of Day -1 and will be completed in the morning of Day 1. Blood draw to establish the baseline for all measure endpoints will be drawn in the morning of Day 1.

**Randomisation:** Following the completion of all baseline assessments on Day 1, eligible subjects will be randomized in equal numbers to double-blind treatment with co-administration of tesofensine/metoprolol or placebo. The first dose of study medication will be administered on Day 1 (subjects will also be stratified based on their background anti-diabetic therapy – on metformin vs. metformin + other agents). Lifestyle (dietary) counselling will be performed and subjects will receive medication supply for 8 days and will be released from the Unit.

**Treatment period:** after the Day 1, subjects will visit the Unit weekly - on Days 7, 14, 21 for safety evaluations and medication supply until Day 28 (visit 6). Subjects will receive medication supply for up to 8 days (dispensed during the visits 3, 4, 5). After the Day 28, subjects will be assessed at interval of 2 weeks on Days 42 and 56 (visits 7, 8), and at interval of 19 days on Day 70 (visit 9). Study medication will be dispensed for up to 15 days during each visit 6, 7, 8 and up to 20 days at visit 9. Visits on days 28 and 56 will also include additional assessments for efficacy evaluation.

**Final admission:** In the afternoon/evening of Day 89 subjects will come in for the final admission. MRS assessment should be performed at Day 89 (in a sub-set). BP measurements will be initiated at Day 89 (six (6) BP measurements in total should be performed during the course of subject's admission, until Day 91 morning). Final 24-h HR monitoring and 9-point glucose profile assessments will be initiated in the morning of Day 90, which will also be the last day when subjects receive the study medication. During the Day 90 the blood will be collected for metabolic endpoint as well as safety measurements. On Day 91 the 24-h



assessments will be completed and then subjects will be released and they receive two days of half-dose dose of metoprolol to take at home in order to gradually reduce the dose of metoprolol and avoid potential undesirable fluctuation in blood pressure; however, only the subjects in the study arm 1) will receive the active medication, subjects in the arm 2) will receive placebo.

**Final follow up visit:** on Day 98 phone call will be performed to check subjects' status and potential AE(s). Subjects will come in for a final efficacy and safety assessment on Day 110. This will conclude their participation in the study and subjects will be instructed to go back to their primary care physician to restart their regular diabetes management.

Subjects who during the study (throughout the whole trial; from screening until the end of study) exceed predefined values of FPG >220 mg/dl (12.2 mmol/l) on two consecutive mornings should contact the investigator to have the FPG checked at the unit. If FPG is still >220 mg/dl (12.2 mmol/l) or if HbA1c is  $\geq 9\%$  during a on-site measurement, the subject should be withdrawn from the study and will be referred to his/her personal physician for further treatment.

Blood pressure measurement devices must be available for the subjects for monitoring BP outside the in-house periods and until the follow-up visit. Subjects will be advised to measure BP every morning. Subjects who during the treatment period have consecutive measures of BP systolic >160, <100 mmHg or diastolic >100, <60 mmHg on two consecutive days must contact the investigator. Subjects with symptoms of hypotension must also contact the investigator immediately. The subject will be excluded from the study after confirmation at investigational site of the BP values outside the mentioned range.

Assessments conducted during each visit are described in the schedule of events.

#### 4.1 STUDY FLOW CHART: VISITS 1 - 6 (all visits are $\pm 1$ day)

Visit	1 Screening  OP	2a Baseline  IP	2a Baseline  IP	2b Randomisation  IP	3, 4, 5  OP	6  OP
Day	-28 to -5*	-2	-1	1	7,14,21	28
ICF, Inclusion/ Exclusion	X	X <sup>f</sup>				
Physical examination, height, BMI	X					
Med. History/ demographics	X					
Vital signs	X	X	X	X	X	X
PHQ-9 Score	X		X		X <sup>g</sup>	X



<b>Admission</b>		X				
<b>Release</b>				X		
<b>Randomization</b>				X		
<b>Administration of first dose of IMP at the Unit</b>				X		
<b>24-h HR measurement</b>			X initiation	X completion		
<b>BP measurement</b>		X initiation	X	X completion		
<b>Weight, waist circumference</b>	X		X	X	X	X
<b>Hematology</b>	X			X		
<b>Blood chemistry</b>	X			X		
<b>Infectious serology</b>	X					
<b>ECG</b>	X	X				
<b>FPG</b>	X <sup>a</sup>		X	X	X	X
<b>HbA1c</b>	X			X		X
<b>1,5-anhydroglucitol, lipids, insulin</b>				X		X
<b>9-p glucose profile</b>			X initiation	X completion		
<b>MRS (liver fat) <sup>b</sup></b>		X				
<b>PK sample</b>				X		
<b>Lifestyle advice</b>				X		
<b>Medication dispensed</b>				X	X	X
<b>AEs</b>				X	X	X
<b>Hypoglycaemia</b>			X	X	X	X
<b>Hyperglycemia</b>			X	X	X	X
<b>Medication accountability</b>					X	X
<b>Concomitant medication</b>	X		X	X	X	X
<b>Blood pregnancy test <sup>c</sup></b>	X					

Urine pregnancy test <sup>c</sup>			X			X
Diary dispensation	X			X	X	X
Diary review		X	X	X	X	X
Diary collection		X			X	X
Glucometer dispensation	X					
BP measurement device dispensation <sup>h</sup>				X <sup>i</sup>		
Subject card dispensation	X					
End of study form						

<sup>a</sup>: During the whole study the subjects will be asked to check the FPG every day

<sup>b</sup>: In a sub-set (Neuss)

<sup>c</sup>: Female subjects of childbearing potential only

<sup>f</sup>: Only re-check of exclusion and inclusion criteria

<sup>g</sup>: Only Day 14

<sup>h</sup>: Only subjects who do not have an adequate one available

<sup>i</sup>: Subjects will be requested to measure BP every day until the follow-up visit

IP = in-patient; OP = out-patient; Ph = phone

\*There will be up to additional 4 weeks in-between screening and admission in those subjects who will need to have their anti-diabetic medication washed out.

## 4.2 STUDY FLOW CHART: VISITS 7 - 12 (all visits are $\pm 1$ day)

Visit	7	8	9	10	10	10	11 F-up	12 F-up
	OP	OP	OP	IP	IP	IP	Phone	OP
Day	42	56	70	89	90	91	98	110
Physical examination, height, BMI <sup>g</sup>					X			X
Vital signs	X	X	X	X	X	X		X
PHQ-9 Score	X		X			X		
Admission				X				
Release						X		
24-h HR measurement					X initiation	X completion		
BP measurement				X initiation	X	X completion		

						on		
<b>Weight, waist circumference</b>	X	X	X		X			X <sup>h</sup>
<b>Hematology</b>					X			
<b>Blood chemistry</b>					X			
<b>ECG</b>				X				
<b>FPG</b>	X	X	X		X	X		X
<b>HbA1c</b>		X			X			X
<b>1,5-anhydroglucitol, lipids, insulin</b>		X			X			X <sup>e</sup>
<b>9-p glucose profile</b>					X initiation	X completion		
<b>MRS (liver fat)<sup>b</sup></b>				X				
<b>PK sample</b>					X			
<b>Urinary pregnancy test</b>		X						X
<b>Medication dispensed</b>	X	X	X			X <sup>d</sup>		
<b>AEs</b>	X	X	X		X	X	X	X
<b>Hypoglycaemia</b>	X	X	X		X	X	X	X
<b>Hyperglycaemia</b>	X	X	X		X	X	X	X
<b>Medication accountability</b>	X	X	X		X			
<b>Concomitant medication</b>	X	X	X		X	X	X	X
<b>Diary dispensation</b>	X	X	X	X				
<b>Diary review</b>	X	X	X	X	X			X
<b>Diary collection</b>	X	X	X	X				X
<b>End of study form</b>								X

<sup>b</sup> In a subset (Neuss)

<sup>d</sup> Dispensation of two half-doses of active / placebo metoprolol

<sup>e</sup> Except lipids and insulin

<sup>g</sup> Conducting physical examination (except height and BMI)

<sup>h</sup> Only body weight measurement

### 4.3 STUDY DESIGN

#### Visit 1 Screening (Day -28 to -5)

Potentially eligible subjects will be given written information about the protocol, study design

and potential risk and benefits. Subjects will be given enough time to read the information and ask the investigator any questions. Subjects who give written informed consent will be assigned a subject screening number and will undergo the screening visit assessments to determine their eligibility for the study.

The following screening procedures will be performed:

- Explanation the study to prospective subjects
- Obtaining written informed consent
- Generating the subject screening number
- Obtaining demographic information and medical/medication history
- Reviewing and checking inclusion/exclusion criteria
- Measurement of vital signs (including body temperature, respiratory rate, pulse rate and blood pressure)
- Obtaining ECG
- Measurement of the subject's body weight, waist circumference, height, calculation of BMI
- Conducting physical examination
- Administering the PHQ-9 questionnaire
- Performing routine haematology, blood chemistry assessment and infectious serology
- Measuring FPG and HbA1c
- Checking the concomitant medications (wash out of allowed anti-diabetics medications, except metformin)
- Performing the blood pregnancy test and providing instructions for acceptable method of contraception for women with childbearing potential
- Glucometer dispensation for home glucose monitoring
- Scheduling the overnight baseline visit

Subjects will be provided with a subject card that includes emergency contact details.

Subjects will be provided with a diary. Subjects will be asked to record the following: date, glucose level, any hypoglycaemia episodes, any hyperglycaemia episodes (FPG >220 mg/dl; 12.2 mmol/l), any other AEs, any other concomitant medication.

**Baseline visit 2a (Day -2 to -1):**

In the late afternoon/evening of the Day -2 (within 28 days after the screening visit), subjects will be admitted to the Unit.

On day -2 the following procedures will be done:

- MRS for liver fat (off site, prior to admission) in a subset of subjects
- Collection of subject diary
- Review of subject diary
- Re-check of exclusion and inclusion criteria
- Measurement of vital signs
- Obtaining ECG
- Initiation of BP measurement (1 BP measurement only)

On Day -1 the following baselines procedures will be performed in this order:

- Performing the urine pregnancy test
- Measurement of vital signs
- Measurement the subject's body weight and waist circumference
- Administering the PHQ-9 questionnaire
- Collection of blood for FPG measurement
- Initiation of the 24-h HR measurement
- Initiation of the 9-point glucose profile measurement
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Review of subject diary
- Subjects will stay at the Unit over night
- Measurement of BP (four BP measurements during the day)

**Randomization visit 2b (Day 1):**

On Day 1, following the completion of all baseline assessments, the investigator will randomize subject into one of the treatment arm. The first administration of study medication will be performed at the Unit by the investigator.

