Clinical Study Protocol

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

Sponsor:	Saniona, A/S Baltorpvej 154 DK2750 Ballerup Denmark
Protocol number:	TM005
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CLINICAL STUDY PROTOCOL SYNOPSIS

Study title	A 24-week phase 2, double-blind (DB), randomized, placebo-controlled, single-center safety and efficacy study to evaluate overall safety and tolerability of co-administration of tesofensine and metoprolol in subjects with hypothalamic injury-induced obesity (HIO), and with a 24-week open-label extension, in total 48 weeks.
Study sponsor	Saniona, A/S Baltorpvej 154 DK2750 Ballerup Denmark
Phase	2a
Number of sites	1 site; Rigshospitalet (RH), Copenhagen, Denmark
Sample size	Minimum of 12 and maximum of 25 adult subjects with HIO.
Study design	• DB, randomized, placebo-controlled, single-center study followed by an open-label extension period. • The study will have two parts: o Part 1: 24 weeks DB treatment, followed by o Part 2: 24 weeks open-label extension – all subjects still participating at the end of part 1 will be given an option to continue for additional 24 weeks on the active drug if evaluated eligible by the investigator • During the part 1 subjects will be randomized into either the active medication or matching placebo in 2:1 ratio • As an integral part of the study all subjects will undergo regular dietary and physical activity counseling during the study • A clinical study report (CSR) will be prepared following the completion of the 24-week DB part of the study and a separate CSR following finalization of the 24-week open labelled study part
Study timelines	Q1 2019 – Q2 2020 – the double-blind part. Q3 2019 – Q1 2021 – the open-label extension part.
Investigational Medicinal Product (IMP) and dosing schedule	Part 1 – the DB part: The active medication arm will be given co-administration of 0.5 mg tesofensine/50 mg metoprolol daily for 24 weeks. The placebo arm will receive matching placebo tablets. Part 2 – the open-label extension part: All active participants at the end of the DB part will be given the active medication 0.5 mg tesofensine/50 mg metoprolol daily for 24 weeks. Each tablet will be formulated separately; a currently available commercial formulation of extended release (ER) metoprolol will be used.

	In case a subject, in the opinion of the investigator, experiences an adverse event that by the investigator is suspected to be potentially related to an undesirable drug concentration of the IMP, the period between dosages can be extended or a drug holiday can be implemented in order to optimally manage the well-being and safety of the subject. Each of these cases should if possible be discussed in advance with the sponsor's medical expert.
Study objectives and endpoints	**Primary objectives:** • To examine overall safety and tolerability of co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment over 24 weeks in subjects with HIO **Secondary objectives:** • To examine the effect on satiety and appetite from from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO • To examine the effect on bodyweight from from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO • To examine the effect on body composition from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO • To examine the effect on quality of life from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO • To examine effect on craving for something sweet, salty, savory and fatty from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO • To examine the effect on thirst from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO • To examine effect on glycaemic control and lipid profile from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO

	• To examine the effect on heart rate (HR) and blood pressure (BP) from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
	• To establish profile of trough values of tesofensine, metoprolol and N-desmethyl-metabolite (NS2360) following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO:
	  o Active arm: the first 24 weeks and then continuously up to week 48.
	  o Placebo arm: start of treatment at week 25 and then continuously up to week 48.
	• To evaluate the effect on BP and HR from baseline to week 24 by 24 hours (24H) home monitoring of BP and 48 H home monitoring of HR.
	• To evaluate overall safety and tolerability from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO.
	
	Primary endpoint
	• Safety and tolerability will be judged from all safety data collected in the period, including number and type of treatment emergent adverse events, laboratory data, BP and HR.
	