On Day 1 the following procedures will be performed:

- Completion of BP measurement (1 BP measurement only)
- Measurement of vital signs
- Measurement of body weight and waist circumference
- Collection of blood for efficacy (HbA1c, FPG, 1,5-anhydroglucitol, lipids, insulin)
- Collection of blood for safety assessments (hematology and blood chemistry)
- Collection of blood for PK baseline
- Completion of the 24-h HR measurement
- Completion the 9-point glucose profile
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Randomization
- Administration of first dose
- Dispensation of subject diary
- Dispensation of BP measurement device (in case the subject does not have an adequate one) for home BP monitoring
- Lifestyle (dietary) consultation
- Review of subject diary
- Medication dispensation for 8 days (1+7)
- Releasing the subject from the Unit

Subjects will be asked to record into the diary the following: date, glucose level, BP values, taking of the study medication, any hypoglycaemia episodes, any hyperglycaemia episodes,

hypotension symptoms, any other AEs, any other concomitant medication.

**Treatment period:****Visits 3, 4 and 5 (Day 7, 14, 21)**

Three weekly visits starting after Randomization (Day 1). Subjects will be seen for the following:

- Measurement of vital signs
- Measurement of body weight and waist circumference
- Administering the PHQ-9 questionnaire (only day 14)
- Collection of blood for FPG measurement
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Collection of subject diary
- Review of subject diary
- Dispensation of subject diary for the next visit
- Medication dispensation **for 8 days** and accountability check

Additional unscheduled visits may be performed if considered clinically necessary by the investigator. The investigations planned for the next scheduled visit will be performed.

**Visit 6 (Day 28)**

Visit 6 is considered to be a more detailed visit for efficacy assessments. Subjects will be seen for the following:

- Performing the urine pregnancy test
- Measurement of vital signs
- Measurement of body weight and waist circumference
- Administering the PHQ-9 questionnaire
- Collection of blood for efficacy (HbA1c, FPG, 1,5-anhydroglucitol, lipids, insulin)
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Collection of subject diary
- Review of subject diary
- Dispensation of subject diary for the next visit
- Medication dispensation **for 15 days** and accountability check
- Schedule a subject visit in 2 weeks

**Visit 7 (Day 42)**

At visit 7 the subjects will be seen for the following:

- Measurement of vital signs
- Measurement of body weight and waist circumference
- Administering the PHQ-9 questionnaire

- Collection of blood for FPG measurement
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Collection of subject diary
- Review of subject diary
- Dispensation of subject diary for the next visit
- Medication dispensation **for 15 days** and accountability check
- Scheduling a subject visit in 2 weeks

**Visit 8 (Day 56)**

At visit 8 the subjects will be seen for the following:

- Performing the urine pregnancy test
- Measurement of vital signs
- Measurement of body weight and waist circumference
- Collection of blood for efficacy (HbA1c, FPG, 1,5-anhydroglucitol, lipids, insulin)
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Collection of subject diary
- Review of subject diary
- Dispensation of subject diary for the next visit
- Medication dispensation **for 15 days** and accountability check
- Scheduling a subject visit in 2 weeks

**Visit 9 (Day 70)**

At visit 9 the subjects will be seen for the following:

- Measurement of vital signs
- Measurement of body weight and waist circumference
- Administering the PHQ-9 questionnaire
- Collection of blood for FPG measurement
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Collection of subject diary
- Review of subject diary
- Dispensation of subject diary for the next visit
- Medication dispensation **for 20 days** and accountability check
- Scheduling a subject for an admission at the Unit in 19 days

**Visit 10 Final admission (Days 89-91)**

On Day 89 in the evening or late afternoon subjects will be admitted to the Unit and all

returned study medication should be checked.

On Day 89 the following assessments will be done:

- MRS for liver fat (off site, prior to admission) in a subset of subjects
- Measurement of vital signs
- Collection of subject diary
- Review of subject diary
- Dispensation of subject diary (until the end of study)
- Obtaining ECG
- Initiation of BP measurement (1 BP measurement only)

Subjects will be still asked to record into the diary the following: date, glucose level, taking of IMP and metoprolol, any hypoglycaemia episodes, any hyperglycaemia episodes, any other AEs, any other concomitant medication.

On Day 90 the following final procedures will be performed:

- Measurement of vital signs
- Measurement the subject's body weight and waist circumference
- Conducting physical examination (except height and BMI)
- Collection of blood for efficacy (HbA1c, FPG, 1,5-anhydroglucitol, lipids, insulin)
- Collection of blood for safety assessments (hematology and blood chemistry)
- Collection of blood for PK
- Initiation of the 24-h HR measurement
- Initiation the 9-point glucose profile measurement
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Medication accountability check
- Review of subject diary
- Measurement of BP (4 BP measurements during the day)
- Subjects will stay at the Unit over night

Day 90 (morning) will be the last day when subjects receive the study medication.

On Day 91 subjects will be released and given two dosages of half-dose of the metoprolol dose taken during the study to take at home, one dosage over the next two days in order to gradually reduce the dose of metoprolol and avoid potential undesirable fluctuation in blood pressure; however, only the subjects in the study arm 1) will receive the active medication, subjects in the arm 2) will receive placebo. For safety purposes the subjects will continue measuring BP and annotating the values in the diary until the follow-up visit. The withdrawal criteria regarding BP will not apply during these days.

On Day 91 the following final procedures will be performed:

- Completion of BP measurement (1 BP measurement only)
- Measurement of vital signs
- Administering the PHQ-9 questionnaire



- Collection of blood for FPG measurement
- Completion the 24-h HR measurement
- Completion the 9-point glucose profile
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Dispense of two half-doses of active / placebo medication
- Releasing the subject from the Unit

Phone call visit on Day 98 will be scheduled and subjects will be invited for the final follow up visit on Day 110.

### **Visit 11 Follow-up (Day 98) - Telephone contact**

At the phone call visit Day 98 the following final procedures will be performed:

- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications

### **Visit 12 End of study (Day 110)**

This visit is considered as the subject's end in the study. The "End of Study" or "Early termination" (as applicable) must be entered into the eCRF and subject's source documents must be completed.

On Day 110 the following final procedures will be performed:

- Performing the urine pregnancy test
- Measurement of vital signs + body weight
- Collection of blood for efficacy (HbA1c, FPG, 1,5-anhydroglucitol)
- AEs assessment
- Assessment of hypoglycaemia
- Assessment of hyperglycaemia
- Assessment of concomitant medications
- Review and return of subject diaries
- Completion of "End of study Form"

## **4.4 END OF STUDY**

The end of study is defined by LPLV for TM001. If a subject withdraws from the study during the treatment period, or has to discontinue for any reason, a visit will be organized at which the assessments planned for Days 28/56 will be performed. If a subject refuses to attend a visit, the investigator should make every effort to obtain the information over the telephone from the subject regarding the safety. When a subject ends the study, either per protocol or before of any reason, he/she will be instructed to immediately contact his/her personal primary care physician to resume to his/her entire diabetic treatment.

## 4.5 STUDY PARTICIPANTS

The target population is adult subjects suffering from T2DM. Subjects will be recruited from local population around the Units. This study will be conducted at two investigational sites (Units) in Germany. Subjects who fulfil all of the following inclusion criteria and none of the exclusion criteria are eligible to enter the baseline phase of the study.

## 4.6 INCLUSION CRITERIA

1. Males and females
2. Confirmed diagnosis of T2DM (either by being on anti-diabetic medication or by confirmed or repeated laboratory findings)
3. 18-70 years of age
4. Normal BP or well managed hypertension (only if dose of BP medication(s) has been stable for at least 2 months)
5. Normal lipid profile or well managed dyslipidemia (only if dose of lipid-lowering medication(s) has been stable for at least 2 months)
6. No history of CV or any other major disease
7. On any dose of metformin stable for at least two months, or
8. On any dose of metformin plus one other oral antidiabetic agent (except TZDs); the other oral agent will be washed out prior to randomization
9. HbA1c  $\geq 7.0\%$

## 4.7 EXCLUSION CRITERIA

1. BP  $> 140/90$  (excluding white-coat hypertension; therefore, if a repeated measurement shows values within the range, the subject can be included in the trial)
2. HbA1c  $> 8.5\%$
3. Fasting plasma glucose  $> 200$  mg/dl at screening
4. HR  $\geq 90$ ,  $< 50$  bpm
5. BMI  $< 27$  kg/m<sup>2</sup>
6. Hypersensitivity to tesofensine/metoprolol
7. Heart failure class II or greater according to the New York Heart Association (NYHA) or decompensated heart failure
8. History of myocardial infarction or stroke within 12 months prior to enrolment
9. History of coronary revascularisation or angioplasty in the last 12 months prior to enrolment
10. Patients reporting angina in the last 6 months prior to enrolment
11. Treatment with insulin and/or other injectable anti-diabetic medications, or TZDs
12. Any clinically significant cardiac arrhythmia
13. Treatment with calcium channel blockers or beta blockers or their combination
14. Current treatment with medications which should not be co-administered according to the excluded medications list (Appendix I)
15. Concomitant use of monoaminooxidase inhibitors
16. Bulimia or anorexia nervosa
17. Any agent used for weight loss within the last 3 months
18. Patients with history of major depressive disorder or any history of suicide attempt/ideation
19. Patients with family history of severe psychiatric diseases
20. Patients using selective serotonin reuptake inhibitors (SSRIs), antidepressants or anxiolytics

21. PHQ-9 score  $\geq 10$  or any score  $> 0$  on question 9
22. Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using highly effective contraceptive methods (highly effective contraceptive methods are considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilisation, hormonal intrauterine devices (coil), sexual abstinence or a surgically sterilised partner) or postmenopausal women being amenorrheic for less than 1 year and not using highly effective contraceptive methods
23. Contraindications to administration of metoprolol per current summary of product characteristics
24. Untreated hypo- or hyperthyroidism
25. Clinically significant liver ( $>3 \times \text{ULN}$ ) and/or kidney impairment ( $\text{GFR} < 45 \text{ ml/min}$ )
26. More than 5% weight loss within the last 3 months
27. Any clinically significant history of hypotension
28. Any other clinically meaningful condition, in the opinion of the investigator, which would make participation potentially unsafe
29. Inability to undergo a MRS scan for any reason

#### **4.8 SCREENING FAILURES**

If a subject fails during the screening phase, before randomisation, (e.g. due to the subject's decision, etc.) his/her relevant data will be listed in the screening log and filed in the study documents.

#### **4.9 DISCONTINUATION CRITERIA**

The subject has a right to discontinue study participation at any time for any reason. The reason for discontinuation will be documented in the subject's source documents and in the eCRF. In the event of an early termination, all procedures described for a subject completing the study Days 28/56 should be performed. Subjects discontinuing due to adverse events will be followed-up until complete resolution of the adverse event or until there is a satisfactory explanation of the changes observed.

#### **4.10 WITHDRAWAL CRITERIA**

Subjects may be withdrawn if any of the following items is met and documented:

- Request by subject (withdrawal of informed consent)
- Pregnancy or not using a reliable method of birth control
- Investigator's decision
- Acute allergic reaction to study medication
- Deterioration of glycaemic control which will require additional medical management as defined in the rescue criteria from T2DM
- Subjects who during the whole duration of the study exceed predefined values of FPG  $> 220 \text{ mg/dl}$  ( $12.2 \text{ mmol/l}$ ) on two consecutive mornings and confirmed at the investigational site
- $\text{HbA1c} \geq 9\%$  in any on-site measurement
- Subjects who during the treatment period exceed BP systolic values  $> 160$ ,  $< 100 \text{ mmHg}$ , or diastolic  $> 100$ ,  $< 60 \text{ mmHg}$  on two consecutive mornings and confirmed at the investigational site
- Any event, including hospitalization of the subject in another location where the

investigator will not be able to follow the subject

- Evidence of the use of recreational medications or prohibited medications during the study
- Failure to comply with the study stipulations
- Score of PHQ questionnaire  $\geq 10$  during the study or any score  $> 0$  on question 9
- Severe symptomatic bradycardia (heart rate  $< 50$  bpm) during the study
- Lost to follow-up. Subjects will be deemed lost to follow-up if they do not return for scheduled visits without giving a reason, and if the investigator is unable to contact the subject directly or indirectly (e.g. via the subject's family). If a subject does not attend a scheduled visit, the investigator will make best efforts to obtain information about the subject before considering the subject lost to follow up

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 eCRF.

#### **4.11 REPLACEMENT OF WITHDRAWN SUBJECTS**

Enrolment will continue until a total of 60 subjects are randomized. Subjects excluded during the screening period (Day -28 to -5) may be considered for another selection visit at a later date but will need to undergo complete rescreening. Randomized subjects who withdraw or are withdrawn from the study for any reason will not be replaced.

#### **4.12 PREMATURE STUDY DISCONTINUATION**

The sponsor has the right to terminate this study at any time. If the sponsor, the investigators, or the competent authorities discover conditions arising during the study that indicate the study should be halted, it may be terminated after appropriate consultation between the study sponsor and the investigator.

Reasons for terminating the study may include the following:

- The incidence or severity of AEs in this study indicates a potential health hazard to study subjects
- Subject enrolment is unsatisfactory
- Data recording is inaccurate or incomplete
- The sponsor's decision to suspend or discontinue development of the study medication

#### **4.13 EARLY TERMINATION OF A STUDY SITE**

The sponsor may close the Unit if no subjects are recruited within four weeks after initiation of the Unit or if severe protocol deviations are observed. Depending on overall enrolment, a new country may be selected by the sponsor.

#### **4.14 STUDY SITES**

The study will be conducted at two Units in Germany, randomizing 60 eligible subjects. It is recommended that each Unit should randomize at least 15 and no more than 40 eligible subjects.

#### 4.15 STUDY DURATION

The projected start date for the inclusion of study subjects is Q1 2016. The individual study duration for one subject is up to 138 days including screening period, baseline, the treatment period and the final visit. The projected duration of the study is ~12 months. The end of study is defined by the Last Visit of the Last Patient for TM001.

#### 4.16 BENEFITS AND RISKS FOR STUDY PARTICIPANTS

It is expected that tesofensine and metoprolol combination will be well tolerated. This assessment is based on a large body of experiences from previous preclinical and clinical studies of tesofensine and metoprolol. The study design itself does not increase the risk for the subjects since no invasive interventional procedures are planned except blood sampling, which is similar to clinical practice and subjects will be monitored thoroughly and rigorously following the first administration of tesofensine and metoprolol both at home and during repeated visits at the Unit.

##### Tesofensine

The majority of treatment related adverse events seen in the clinical studies with tesofensine were dry mouth, headache, nausea, insomnia, diarrhoea and constipation side effects. A dose-dependent pattern was observed for dry mouth and insomnia. The overall withdrawal rate due to adverse events in clinical studies in the obese population was 13% with tesofensine and 6% with placebo. Blood pressure and heart rate increased with the therapeutically relevant doses of tesofensine (0.25 mg and 0.5 mg) were 1–3 mmHg and up to 8 bpm, respectively. For more information see the IB. (IB version 12 and any updates thereof).

Due to the CNS-located mechanism of action of tesofensine, a monoamine reuptake inhibitor, there could be a concern regarding psychiatric side effects. In obese subjects dosed for up to 24 weeks, common psychiatric symptoms were insomnia and depressed mood. Occurrence of insomnia displayed a clear dose-dependency with the highest incidence on the highest dose (1 mg). Psychotic phenomena, like those encountered in patients with dementia of the Alzheimer's type or Parkinson's disease, were not registered in the population of obese subjects. Pooled data from studies NS2330-001 and NS2330-004 did not reveal an increased incidence of psychiatric events following long-term extension study, i.e. 18 months of treatment. Current data from the clinical studies with obese patients do not suggest that tesofensine at doses of 0.25 mg and 0.5 mg once daily are associated with any clinically significant undesirable psychiatric profile. (IB version 12 and any updates thereof).

##### Metoprolol adverse reactions – post marketing experience

- Blood and lymphatic system: thrombocytopenia, leukopenia, agranulocytosis
- Cardiovascular: cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension
- Respiratory: wheezing (bronchospasm), dyspnea, rhinitis
- Central Nervous System: confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia
- Psychiatric: changes in personality, depression
- Gastrointestinal: nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting, abdominal pain, retroperitoneal fibrosis
- Hypersensitive Reactions: pruritus

- Miscellaneous: fatigue, hyperhidrosis, hepatitis, increased liver enzymes, musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, dry eyes, psoriasis-like dermatitis, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance, gangrene

For more information regarding the adverse events please see the Summary of Product Characteristics of MetoHEXAL® 100 mg retard.

It is anticipated that the subject receiving the study medication will experience a reduction in their body weight and improvement in their glycaemic control. Although tesofensine has not been previously investigated in patients with T2DM, based on the highly statistically and clinically meaningful degree of weight loss and the available literature it is anticipated that participants in this trial will experience improvement in their glycaemic control (including those on placebo who will receive diet, exercise and lifestyle modification guidance). In addition, all patients will have access to a state-of-the-art clinical care that they will receive for the duration of the study. Subjects randomized to the placebo arm will receive state of the art clinical study for almost 5 months with regular visits and multiple sophisticated assessment of their health status, including their diabetes, as well as lifestyle guidance from a dietician.

## **5 TREATMENT OF STUDY PARTICIPANTS**

### **5.1 DESCRIPTION OF STUDY MEDICATION**

#### **Investigational Medicinal Product**

Tesofensine is a serotonin-noradrenaline-dopamine reuptake inhibitor, for oral administration, which is manufactured, packed and labelled by Delpharm in Reims (France). Its chemical name is (1R,2R,3S,5S)-3-(3,4-dichlorophenyl)-2-(ethoxymethyl)-8-methyl-8-azabicyclo octane. Designated contractors will supply study medications directly to the sponsor CRO's pharmacies.

Metoprolol is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration. It has been formulated into the extended release tablets to provide a controlled and predictable release of metoprolol for once-daily administration. Original extended release metoprolol will be purchased and supplied by sponsor CRO directly and distribute to the sponsor CRO's pharmacies.

The IMP is a kit of one tablet of tesofensine 0.5mg and one tablet of metoprolol 100 mg, both formulated for oral use once a day.

#### **Placebo**

The placebo formulation is identical in presentation and appearance to the tesofensine and metoprolol tablets but includes only the excipients; it does not contain any active ingredients.

### **5.2 PROCEDURES TO ASSURE DOUBLE BLINDING**

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

- The IMP will look similar to placebo with regard to size, colour and general



appearance

- The labelling of the IMP will identify the study and the investigational product but will not indicate the contents
- Randomization will be performed by a third party and the site staff will not have access to the actual treatment assignments (except pharmacists)
- Only the site pharmacist will be able to match the randomization list and treatment assignment and he/she will be dispensing the study medication to the investigator; however, at no time he/she will be in contact with the subjects

### **5.3 IMP HANDLING PROCEDURES AT THE UNIT'S PHARMACY**

The designated pharmacist at the Unit (investigational site) is responsible for storage of received study medication, blinding, dispensing and record keeping of the IMP including:

- Acknowledgment of receipt of the original bottles/ boxes of IMP by signing the receipt forms
- Storing the IMP on Unit in a secured area with restricted access as instructed on the study kits labels
- Blinding the IMP and repacking
- Dispensing IMP according to the protocol

Randomization will be balanced by using the randomization list. The investigator will obtain the randomization number and ask pharmacist to prepare the relevant IMP for subjects. At the time of dispensing, the pharmacist will write the randomisation number and the visit name on each kit on spaces reserved for this purpose.

The investigator and pharmacist are responsible for study medication kits accountability. The pharmacist is responsible for maintaining accurate records of all information relating to the management of the study medication. If any quality issues are noticed on receipt or use of the IMP (e.g. damaged condition, faults in appearance, errors in the documentation, incorrect labelling, and short expiry date) these should be notified promptly to the study monitor and sponsor. The investigator should also inform the study monitor/sponsor of any complaints about the IMP made by the study subjects.