	Secondary efficacy endpoints
	• Change in satiety and appetite using the composite satiety score (CSS) baseline to week 24, from baseline to week 48 and from week 24 to week 48
	• Change in body weight from baseline to week 24, from baseline to week 48 and from week 24 to week 48
	• Change in body composition i.e. body fat and lean body mass by Dual-energy X-ray absorptiometry (DEXA) from baseline to week 24, from baseline to week 48 and from week 24 to week 48
	• Change in quality of life by the use of the SF-36 questionnaire from baseline to week 24, from baseline to week 48 and from week 24 to week 48
	• Change in craving for something sweet, salty, savory and fatty by the use of Visual Analogue Scale (VAS) scales from baseline to week 24, from baseline to week 48 and from week 24 to week 48
	• Change in thirst by the use of a VAS scale from baseline to week 24, from baseline to week 48 and from week 24 to week 48
	• Change on glycaemic control and lipid profile from

	baseline to week 24, from baseline to week 48 and from week 24 to week 48 • Change in waist circumference from baseline to week 24, from baseline to week 48 and from week 24 to week 48 **Secondary safety and pharmacokinetic (PK) endpoints** • Change on HR and BP from baseline to week 48 and from week 24 to week 48 • Trough values of tesofensine, metoprolol and N-desmethyl-metabolite (NS2360) o Active arm: the first 24 weeks and then continuously up to week 48. o Placebo arm: start of treatment at week 25 and then continuously up to week 48. • Change of 24H BP/48H HR and QT from baseline to V5 and V8 and from V5 to V8 measured by home monitoring • Number and type of adverse events (AEs) from week 24 to week 48
Study population (inclusion/exclusion criteria)	In total, a minimum of 12 and a maximum of 25 subjects with HIO. HIO is defined as obesity developed in relation to damage to the hypothalamus, whether it is from an injuring trauma, bleeding, infarction, tumor, surgery or irradiation.
Inclusion criteria	1. Informed consent obtained before any trial-related activities 2. Males and females, aged 18-75 3. Confirmed diagnosis of HIO 4. Body Mass Index (BMI) ≥27 kg/m^2 (where overweight is related to the HIO) 5. Well managed and stable substitution of hypopituitarism >2 months as judged by the investigator 6. Normal BP or well managed hypertension (only if dose of BP medication(s) has been stable for >2 months) 7. Type 2 diabetes is allowed, but the following criteria must be met: • Hemoglobin A1c (HbA1c) <86mmol/mol • Subjects taking glucagon like peptide 1 (GLP-1) analogues must have been on stable dose for >3 months • Fasting plasma glucose (FPG) <11.0 mmol/l measured on site.
Exclusion criteria	1. BP ≥160/90 mmHg 2. HR ≥ 90, <50 bpm 3. Hypersensitivity to tesofensine/metoprolol or any component of the products 4. Type 1 diabetes, Cushings disease, acromegaly,

	hypophysitis, infiltrative diseases or Prader-Willi syndrome 5. Heart failure New York Heart Association (NYHA) level II or greater, decompensated heart failure 6. Previous myocardial infarction or stroke within the last 5 years 7. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other DSM-III disorders, or any other psychiatric condition, which in the investigator's opinion will interfere significantly with study compliance 8. Physical impairment, which in the investigator's opinion will interfere significantly with study compliance 9. Any clinically significant cardiac arrhythmia 10. Treatment with calcium channel blockers and beta blockers 11. Concomitant use of monoaminooxidase inhibitors 12. Use of recreational medication 13. Bulimia or anorexia nervosa 14. Any agent used for weight loss in the past 3 months, except GLP-1 compounds 15. Untreated hypo- or hyperthyroidism 16. Clinically significant liver (>3x ULN) and/or kidney impairment 17. More than 5% weight loss within the last 3 months 18. Subject is pregnant or lactating or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (Spiral or hormonal contraception, birth control pills, implant, transdermal patch, vaginal ring or depot injection) 19. Male subjects not agreeing to use a condom without spermicide or oil-containing products (e.g., lubricants) during sexual activity with female partners of childbearing potential throughout the trial until at least 8 weeks after the last administration of IMP 20. Any contraindication for metoprolol according to the Summary of Product Characteristics (SmPC), e.g. severe peripheral arterial disease, untreated pheochromocytoma, concomitant intravenous administration of calcium antagonists of verapamil and diltiazem, due to the risk of hypotension, AV conduction disturbances, or left ventricular insufficiency 21. Subject has lactose intolerance or a rare hereditary problem of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency 22. Subject is unable to understand and communicate in