In the event of a batch recall, the sponsor or its representative will inform the investigator or pharmacist in writing. Upon receipt, and as instructed, the investigator or pharmacist should immediately contact any study subject in possession of the corresponding study medication kits.

	<b>IMP kit</b>	<b>Placebo kit</b>
<b>Kits supplied at the visit 2 will consist of:</b>	<p><b>Medication for Day 2:</b> 1 kit containing 2 tablets of tesofensine 0.5mg and 1 tablet of MetoHEXAL® 100 mg retard (First 2 days a loading dose of 1.0 mg/d of tesofensine will be given, one dose will be already given the Unit at Day 1.)</p> <p><b>Medication for Day 3-7:</b> 1 plastic bottle containing 7 tablets of tesofensine</p> <p>and 1 plastic bottle containing 7 tablets of MetoHEXAL® 100 mg retard</p> <p>the medication will be sufficient for 8 days (1 extra day to allow for flexibility between scheduled visits).</p>	<p><b>Medication for Day 2:</b> 1 kit containing 2 tablets of placebo matching tesofensine 0.5mg and 1 tablet of placebo matching MetoHEXAL® 100 mg retard</p> <p><b>Medication for Day 3-7:</b> 1 plastic bottle containing placebo matching 7 tablets of tesofensine 0.5mg</p> <p>and 1 plastic bottle containing placebo matching 7 tablets of MetoHEXAL® 100 mg retard</p> <p>the medication will be sufficient for 8 days (1 extra day to allow for flexibility between scheduled visits).</p>
<b>Kits supplied at the visit 3,4,5 will consist of:</b>	<p>1 plastic bottle containing 8 tablets of tesofensine</p> <p>and 1 plastic bottle containing 8 tablets of MetoHEXAL® 100 mg retard</p> <p>1 pack of medication (2 bottles) will be sufficient for 8 days (1 extra day to allow for flexibility between scheduled visits).</p>	<p>1 plastic bottle containing placebo matching 8 tablets of tesofensine</p> <p>and 1 plastic bottle containing placebo matching 8 tablets of MetoHEXAL® 100 mg retard</p> <p>1 pack of medication (2 bottles) will be sufficient for 8 days (1 extra day to allow for flexibility between scheduled visits).</p>
<b>Kits supplied at the visit 6,7,8 will consist of:</b>	<p>1 plastic bottle containing 15 tablets of tesofensine</p> <p>and 1 plastic bottle containing 15 tablets of MetoHEXAL® 100 mg retard (1 extra day to allow for flexibility between scheduled visits).</p>	<p>1 plastic bottle containing placebo matching 15 tablets of tesofensine</p> <p>and 1 plastic bottle containing placebo matching 15 tablets of MetoHEXAL® 100 mg retard (1 extra day to allow for flexibility between scheduled visits).</p>
<b>Kits supplied at the visit 9 will consist of:</b>	<p>1 plastic bottle containing 20 tablets of tesofensine</p> <p>and 1 plastic bottle containing 20 tablets of MetoHEXAL® 100 mg retard (1 extra day to allow for flexibility between scheduled visits).</p>	<p>1 plastic bottle containing placebo matching 20 tablets of tesofensine</p> <p>and 1 plastic bottle containing placebo matching 20 tablets of MetoHEXAL® 100 mg retard (1 extra day to allow for flexibility between scheduled visits).</p>



		between scheduled visits).
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#### **5.4 LABELS FOR STUDY MEDICATION**

The label texts will be translated or adjusted as necessary so that they comply with the applicable national laws and regulatory requirements of the country in which the study will be conducted. The label text will include the following information as minimum:

- Name of Sponsor
- Name of CRO or Investigator
- Protocol number
- Dosing instructions
- Batch number
- Expiry date
- Randomization number (double-blind)
- Visit number
- The words 'For clinical study use only'
- The words 'Keep out of reach of children'
- Storage conditions

#### **5.5 PACKAGING AND DESTRUCTION**

Medication will be distributed to the subjects in plastic bottles labelled with the appropriate study medication number. Bottles for the respective investigational medicinal products will be identical in colour, size and shape to preserve the blinding of the study. Unused study medication will be collected by the investigator and pharmacists. Sponsor's CRO is responsible for central destruction of all study medication (partially used and unused).

#### **5.6 HANDLING OF THE STUDY MEDICATION**

Study medication will be distributed to the subjects during the visits 2, 3, 4, 5, 6, 7, 8, 9 at the Unit. First administration will be done on Day 1, at the Unit. Subjects will be asked to use study medication every morning with or right after a meal and not to crush or chew the tablets. Subject will be asked to store the medication at room temperature (15 - 25 °C) and return the unused study medication on each in-person visit at the Unit.

#### **5.7 SUPPLY AND STORAGE OF THE STUDY MEDICATION**

##### **Study medication supplies**

Tesofensine and tesofensine placebo will be supplied by the sponsor. MetoHEXAL® 100 mg retard and MetoHEXAL® 100 mg retard placebo will be purchased directly by Profil. IMP will be shipped to the Units under temperature control and monitoring. The receiving Unit has to confirm the receipt and the condition of the delivery in writing on provided forms. The temperature-monitoring device will indicate if the specified shipment conditions were not maintained during the transport than the IMP must be quarantined such that it cannot be used unintentionally and the sponsor must be contacted immediately. Upon receipt IMP will be

stored at room temperature (15 - 25 °C) and protected from light in a place with restricted and controlled access.

Prior to the initial shipment of the study medication to the Unit(s), the following essential documents must be available in the Study Master File:

- IEC/RA approval
- IEC/RA approved subject information/informed consent form
- Clinical study protocol signed by the principal investigator
- Study agreement/contract signed by the principal investigator

#### **Study medication storage**

All study medication must be stored at the Unit's pharmacies, in restricted place at room temperature (15 - 25 °C)

### **5.8 STUDY MEDICATION COMPLIANCE**

The investigational medicinal products will be self-administered by the subjects at home. Subjects with compliance for the entire study below 80% for any of the study medication (determined by calculating returned bottles and count of returned tablets) will be considered protocol violators and will not be included in the per protocol analysis. For the monitoring of study medication, subjects will be instructed to return all bottles with study medication at each visit, whether full, partially empty, or empty.

### **5.9 SCREENING AND RANDOMISATION**

Subjects who sign the informed consent will be identified at the screening visit by a unique screening number consisting of a two (2) digit Unit number and three (3) digit subject number. The screening number together with the study number uniquely identifies every subject eligible for the study. Subject numbers will be assigned sequentially in ascending order per Unit starting with running number 001, 002, 003, etc.

Screening number Example:	Study Number	Study Unit Number	Subject Number
	TM001	01	001
	TM001	02	001

Randomization of eligible subjects to one of the study medication groups will be done at Baseline visit 2b Day 1, following successful completion of all baseline assessments, using a study medication number defined by the center-specific assignment list.

Subjects will be randomly allocated to either study medication group in a 1:1 randomization (with stratification for the anti-diabetic treatment, those on metformin only or metformin plus other agents). The randomization codes will be generated within the Biometrics Department of the sponsor's CRO by a statistician. The randomization list will be used for the randomization procedure. The randomization codes and the complete generation procedure will be filed at a secure place by sponsor's CRO statistician until the study database is closed. The only person on Unit with access to the randomization list and assignments will be the designated pharmacist. The study medication number consists of four digits. All kits assigned

to a subject will have the same study medication number. This procedure will be checked by the monitor.

### **5.10 UNBLINDING**

The study will be double blind. Neither the investigators nor the subjects will be informed about the type of subject's medication. In general, emergency unblinding is to be done only when absolutely necessary for the clinical management of an individual subject and where stopping the blinded medication is not sufficient in the opinion of the investigator. The justification for the unblinding should always be discussed with the sponsor prior to unblinding to ensure that unblinding is truly necessary and that appropriate steps for subject's welfare and management are being taken.

In addition, the study medication code may be unblinded by the sponsor if unblinded reporting of a serious adverse event that is both unexpected and reasonably associated with the use of the IMP is required by Regulatory or other local Competent Authorities.

#### Emergency Unblinding:

Emergency unblinding can be performed using sealed envelopes. The randomization code may only be unblinded in case of an emergency situation as described above. Opening of the code envelope must be documented with providing justification for unblinding. The investigator must immediately inform the sponsor about any unblinding. The information will be forwarded to the Regulatory Authority and IEC, if necessary, and decide if the study will be continued/discontinued for the remaining subjects. The investigator will forward the randomization numbers of un-blinded subjects to the biometrician as soon as un-blinding takes place.

#### Routine Unblinding:

After terminating the study, establishing the statistical analysis plan, locking the clinical data base and the data clearing/blind review procedure are finished, a formal Blind Review Report will be presented to the sponsor. After final acceptance of this report, the sponsor will authorize the biometrician to perform study unblinding. Formal records will be kept on measures and dates of each step.

### **5.11 DISPENSATION OF STUDY MEDICATION**

A medication-dispensing log will be kept current by the investigator, detailing the dates and quantities of study medication dispensed to each subject. The inventory will be available to the monitor to verify products accountability during the study. Any unused reusable study medication, either not dispensed or returned by the subject, including empty bottles will be accounted for and returned to the investigator and destroyed by the Unit.

### **5.12 ACCOUNTABILITY OF THE STUDY MEDICATION**

The investigators will make every effort to encourage subjects to comply with the dosage regimen. A record of the study medication dispensed, used and returned will be made at each visit. The investigator, his/her designee must maintain an adequate record of the receipt and distribution of all study medications using a Drug Accountability Form. These forms must be available for inspection at any time. The investigator will only use the study medications within the framework of this clinical study and in accordance with the existing study protocol. The monitor will check and document the number of returned bottles on-site. The delivery to, use by and return from the subject must be documented. All opened and unopened bottles,

together with remaining contents, will be returned by the subject to the site staff and maintained by the investigator in a secure place. The site staff/ monitor will count the returned medication and document in the appropriate record before destruction. A written explanation must be given for any bottle that is missing. It is the investigator's responsibility to instruct the subjects about using and returning of study medication.

### **5.13 CONCOMITANT MEDICATION**

Any other concomitant medication taken, as well as any changes in concomitant medication will be documented in the subject's source documentation and eCRF indicating the:

- Trade name of medication
- Start date
- End date / on-going
- Route of administration
- Total daily dose and units, and
- Reason for administration

### **5.14 PROHIBITED MEDICATION**

Any anti-diabetic medication oral or injectable (except metformin), calcium-channel blockers, beta-blockers (except metoprolol), monoaminooxidase inhibitors. For additional prohibited concomitant medication, please refer to Exclusion Criteria.

Paracetamol is an exception and may occasionally be taken by the subjects in the treatment of acute pain (e.g. headache or toothache). In such case, the subjects will be asked to keep record in the diary.

### **5.15 STUDY PROCEDURES AND OTHER EXAMINATIONS**

#### **Informed Consent**

The subject will receive an original of the written subject information containing a complete and comprehensive explanation of the significance, nature, extent and possible risks of the study, duties concerning insurance and the statement that the subject is free to withdraw from the study at any time without any negative consequences. In addition, the investigator will carry out an oral information session during which the subjects will be given sufficient time and opportunity to clarify remaining questions. After this, two original forms for written informed consent will be given to the subjects for signature. One is to be kept by the subject and one is to be filled in the Investigator's Study File. The investigator will confirm that each individual subject has received an explanation in accordance with the study protocol and has signed the appropriate consent form.

#### **Vital Signs**

Vital signs include body temperature, respiratory rate, pulse rate and blood pressure.

#### **Physical Examination**

The physical exam includes: heart, lung, head and neck exam, and abdominal, neurological and dermatological exam.

#### **Blood pressure measurement**

- Subject should avoid food immediately before the measurement. Tobacco, caffeine and alcohol will not be allowed during the entire in-house period.

- Subject should go to the toilet before BP measurement. A full bladder can increase blood pressure slightly
- Subject should sit for five minutes in a comfortable position with his/her legs and ankles uncrossed and his/her back supported against a chair before and during a measurement
- Subject should be asked to sit quietly before and during monitoring
- When subject is ready to take his/her blood pressure, subject should be calm and not think about stressful things and not to talk at all
- Subject's arm must be positioned properly. Same arm must be always used when taking subject's blood pressure. Subject should rest his/her arm, raised the arm to the level of his/her heart, and put the arm on a table, desk or chair arm. If needed, a pillow or cushion should be placed under subject's arm to elevate the arm high enough.
- The cuff must be placed on bare skin, not over clothing. The appropriate sized cuff should be always used!
- Three measurements should be performed, repeat the BP measurement after 3 minutes. If the monitor doesn't automatically log blood pressure readings or heart rates, the measurement should be repeated until a valid reading is available (for every time point there have to be three BP values).

BP as an endpoint will be measured as following:

**First admission at the Unit (Day -2, Day -1, Day 1):**

- Evening Day -2 (~9 PM)
- Morning of Day -1 pre-breakfast (~6 AM )
- Noon Day -1 (~12 PM )
- Pre-dinner Day -1 (~6 PM)
- Midnight Day -1 (~12 AM)
- Morning Day 1 (~6 AM )

**Second admission at the Unit (Day 89, Day 90, Day 91):**

- Evening Day 89 (~9 PM)
- Morning of Day 90 pre-breakfast (~6 AM )
- Noon Day 90 (~12 PM )
- Pre-dinner Day 90 (~6 PM)
- Midnight Day 90 (~12 AM)
- Morning Day 91 (~6 AM )

The average of those six measurements (each measurement should be a mean of three separate measurements) will be the mean SBP/DBP used as a secondary endpoint. Those six BP measurements will also be plotted over time and looked at as an exploratory endpoint.

**Body weight** - subject must be undressed with the exception of underwear.

**Waist circumference** will be measured just after subjects breathe out, in standing position, just above hipbones (also in underwear).

**Blood pregnancy test** will be done for any women of childbearing potential at the Unit at the Screening.

**Urinary pregnancy test** will be done for any women of childbearing potential at the Unit at the Baseline, and on Days 28, and 110.

**24-hour HR monitoring:** monitoring will be based on Telemetry measurements. HR as an endpoint will be measured as following:

- **First admission at the Unit (Day -2, Day -1, Day 1):** monitoring will start at ~7 AM on Day -1, approximately 24 hours before first dosing. Monitoring will be carried out to complete at least 24 hours of measurement. The data interval for analysis will be based on the beginning of the measurement and the completion of the 24 hours.
- **Second admission at the Unit (Day 89, Day 90, Day 91):** monitoring will start at ~7 AM on Day 90, one hour before last dosing. Monitoring will be carried out to complete at least 24 hours of measurement. The data interval for analysis will be based on the beginning of the measurement and the completion of the 24 hours.

During the monitoring time the subjects will be allowed to walk around his/her room and the clinic facilities. Subjects will not be allowed to perform any additional physical activity apart from that resulting from the routine activities in the clinic.

Subjects will be requested to adopt a resting position for the time corresponding to 13 hours after the initiation of the measurement (~8 PM). Subjects will be asked to remain for one hour in a supine position and not to fall asleep. Passive activities such as reading or watching will be allowed during this time.

#### **MRS for determination of liver fat**

Lipid content of abdomen and liver will be determined non-invasively using  $^1\text{H}$  (proton) Magnetic resonance spectroscopy (MRS) on a 3-Tesla clinical magnetic resonance imaging scanner. MRS is a technique that can be used in the characterization of tissue. During the scans, the subjects will receive a buzzer to let the researcher know when they are uncomfortable and they will remain in contact with the researcher via an intercom communication system.

$^1\text{H}$  MRS will be used to quantify the lipid content in the liver. The intensity of the lipid signal will be expressed as the lipid/water ratio. During the  $^1\text{H}$  MRS measurement in liver, the subject will be asked to breath in the rhythm of the measurement (a 4s rhythm) to minimize motion artefacts. The procedure will last ~60 minutes.

#### **9-point profiles for blood glucose**

Sample no.	Approx. hour <sup>1</sup>	Nominal timing	Blood Glucose
1	08:00 h	Before breakfast	X
2	10:00 h	2 hours after breakfast	X
3	12:00 h	Before lunch	X
4	14:00 h	2 hours after lunch	X

Sample no.	Approx. hour <sup>1</sup>	Nominal timing	Blood Glucose
5	18:00 h	Before dinner	X
6	20:00 h	2 hours after dinner	X
7	22:00 h	Before going to bed	X
8 <sup>2</sup>	03:00 h	Bed time	X
9 <sup>2</sup>	08:00 h	Fasting day after	X

<sup>1</sup> The actual time of sampling is approximate; the nominal timing should be followed in any case (time windows: within 30 min before start of meal, 2 hours  $\pm$  30 min from start of meal, no time window for bedtime blood glucose sample).

<sup>2</sup> This sample is taken in the morning of the following day  
Standardized meal will be provided by the Unit.

### PHQ-Questionnaire

The PHQ-9 (Appendix II) was originally developed as a screener for depression in primary care and is commonly used in medical settings. The PHQ-9 demonstrated a strong correlation with a well-established measure of depression, and a score  $\geq 13$  demonstrated good sensitivity (83%) and specificity (72%) to that end (10).

The questionnaire consists of 9 questions with a rating corresponding to the answer of the subject. The scores range from 0 to 27. Question 9 assesses suicidal ideation, and in this study any score  $> 0$  at screening will be considered as suicidal ideation and such subjects will not be included in the study. PHQ-9 will be performed at screening, baseline, days 14, 28, 42, 70 and 91. If at any moment PHQ  $\geq 10$  or the score of question 9  $> 0$  the subjects will be withdrawn from the study.

## 5.16 LABORATORY EVALUATIONS

Laboratory samples will be collected from subjects at the Unit, and will be shipped to the central laboratory (MLM Medical Labs GmbH, Dohrweg 63, 41066 Mönchengladbach, Germany) for analysis in ambient conditions.

The investigator will receive the data from laboratory safety analyses from the central laboratory and will review, evaluate, sign and date the laboratory report electronically. The investigator must evaluate all results outside the reference range and mark whether they are considered to be 'clinically significant' or 'not clinically significant'. The signed and dated version of the laboratory report will be filed electronically.

The investigator's evaluation ('normal', 'abnormal and not clinically significant' or 'abnormal and clinically significant') will be entered with the program Labor Master plan at the CRO and will be part of the laboratory results transferred to the sponsor.

If a laboratory result is considered clinically significant and it fulfils the criteria for a clinical laboratory AE, it should be reported in accordance with section 6.2. Clinically significant laboratory findings from the screening visit should be recorded as concomitant illness.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the study database, but abnormal values will be reported to the investigator. The investigator must



review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

- **Hematology:** blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets, will be analysed by central laboratory.
- **Blood chemistry:** creatinine, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, GFR and urea will be analysed by central laboratory.
- **Infectious serology:** Hepatitis B surface antigen, Hepatitis C antibodies, HIV-1/2 combi
- **HbA1c** will be analysed by central laboratory.
- **1,5-anhydroglucitol, lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), serum insulin** will be analysed by central laboratory.
- **Fasting plasma glucose test** before taking the blood glucose test, subject will not be allowed to eat anything for at least eight hours. Blood will be drawn and analysed at the Unit.

**PK Sampling** will be evaluated for presence/absence of tesofensine/metoprolol. The evaluation will be done by sponsor selected external laboratory: Bioanalytical and ADME Labs. Q2 Solutions, a Quintiles Quest Joint Venture, Molenstraat 110, 5342 CC, Oss. The Netherlands

## 5.17 SUBJECTS' DIARIES /CARDS

Subject diaries and cards will be provided. Subjects will be asked to record in the diary depending on the study period the following: date, glucose level and time for assessment, BP values, taking of the study medication, any signs of hypoglycaemia, any signs of hyperglycaemia, any hypotension symptoms, any other AEs, any other concomitant medication.

## 6 SAFETY REPORTING

All AEs occurring after the randomization of the subject will be reported. The report will include information on onset and stop dates, nature, severity, duration, interventions and medications required. Possible SAEs will be reported to the regulatory authorities and Independent Ethics Committees (IECs) according to local regulations, and will be followed-up until the resolution of the event.