	Danish language or to understand the protocol requirements, instructions and study-related restrictions, the nature, scope and possible consequences of the clinical study or is unlikely to comply with the study requirements; e.g., uncooperative attitude and improbability of completing the clinical study 23. PHQ-9 (Patient Health Questionnaire): a. If a score of at least 5 in question 1 and 2 coming from the area of "More than half the days" or Nearly every day" or b. PHQ-9 score ≥ 10 when counts from questions 3-5 have been subtracted or c. If a tic in question 6 in "More than half the days" or "Nearly every day" or d. Any score > 0 on question 9 at screening and baseline 24. Any suicidal behaviour within the past 30 days since screening 25. Subject has been enrolled in another clinical study within the past three months 26. Any other clinically meaningful condition, which in the opinion of the investigator, would make participation potentially unsafe
Study procedures	Due to the special nature and the rarity of the investigated population, limiting the need to travel and to meet the requirement of a reflection period, subjects will be contacted by the investigator and potentially interested subjects will subsequently receive mailed information describing the study. <u>Visit 1, Days -7 to -21</u> Subjects will be invited for screening. First, informed consent process will be completed and signed by the subjects prior to any study-related procedures. Then blood will be drawn, followed by other screening procedures to establish their eligibility for the study. Subjects will be instructed in having home 24H BP/48H HR monitoring done, the devices will be put on, and instructions handed out. <u>Visit 2, Day 1</u> Blood will be drawn, BP, HR, weight and other endpoints will be collected. The first dose of study medication will be administered, dietary consulting will be performed and subjects will receive study drug supply sufficient for one month's treatment. Subjects will be instructed in home BP monitoring

	twice daily before breakfast and dinner (three measurements at each time point) once weekly during the whole study. Subjects with type 2 diabetes mellitus (T2DM) will be instructed in doing weekly 8-point glucose measurements. Subjects will receive a diary for BP reporting and if applicable reporting of blood glucose (BG). DEXA will need to be scheduled in advance so that it can be performed on Day 1. Devices for home 24H BP/48H HR monitoring will be collected. <u>Days 28-168 DB part</u> On Days 28, 56, 84, 112, 140 and 168 (±3 days) the subjects will return to the site for safety evaluations, efficacy assessments, PK and drug supply (see the flow chart (FC) for details). Assessments will include blood sampling, BP, HR, weight and various questionnaires. Also, life style counseling including dietary and physical activity guidance, will be performed. Subjects will always receive study drug supply sufficient until next visit. At Day 84 (± 36) subjects will receive devices for 24H BP/48H HR home monitoring. Visit 8 on Day 168 (±3 days) will be the end of the DB part of the study and all assessments from the baseline visit (visit 2) will be repeated. At Day 168 (÷36/+3) subjects will receive devices for 24H BP/48H HR home monitoring. <u>Days 168 – 336 Open-label part</u> On Day 168 (±3 days) (visit 8) all subjects still participating in the study if evaluated eligible by the investigator will be invited for the open-label extension part where all subjects will be given the active medication. Subjects will be returning monthly for evaluations as described in the FC and drug supply. Visit 14 on Day 336 (±3 days) will conclude their participation in the study. On that day safety and efficacy assessments will be performed and subjects will be given two days of half dose of metoprolol to take at home in order to gradually reduce the dose of metoprolol and avoid potential undesirable fluctuation in BP. Subjects who during the study exceed predefined values of HbA1c (>10%), FPG >11.0 mmol/l) or BP>160/100 mmHg will be treated at the discretion of the investigator per established guidelines to improve the subjects glycaemic/BP control while remaining in the study. Assessments conducted during each visit are described in the FC. <u>Phone visits part 1 and 2:</u> At phone visits follow ups will be performed to discuss status

	and experiences of AEs, hypoglycemic events, 8-point BG measurements, BP and HR measurements, and to reinforce behavioural modifications discussed during the counseling sessions. A follow-up phone visit will be performed 45 days after end of treatment to collect any AEs.
Statistics	All analyses will be performed in two steps – first after the completion of the DB part, then following the completion of the open-label extension part. Primary endpoint will be analyzed based on the following: • The number and type of treatment emergent AEs over the first 24 weeks • Change in laboratory data (hematology and blood chemistry) from baseline to week 24 • Change in BP and HR from baseline to week 24 No inferential statistical test will be performed for the primary endpoint. Continuous efficacy secondary endpoints will be compared between treatment arms by means using analysis of covariance (ANCOVA) including treatment as fixed factor and baseline value as covariate. Estimates and 95% confidence intervals (CIs) of treatment differences will be calculated. Safety analyses will include all participants who took at least one dose of IMP or comparator. 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. AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing AEs in each treatment group will be tabulated by MedDRA system organ class and preferred term. **Sample size estimate, power calculation:** As this is an exploratory study, no formal sample size or power calculation was performed.

INVESTIGATOR STATEMENT

TM005: A 24-week phase 2, DB, randomized, placebo-controlled, single-center safety and efficacy study to evaluate overall safety and tolerability of co-administration of tesofensine/metoprolol in subjects with Hypothalamic injury-induced obesity (HIO) with a 24-week open-label extension, in total 48 weeks.

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, International Conference on Harmonization (ICH) Good Clinical Practice (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 independent ethics committee (IEC) and/or to the competent authorities (CA) 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.

_____

Principal/Coordinating Investigator Signature: Date:

Professor Ulla Feldt-Rasmussen, MD, DMSc

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SIGNATURE PAGE

TM005: A 24-week phase 2, DB, randomized, placebo-controlled, single-center safety and efficacy study to evaluate overall safety and tolerability of co-administration of tesofensine/metoprolol in subjects with HIO with a 24-week open-label extension, in total 48 weeks

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.

Jørgen Drejer, PhD

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LIST OF ABBREVIATIONS

AE	Adverse event
°C	Degrees Celsius
A/S	Aktieselskab
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BEE	Basal energy expenditure
BMI	Body Mass Index
BG	Blood glucose
BP	Blood pressure
Bpm	Beats per minute
CA	Competent authorities
CI	Confidence interval
Cm	Centimeter
CRF	Case report form
CRH	Corticotropin releasing hormone
CRO	Contract Research Organization
CRA	Clinical Research Associate
CSR	Clinical study report
CSS	Composite satiety score
CYP	Cytochrome P450
DAT	Dementia of Alzheimer type
DB	Double-blind
DBL	Database lock
DBR	Database release
DDI	Drug-drug interaction
DEXA	Dual-energy X-ray absorptiometry
Dl	Deciliter
DM	Drug metabolism
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
ER	Extended release
FC	Flow chart
FDC	Fixed-dose combination
FFA	Free fatty acid
FPG	Fasting Plasma Glucose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GHRH	Growth hormone-releasing hormone
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon like peptide 1
HbA1C	Hemoglobin A1c
HDL	High-density lipoprotein
HIO	Hypothalamic injury-induced obesity
HR	Heart rate