### 6.1 DEFINITIONS

An adverse event (AE) is any unintended medical occurrence in a subject in a clinical study who is treated with a drug or medical device. This includes all unintended or unforeseeable signs and symptoms, including abnormal laboratory findings, diseases and psychological symptoms, including aggressive behaviour against themselves or others, that occur in a temporal association with the use of the drug or medical device, independent of a causal relationship with the use.

### 6.2 ADVERSE EVENT

All AEs encountered after the randomization will be recorded in detail indicated in the eCRF, regardless of their relationship to the investigational study product as assessed by the



investigator. It is the responsibility of the investigator to document all AEs, which occur during the study. AEs will be coded by use of an internationally recognized dictionary. Details are described in the study specific Data Management Plan.

Intensity of AEs:

The following three-point rating scale will be used for rating the intensity of each AE:

- Mild: Awareness of signs or symptoms, no interference with daily activities
- Moderate: Symptoms cause discomfort with some interference with daily activities (disturbing)
- Severe: The subject is unable to work or conduct usual daily activities (disabling)

Causality of AEs:

The following five-point scale will be used for rating the causal relationship of the AE to the investigational study product:

- Not related: The adverse event is clearly not related to the study treatment - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration; and/or a causal relationship is considered biologically implausible.
- Unlikely: In cases where sufficient information exists to establish beyond reasonable doubt that study treatment causality was not likely to be the cause of the event then such reports should be classified as unlikely related.
- Possible: An event that follows a reasonable temporal sequence from administration of the study treatment follows a known or expected response pattern to the suspected study treatment, but that could readily have been produced by a number of other factors.
- Probable: For inclusion in this category it is recommended that all the following minimum criteria should be complied with:
1. There should be a reasonable association in time between the administration of the study treatment and onset and duration of the reported event.
  2. The description of the clinical phenomena should be consistent with, or at least plausible, given the known pharmacology and toxicology of the study treatment.
  3. There should be no other equally plausible explanation(s) of the case. In particular, concurrent use of other medicinal products (and possible drug interactions) or intercurrent disease should be taken into account in the assessment.
- Definitely The adverse event is clearly related to the study treatment – i.e. an event that

related follows a reasonable temporal sequence from administration of the study treatment, follows a known or expected response pattern to the suspected treatment, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the Subject's clinical state.

#### Outcome of AEs:

Outcome of adverse event may include at time of last observation:

- Recovered / resolved
- Recovering / resolving
- Not recovered / not resolved
- Recovered / resolved with sequelae
- Fatal
- Unknown

The outcome type and duration of the follow-up of subjects with AEs should be specified.

#### Action Taken for AEs:

AEs requiring therapy must be treated by recognized standards of medical care to protect the health and welfare of the subject. Appropriate equipment and medicines must be available to ensure the best possible treatment of emergency situations. Action(s) taken:

- Study treatment withdrawn
- Dose reduced
- Dose increased
- Dose not changed
- Unknown
- Not applicable

### **6.3 UNEXPECTED ADVERSE REACTION**

An Unexpected Adverse Reaction is an Adverse Drug Reaction (ADR), the nature or severity of which is not consistent with the applicable product information, e.g. investigator's brochure for an unauthorized study treatment, or summary of product characteristics for an authorized product.

### **6.4 SERIOUS ADVERSE EVENT**

A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose:

- Results in death
- Life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Or causes a congenital anomaly/birth defect
- Or is judged as medically important condition

#### **Life threatening AE**

An AE is life threatening when the subject is at immediate risk of death from the event as it occurred; i.e. it does not include a reaction, which if it had occurred in a more serious form might have caused death.

**Hospitalization**

In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., elective surgery for a pre-existing condition) need not be considered AEs.

**Disabling/incapacitating AE**

An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal every-day activities.

**Medically important condition**

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Any event, which resulted into a fatal outcome, must be fully documented and reported, including if the death occurred within four weeks after treatment end, and regardless of causality relationship to the investigational study product.

**6.5 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION**

A suspected unexpected serious adverse reaction is an adverse reaction that is both unexpected (not consistent with the applicable product information) and meets the definition of a Serious Adverse Event.

**6.6 PROCEDURES FOR RECORDING ADVERSE EVENTS**

AEs will be collected with a non-leading question at each clinic visit: "Have you had any new or worsening health problems since the last visit?" as well as by reporting those events directly observed and spontaneously reported by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome whenever possible.

Laboratory or vital signs abnormalities are to be recorded as AEs only if they are medically relevant, i.e., symptomatic, requiring corrective study medication, leading to discontinuation or fulfil a criterion for an SAE. In the case of chronic disease, if the disease is known and documented when the subject enters the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an AE.

**6.7 REPORTING OF ADVERSE EVENTS**

At each visit/assessment/call after the randomization, all adverse events, either observed by the investigator, or reported by the subject spontaneously, or reported in response to a direct question, must be evaluated by the investigator and recorded in subject's source documentation and on the AE form of the eCRF.

**Pre-existing Conditions**

Pre-existing conditions or hospitalization for elective surgery or routine clinical procedures that are not the result of an adverse event need not be considered adverse events. Pre-existing condition should be recorded in subject's source documentation and on the medical history form of the eCRF.

**Overdose**

An overdose of the tesofensine is defined in this study as greater than 3mg single dose and metoprolol as a daily dose > 400 mg with 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.

**Pregnancy**

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the study. Pregnancies occurring during the study must be reported by the investigational staff within 24 hours of their knowledge of the event using the AE Form. Any subject who becomes pregnant during participation in this study must be promptly withdrawn from the study. Study medications will be immediately discontinued and study medications will not be tapered. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Pregnancy will be recorded as an AE in all cases. It will be classified as an SAE only if it fulfils SAE criteria. ECRF will be completed and pregnant subjects will be follow-up until the outcome of the pregnancy has been determined.

**Hypoglycaemia**

Plasma glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- $\leq 3.9$  mmol/L (70 mg/dL) or
- $\geq 3.9$  mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms should be recorded by the subject. These must be transcribed into the eCRF throughout the study.

The record should include the following information:

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" if oral carbohydrate, glucagon or IV glucose had to be administered to the subject by another person. Oral carbohydrate should not be given if the subject is unconscious.

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE then a SAE form and a safety information form must be filled in.

Classification of hypoglycaemic episodes:

Minor hypoglycaemic episode

- $\leq 3.9$  mmol/L (70 mg/dL), or
- $> 3.9$  mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms

Major hypoglycaemic episode

- If oral carbohydrate, glucagon or IV glucose was administered to the subject by another person

Nocturnal hypoglycaemic episode

- A hypoglycaemic episode occurred between 24:00 – 06:00.

## **6.8 REPORTING PROCEDURES FOR SERIOUS ADVERSE EVENTS**

The investigator must complete and submit an SAE report for all SAEs, regardless of the causal relationship to study medication as soon as possible, in any case within 24 hours of having received information on the event. The initial report can be followed by a follow-up report as soon as the investigator obtains more specific information on the event.

Any serious AE or unexpected ADR must be reported by investigator to the pharmacovigilance department by fax +49-511-53216-2794 within 24 hr. Such events will be documented in the best possible detail on the Serious Adverse Event Report Form and must be also transmitted to the sponsor by email within 24hr.

The contact information of the pharmacovigilance department is as follows:

Address: Institute of Clinical Pharmacology  
Hannover Medical School, Carl-Neuberg-Str. 1  
D-30625 Hannover, Germany  
Telephone: +49-511-532-3959  
Fax: +49-511-53216-2794  
Email: sae-reporting@mh-hannover.de

The investigator must also send (preferably by e-mail) photocopies of all reports of all examinations carried out and the dates, on which these examinations were performed, to the pharmacovigilance officer:

Email: sae-reporting@mh-hannover.de

Care should be taken to ensure that the subject's identity is protected and the subject's identifiers in the clinical study are not included on any copy of source documents provided to the sponsor. Post-study SAEs may be reported in an expedited manner to the sponsor if the causality to the investigational study product is possible or probable.

All data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (e.g. laboratory data, concomitant medication, subject status) should be sent (by e-mail) to the sponsor within 24hours of knowledge. In addition, every effort should be made to document further any SAE that is fatal or life threatening within 1 week (7 days) following initial notification.

The sponsor's CRO will make expedited reports of all SAEs that are both unexpected and causally related to the IMP, to the Regulatory Authorities, IECs as appropriate and to the investigators at other investigational sites. In addition, the sponsor's CRO may make expedited reports of all SAEs that are expected and causally related to the IMPs to the Competent Authorities, according to the European directive 2001/20/EC and the local regulations. The sponsor's CRO will report all safety observations made during the conduct of the study in the clinical study report.

## **6.9 FOLLOW-UP OF ADVERSE EVENTS**

The investigator must ensure that follow-up of the subject is appropriate to the nature of the event, and that follow-up continues until the event is stabilized or resolved. The investigator must immediately inform the sponsor of any secondary worsening that meets at least one criterion for seriousness. The investigator should take all appropriate measures to ensure the safety of the subjects, in particular he or she should follow up the outcome of any AEs until they return to normal or the subject's condition stabilizes.

Subjects who have experienced SAEs must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the subject has left the clinical study and that additional investigations may be requested by the sponsor. If the follow-up of the subject is not done by the investigator him or herself (e.g. hospitalization followed by a specialist or the subject's general practitioner), the investigator will do everything to establish or maintain contact with the person or department in charge of follow-up of the subject to obtain any follow-up information.

If the investigator learns of an SAE within 30 days after the end of the study, this should be reported to the sponsor within 24 hours from the investigator becoming aware of the event, regardless of whether or not there is a causal relationship with the IMP.

## **6.10 DEVELOPMENT SAFETY UPDATE REPORTS**

At the anniversary date of the first inclusion, the Profil's hired pharmacovigilance department will write down a Safety Report, which will contain an exhaustive list of Serious Adverse Events susceptible to be linked to the study medication, including expected and unexpected adverse events and an analysis of the study's subjects' safety. This report will be sent to Regulatory Authorities and to the IECs in the 60 days after the anniversary of the first inclusion.

# **7 DESCRIPTION OF STATISTICAL METHODS**

## **7.1 DESCRIPTION OF STATISTICAL METHODS**

Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany, will be responsible for the statistical analysis. The statistical planning and conduct of analyses of the data from this study will follow the principles defined in relevant ICH guidelines and Profil's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this chapter, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before data base lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.4 or later.