HRQoL	Health related quality of life
IB	Investigator brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
INR	International Normal Ration
IP	In-person
IR	Immediate release
kg	Kilogram
l	Liter
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LPLV	Last patient last visit
LSLV	Last Subject Last Visit
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mental Health Practitioner
mg	Milligram
mITT	Modified intention-to-treat population
ml	Milliliter
mmHg	Millimeter of mercury
mmol	Millimol
N (No)	Number
ng	Nanogram
NSAIDs	Non-Steroide Anti-Inflammatoriske Drugs
NYHA	New York Heart Association
OTC	Over the counter
PD	Parkinson's disease
Ph	Phone
PHQ9	Patient health questionnaire 9
PI	Principal investigator
PK	Pharmacokinetic
PPP	Per Protocol Population
PWS	Prader-Willi syndrome
Q	Quarter
QA	Quality assurance
QC	Quality control
RH	Rigshospitalet
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard Deviation
SF36	Short Form 36 Quality of Life Questionnaire
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 diabetes mellitus
TEAEs	Treatment Emergent Adverse Events
TEE	Total energy expenditure

Tmax	Time of the maximum
TRH	Thyrotropin-releasing hormone
TSH	Thyroidea Stimulating Hormone
TZD	Thiazolidinediones
ULN	Upper Limit of Normal range
USA	United States of America
VAS	Visual Analogue Scale
WHO DD	World Health Organization Drug Dictionary

1 GENERAL INFORMATION

1.1 Introduction

Hypothalamus is an important site for appetite regulation and energy expenditure. It is a central neuroendocrine area in the midbrain that integrates afferent stimuli from the vagus nerve and from peripheral hormones that reflect the nutritional state, such as leptin, ghrelin, peptide YY and insulin (6-8). The output from the hypothalamus includes humoral regulation of appetite and metabolic rate through corticotropin releasing hormone (CRH), somatostatin, growth hormone-releasing hormone (GHRH), and Thyrotropin-releasing hormone (TRH) released from the parvocellular neurons to the anterior pituitary gland, and through efferent signaling to the limbic system and via vagal- and sympathetic nerve fibers (8-10).

HIO is the significant weight gain that can occur after extensive suprasellar operations or other lesions to the hypothalamus (1-5). Patients with HIO can have a greater sensation of hunger than controls (11). Reported energy intake ranges from below normal to hyperphagia (12-14). These patients are less physically active and have a lower basal metabolic rate than obese controls (12,15), however, these findings are not consistent (16).

The complexity of the syndrome requires simultaneous targeting of the multitude of mechanisms that are deranged in the HIO patients, while taking into consideration the autonomous dysfunction that can potentially render this population more vulnerable to the effects of sympathomimetics on heart rate (HR) (17).

In a number of case-control studies (number of cases 23 to 25) in patients with hypopituitarism that were well substituted, it has been demonstrated that these subjects had a decreased urinary excretion of epinephrine, that obese patients had a higher level of fasting Gastric inhibitory polypeptide (GIP) and lean female patients had higher leptin levels compared to Body Mass Index (BMI) matched controls. It was found that energy expenditure, fasting glucagon like peptide 1 (GLP-1), c-peptide, plasma glucose, and insulin were comparable between patients and controls (26,27). The effect of sibutramine, diet and exercise on body weight was studied in the same population (28): 90 % (n=9) of hypopituitary patients achieved a 5% weight loss, and 60% (n=6) lost >10% weight within 11 months

A wide range of pharmacological treatments has been attempted in patients with HIO in small studies, such as sympathomimetics like dexamphetamine, ephedrine and caffeine, T3 mono treatment, GLP-1 analogues and octreotide with varying results (18-24). A literature review looked at the effect of bariatric surgery in patients with HIO, and found that gastric bypass was the most effective treatment for weight reduction with loss of -33.7 kg (95% CI -80.7; +13.3) after 12 months (n = 6) (25).

Given the mechanism of action of tesofensine and the results from clinical studies in other patient populations it is anticipated that treatment with tesofensine could have a significant impact on appetite, satiety, food craving and weight in patients with HIO.