## 7.2 SAMPLE SIZE CALCULATION

As this is an explorative study no formal sample size calculation was done. The chosen sample size is a balance between exposing the lowest possible number of patients to the IMP, while still being able to compare the effects of tesofensine/ metoprolol treatment vs. placebo.

## 7.3 SELECTION OF SUBJECTS FOR ANALYSES

The following analysis sets are defined in accordance with the ICH-E9 guidance (11):

### **Per-Protocol Population (PPP):**

includes all randomized subjects without any major protocol violations. Subjects in the PPP will contribute to the evaluation ‘as treated’.

### **Safety Analysis Set:**

Includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set will contribute to the evaluation ‘as treated’.

Analyses of primary and secondary endpoints will be based on the PPP. The analysis of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. This review will be performed without revealing which IMP the subjects are assigned to. The blinding of the IMPs will be maintained for everyone involved in allocating subjects to the analysis sets until data are released for statistical analysis. Furthermore, outliers will be identified by data review according to ICH-E9 (11), and a fake randomisation. In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis. Obviously erroneous data points may be excluded from the analyses. The decision to exclude data points from the statistical analysis is the joint responsibility of the sponsor, the investigator and the CRO statistician.

The subjects or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining study documentation. The subjects and observations excluded from analysis sets, and the reason for this will be described in the clinical study report.

## 7.4 STATISTICAL METHODS

All primary and secondary endpoints will be summarised by treatment and visit using descriptive statistics. Continuous endpoints are summarised by the arithmetic mean, geometric mean, median, standard deviation, coefficient of variation (CV), minimum and maximum value. Categorical endpoints are summarised by the number (N) and percentage (%). Moreover, complete listings of individual values for all endpoints will be provided. Individual and mean curves for the 24h- profiles will be plotted by treatment and visit over the sampling period. Further figures will be chosen and described in the SAP. Subject disposition will be tabulated including the numbers of screened subjects, screening failures, subjects exposed to study product, subjects completing the study and subjects in the PPP and



Safety Analysis Set. Subjects withdrawn from the study will be listed including the primary reason for withdrawal.

## **7.5 ANALYSIS OF THE PRIMARY ENDPOINT**

The primary endpoint will be derived from the individual heart rate measurements of the 24-h profile. The means of all individual concentrations per visit will be calculated. The primary endpoint will be analysed without transformation, if a l-normal distribution can be shown. In case of non-normal distribution alternatives will be described in the SAP. As this study will be conducted at two centres, it will be checked before any analysis, if a centre-effect may exist. If this is the case, the analysis has to be provided per centre. Otherwise the analysis can be conducted as described below. The primary endpoint will be compared between treatment arms by means of an ANCOVA model including treatment as fixed factor and baseline value as covariate. Least square means and 95% confidence of treatment differences will be estimated.

## **7.6 ANALYSIS OF THE SECONDARY & EXPLORATORY ENDPOINTS**

- Change from baseline (visit 2a) to end of treatment in mean SBP
- Change from baseline (visit 2a) to end of treatment in mean DBP
- Change from baseline (visit 2a2b) to end of treatment in body weight
- Change from baseline (visit 2b) to end of treatment in HbA1c
- Change from baseline (visit 2a) to end of treatment in FPG
- Change from baseline (visit 2a) to end of treatment in 9-point blood glucose profiles (AUC)
- Change from baseline (visit 2a) to end of treatment in liver fat
- Change in fasting insulin from baseline (visit 2b) to end of treatment
- Change in 1,5 anhydroglucitol from baseline (visit 2b) to end of treatment
- Change from baseline (visit 2a) to end of treatment in waist circumference
- Change from baseline (visit 2a) to end of treatment in PHQ-9 score
- Other secondary endpoints may be added and will be described in the SAP

The individual data per visit and time point will be presented as well as the mean values of the 24-h profiles (if applicable). The analysis will be conducted as described for the primary endpoint.

## **7.7 SAFETY CRITERIA**

- AEs
- Number and severity of hypoglycaemic events
- Clinical labs (Haematology, Blood Chemistry)
- ECG
- Vital signs
- Physical examination
- PHQ-9 scores

The safety endpoints will be based on the Safety Analysis Set. Continuous data will be summarized using non-missing counts, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using counts and percentages.

Frequency analysis of AEs between treatments will be done using a logistic regression model with treatment as fixed factor. Odds ratios, p-values, and 95% confidence intervals for the

comparisons between treatments will be estimated. A more detailed description will be done in the SAP.

## **7.8 INTERIM ANALYSIS**

No interim analysis is planned.

## **8 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

Source data are all the information in original records and certified copies of original records of clinical findings, observations, or other activities pertaining to the study, which are necessary for the reconstruction and evaluation of the study. The investigator will ensure direct access to these source data to the study monitor, auditor, ethical committee and regulatory inspector.

For each subject enrolled, the investigator will indicate in the source record(s) that the subject participates in this study. The investigator will maintain adequate case histories for each subject enrolled. Source records should be preserved for the maximum period of time permitted by local regulations.

Permission for direct access to subject's data will be sought in writing by the investigator and from the subject as part of the informed consent procedure. This gives permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of the study. Any party (e.g., domestic and foreign Regulatory Authorities, study monitor and auditors) with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subject's identities and sponsor's proprietary information. It is the monitor's responsibility to verify that each subject has consented, in writing, to direct access. It is to be ensured by the investigator that documents that are given to Saniona A/S or its representatives do not contain the name or address of the subject, or other information that would affect the anonymity of the subject.

The investigator will enter the following data in the source records of the subject: demographic information, medical history, concomitant medication, clinical findings from physical examination, vital signs, finding from urine pregnancy tests (if applicable), notes concerning the study procedures, study medication and all adverse events.

### **8.1 SOURCE DATA**

Source data is information included in the original records and/or certified copies of original records from clinical results, observations or other activities pertaining to the study, which are necessary in order to reconstruct and evaluate a clinical study. The investigator will ensure direct access to these source data to the study monitor, sponsor's representative, auditor, ethical committee and regulatory authority.

For each enrolled subject, the investigator will specify that the subject is taking part in this study. The investigator will maintain adequate case histories and proper notes for each of the included subjects. Source data will be archived for the maximum period of time permitted by local requirements.

The following documentation is considered as source documentation for this study:

- The informed consents and the subject's medical files (including laboratory reports) serve as source data
- Subjects' diaries

The following information must be entered in the subject's source documents:

- Subject identification number
- Gender, body measurement
- Medical history and concomitant illness
- Known duration of T2DM
- Concomitant medication
- Unambiguous reference to the clinical study (clinical study number, subject screening and randomization number)
- Information on inclusion/ exclusion criteria
- Informed consent process
- All visit dates
- Details of study medication administration (start and end dates, study medication number, randomization confirmation)
- Physical examination and result done at each visit and phone calls
- Information about the occurrence, improvement, or worsening of AE(s)/ concomitant illness

## **8.2 SUBJECT IDENTIFICATION LIST AND SCREENING LOG**

In order to permit easy identification of the individual subject during and after the clinical study, the investigator is responsible for keeping an up-dated "Subject Identification List". The monitor for completeness will review this document. A "Screening Log" that reports all subjects that were seen to determine eligibility for inclusion in the clinical study also has to be completed by the investigator. The Subject Screening Log and Subject Identification Log may be combined in one list.

## **9 QUALITY CONTROL AND QUALITY ASSURANCE**

### **9.1 DEFINITIONS**

#### **Quality Assurance**

A quality assurance (QA) audit as well as a regulatory inspection may be performed to determine if the rights and the well-being of the subjects enrolled were protected and if the study was conducted as per protocol, ICH GCP and applicable regulatory requirements, and if the data relevant for the evaluation of the investigational medicinal product were reported to the sponsor. The involved CRO will implement a QA system for their respective study-related activities.

#### **Quality Control**

The monitor will visit the Unit at periodic intervals in order to check the source data and records pertaining to the study, to make sure that the investigator follows the study protocol and to verify the completeness, correctness and accuracy of all eCRF entries compared to source data. The investigator will offer the monitor maximum cooperation, in order to find a prompt solution to any possible discrepancies or inaccuracies.

## **9.2 AUDITS AND INSPECTIONS**

The investigator will make all study-related source data and records available to a medically qualified quality assurance auditor mandated by the sponsor, or to regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the investigational medicinal product have been reported to the sponsor.

## **10 ETHICS**

### **10.1 BASIC PRINCIPLES AND ETHICAL CONSIDERATIONS**

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The study and any subsequent amendment(s) will be reviewed by an Independent Ethics Committee (IEC). The study will be conducted in compliance with the protocol, ICH GCP regulations and the applicable regulatory requirements. The regulatory application or submission for regulatory approval will be made by the sponsor's CRO as required by national law.

### **10.2 APPROVALS**

The sponsor will authorize a CRO for submitting the documents to the IEC and BfArM.

### **10.3 ETHICS COMMITTEE**

This protocol, a sample subject information sheet and informed consent form, and any other materials provided to the subjects will be submitted to the appropriate IEC. The study approval letter must be available before any subject is exposed to a study-related procedure, including screening tests for eligibility. During the study, the following documents will be sent to the IEC for their review:

- Changes to the Investigator's Brochure
- Reports of adverse events that are serious, unlisted and associated with the IMP
- All protocol amendments and revised informed consent forms (if any)

The sponsor's CRO will provide a safety update of the study to the local IEC including line listings, individual reports of SUSARs, if applicable, and a discussion of AEs annually, or more frequently if requested based on valid legislation requirements. At the end of the study, the investigator will notify the IEC/RA about the study completion. Furthermore, he/she will provide the synopsis of the final report to the RA/IEC within one year after the end of the clinical study.

### **10.4 REGULATORY AUTHORITY**

The study including all relevant documentation and information need to be submitted to the relevant Regulatory Authority for notification or approval according to valid legislation requirements.

### **10.5 PROTOCOL MODIFICATIONS**

Changes to the protocol during the study will be documented as amendments. The amended protocol will be approved and signed by the relevant personnel at Saniona A/S and by the investigator. Depending on the contents of the amendment and local legal requirements, the amendment will be submitted to the relevant IEC and, where necessary, to the relevant Regulatory Authority. The investigator should not implement any deviation from, or changes

of the protocol, without agreement by Saniona A/S and prior review and documented approval/favourable opinion of the appropriate IEC and, if legally required, Regulatory Authority, except where necessary to eliminate an immediate hazard to the subjects, or when the change(s) that were approved by Saniona A/S involve only logistical or administrative aspects of the study.

## **10.6 SUBJECT INFORMATION AND INFORMED CONSENT**

Before subjects enter the study and any study related assessments are performed, the investigator will explain them the nature of the study, its purpose and associated procedures, the expected duration, and potential benefits, constraints and risks associated with the study. The subjects will also be given written information, which has been approved by the IEC. Subjects will be given sufficient time to consider their participation and all of their questions will be answered. The subjects will also be informed of their right to withdraw from the study at any time without giving a reason. The informed consent form must be signed, with name and date noted by the subject.

The investigator will complete the informed consent section of the eCRF for each subject enrolled.

If new information becomes available that potentially affects the subject's safety or willingness to continue in the study, or if a protocol amendment is issued that affects subject's safety, study procedures or any aspects of the study that may influence the subject's willingness to continue in the study, the subject information leaflet and informed consent form will be revised. After the new documents have received approval from the IEC, the subject will be asked to sign the new consent form to confirm his or her willingness to continue in the study.

Each subject will be informed that his/her source records may be reviewed by the monitor, a quality assurance auditor or an IEC/Regulatory Authority inspector, in accordance with applicable regulations. All personal information which the subject will reveal to the investigator and which does not pertain to the study will be considered confidential.

## **10.7 PARTICIPANT CONFIDENTIALITY**

The investigator will ensure that the subject's anonymity will be preserved. On eCRFs or any other documents submitted to the sponsor, the subjects will not be identified by their names, but by a study specific identification code. Documents not intended for the sponsor, i.e. the confidential subject identification code, original consent forms and source records will be maintained by the investigator as strictly confidential and in a secured place. The subjects will be informed that all their study results will be handled in strictest confidence.

## **10.8 INVESTIGATOR QUALIFICATION**

The investigator will be informed of the methods for rating relevant study outcomes and for completing eCRFs in order to reduce discrepancies between participating investigators and study sites. The investigator will be kept informed of important data, which relate to the safe use of the investigational study product as the study proceeds.

## **11 DATA HANDLING AND RECORD KEEPING**

### **11.1 DATA COLLECTION AND DOCUMENTATION**

Relevant study data for statistical analysis and study report are to be recorded in the eCRFs. Subject's data have to be reported on the eCRFs in an anonymous fashion, the subject only being identified by the subject number. The investigator will be responsible for the completeness, accuracy and legibility of the information in the eCRF and other study documents. The study monitors then have to check the eCRFs against the source documents for accuracy and validity as per the monitoring schedule, as applicable. Upon completion of the examination, eCRF completion is expected at each Unit to ensure quality of data and subject safety. Once eCRFs are completed, they will be available for review by the study monitor and CRO Clinical Data Management. Completed eCRFs will be reviewed remotely for logical discrepancies. The study monitor will ensure that all data queries and subsequent amendments in the eCRF documentation are made according to GCP guidelines.

### **11.2 STUDY MONITORING AND SOURCE DATA VERIFICATION**

The study monitor will contact and visit the investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries compared to source data. The investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the study monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, etc.), and has adequate space to conduct the monitoring visit. For this study, the average number of the monitoring visits is intended to be 3-4 monitoring visits/Unit (initiation and close-out visit is not included).

In general, during monitoring visits the monitor will ensure that the study is being conducted according to the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines and other applicable regulations, and will compare the eCRF entries to original source data. He or she will also make sure the informed consent procedure has been appropriately carried out and will ensure that all SAEs have been reported within applicable timeframes. He or she will also ensure that IMP accountability has been maintained and will, after completion of the study, perform final accountability and arrange for the return or destruction of IMP.

### **11.3 DATA MANAGEMENT PLAN**

Data Management is the responsibility of Profil Institut für Stoffwechselforschung GmbH, Neuss Germany. The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this study.

### **11.4 CASE REPORT FORMS (CRFs)**

The Data Management Department of Profil Institut für Stoffwechselforschung GmbH will provide the CRFs. All further information regarding the CRFs and the data flow will be described and agreed on in the Data Management Plan for this study.

#### **Database Lock**

All data entry, validation and medical encoding activities will be finalized before the database



will be locked. All unnecessary user privileges to the study will be removed, except for the data manager who will perform the database lock.

In exceptional circumstances, when critical reasons justify, there may be a need to perform updates to the database after it has been locked. A database that is locked and released for analysis will only be unlocked if an error is identified that will significantly affect the statistical outcome of the analysis of the efficacy parameters or change the safety profile of the study.

### **11.5 INVESTIGATOR FILE**

The investigator will be responsible for keeping all records so that the course of the study is duly documented. Copies of essential documents related to the study must be filed by the investigator as required by ICH GCP and applicable regulatory requirements. No document concerning the study may be destroyed without prior written agreement between the investigator and the sponsor. Should the investigator elect to assign the study documents to another party, or to move them to another location, the sponsor must be informed without delay.

### **11.6 USED SUBJECT AND MEDICATION LOGS**

The investigator or pharmacists will be responsible for recording and keeping all records regarding study medication shipment; dispensing and accountability records and these must be filed by the investigator as required by GCP and applicable regulatory requirements. The investigator will ensure an adequate confidentiality of the subjects' identification list providing the only connection between source data, and anonymous data in the eCRF for the sponsor. The investigator will ensure that this secret list is maintained securely for a period of 15 years at minimum.

### **11.7 PROTOCOL COMPLIANCE**

The investigator agrees by signing the protocol that the study will be conducted in compliance with the protocol, ICH GCP and the applicable regulatory requirements.

### **11.8 RECORD KEEPING**

The investigator must retain the informed consent documentation, disposition of the study medication, eCRFs, subjects' source documents, and other source data for at least 15 years or 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 the clinical development of the study medicine. It is the responsibility of the sponsor to inform the investigator as to when these documents no longer need to be retained. If the investigator retires, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to another person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the sponsor.

In addition, the sponsor will retain copies / originals (as appropriate) of any study-related documents in the Study Master File for at least 15 years or 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 the clinical development of the study product.



## **12 FINANCE AND INSURANCE**

### **12.1 COMPENSATION TO INVESTIGATOR**

Financial contracts will be signed between the sponsor and the investigator (or a representative of the hospital/clinic/unit) before commencement of the study.

### **12.2 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 Profil.

## **13 PUBLICATION POLICY**

### **13.1 REPORTING AND PUBLICATION**

Profil will prepare a study report 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. In accord with standard editorial and ethical practice, the sponsor will support publication of multicentre studies only in their entirety and not as individual site data.

## 14 REFERENCES

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## 15 Appendices

### 15.1 Appendix I: table of recommended concomitant medication use

Drug Class	Episodic Use	Chronic Use	Comment
Antiarrhythmic (Amiodarone, <u>quinidine</u> )	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 ( <u>terbinafine</u> )	N	N	Moderate inhibitor of CYP2D6
Muscarinreceptor blocker Darifenacin	N	N	Moderate inhibitor of CYP2D6
Barbiturates	N	N	
Benzodiazepines	Y	N	Prohibited for 2 weeks prior to randomisation, however, hypnotics and/or anxiolytics at a stable dose for at least 4 weeks prior to screening and up to the follow-up visit could be allowed, i.e. up to zolpidem (10 mg/day), choral hydrate (1 g/day), triazolam (0.5 mg/day), or lorazepam (1 mg/day)
Beta- blockers	N	N	Per protocol
Bupropion (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	
<u>Hypnotic sedative (glutethimide)</u>	N	N	Strong inducer of CYP2D6
<u>H2-receptor antagonist (cimetidine)</u>	N	N	Weak inhibitor of CYP2D6
Immunosuppressives	N	N	
Insulin and/or other injectable anti-diabetic medications, or TZDs	N	N	Per protocol
Lithium	N	N	
Monoamine oxidase (MAO) inhibitors	N	N	
Opioids, cannabinidiols	N	N	
Oral hypoglycemics	-	-	Per protocol
Orlistat	N	N	
Phenothiazines	N	N	
Selective serotonin reuptake inhibitors (SSRIs)	N	N	
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	N	N	

<b>Drug Class</b>	<b>Episodic Use</b>	<b>Chronic Use</b>	<b>Comment</b>
Tricyclic antidepressants	N	N	
Drug inducing ocular toxicity Chloroquine Hydrochloroquine	N	N	
<b>Non-drugs</b>			
Weight loss supplements	N	N	
Anti-depression, anxiety, epilepsy, psychotics OTC, supplements	N	N	

## 15.2 Appendix II: The Patient Health Questionnaire (PHQ-9; Version in German)

### Gesundheitsfragebogen für Patienten (PHQ-9)

Wie oft fühlten Sie sich im Verlauf der <u>letzten 2 Wochen</u> durch die folgenden Beschwerden beeinträchtigt?	Überhaupt nicht	An einzelnen Tagen	An mehr als der Hälfte der Tage	Beinahe jeden Tag
a. Wenig Interesse oder Freude an Ihren Tätigkeiten	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Niedergeschlagenheit, Schwermut oder Hoffnungslosigkeit	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c. Schwierigkeiten ein- oder durchzuschlafen oder vermehrter Schlaf	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d. Müdigkeit oder Gefühl, keine Energie zu haben	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
e. Verminderter Appetit oder übermäßiges Bedürfnis zu essen	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
f. Schlechte Meinung von sich selbst; Gefühl, ein Versager zu sein oder die Familie enttäuscht zu haben	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
g. Schwierigkeiten, sich auf etwas zu konzentrieren, z.B. beim Zeitunglesen oder Fernsehen	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
h. Waren Ihre Bewegungen oder Ihre Sprache so verlangsamt, dass es auch anderen auffallen würde? Oder waren Sie im Gegenteil „zappelig“ oder ruhelos und hatten dadurch einen stärkeren Bewegungsdrang als sonst?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
i. Gedanken, dass Sie lieber tot wären oder sich Leid zufügen möchten	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

Gesamtwert \_\_\_\_\_ = Addition \_\_\_\_\_ + \_\_\_\_\_ + \_\_\_\_\_  
der Spaltensummen