1.2 Tesofensine

Tesofensine increases neurotransmission for serotonin, noradrenaline and dopamine by inhibiting their presynaptic re-uptake, and thereby reduces appetite/increases satiety (serotonin and noradrenaline), increases energy expenditure (noradrenaline) and reduces food craving (dopamine).

Tesofensine was initially noted to cause a notable weight loss in overweight subjects with Parkinson's disease (PD) and dementia of Alzheimer type (DAT), even though no attempts to promote weight control were included in these studies. The weight reducing effect was confirmed in a subsequent phase 2 clinical study in obese subjects (TIPO-1), exceeding benchmarks set by the regulatory agencies for approval of weight loss agents (29). Although tesofensine was generally well tolerated in these studies, an increase of blood pressure (BP) of 1–5 mmHg and an increase of HR up to 8 beats per minute (bpm) were observed in subjects dosed with 0.25 to 1.0 mg of Tesofensine once daily.

These increases could potentially have an adverse impact on the cardiovascular safety in the target subject population. This led to the addition of metoprolol, a β1-(cardio) selective adrenoceptor blocking agent to mitigate these effects, and provide a favourable benefit/risk profile.

To date, **co-administration** of tesofensine and metoprolol to humans has been investigated in three completed clinical studies. Firstly, a phase 1 drug-drug interaction (DDI) study (Q-21125) where a single dose of metoprolol was added to tesofensine administered for 14 days to study pharmacokinetics (PK) of both when administered together. Secondly, a phase 2 study in obese and overweight subjects with type 2 diabetes mellitus (T2DM) (TM001) designed to provide the proof-of-concept data that addition of metoprolol mitigates the tesofensine-induced increase in HR and BP. In both studies, the co-administration of the drugs was generally well tolerated and the collected data have provided good base for future investigation of a fixed combination of tesofensine and metoprolol (Tesomet) for various indications. Thirdly, a phase 1 study (TM003) to evaluate PK profile and relative bioavailability of a single dose of the Tesomet fixed-dose combination (FDC) tablet and co-administration of tesofensine plus commercial metoprolol has been conducted. In the same study the PK profile and relative bioavailability of a single dose of the Tesomet FDC tablet was evaluated in the fed state. Currently, there is an on-going phase 2 study in adolescents with Prader-Willi syndrome (PWS) (TM002). Initial results from the adult part of the study showed a significant effect of Tesomet on hyperphagia score and body weight in patients with PWS. Finally, a pharmacodynamic (PD) study (TM004) with various dosage combinations of tesofensine and metoprolol to identify the ideal dose of metoprolol for any given dose of tesofensine is on-going.

The clinical development program of Tesomet draws heavily on a substantial body of data available for tesofensine, for which - despite not being approved or developed as a stand-alone agent - there is a complete pre-clinical efficacy and safety data package available and has been to date studied in more than 1300 subjects.

1.3 Metoprolol

Metoprolol is a beta$_1$-selective (cardio selective) adrenoceptor blocking agent, for oral administration, which was 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 available as immediate release (IR) and extended release (ER) tablets. Metoprolol succinate "Orion" 50 mg retard, containing 50 mg of metoprolol succinate, has been formulated to provide a controlled and predictable release of metoprolol for once daily administration. This is the formulation selected for this study (for more information please see the SmPC for Metoprololsuccinat "Orion", depottabletter) (30). Metoprolol was approved in the United States of America (USA) in 1978 and has since become one of the most widely used drugs ever with millions of subject-years of safety data available.

1.4 Co-administration of Tesofensine and metoprolol (PK data)

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

1.5 Safety in previous clinical studies with Tesofensine

Seventeen phase 1 studies with 359 healthy volunteers have been completed, with 309 subjects being exposed to tesofensine. Tesofensine was well tolerated up to and including single oral doses of 6.75 mg. Multiple daily doses up to 1.0 mg and loading doses up to 2.0 mg in phase 1 studies were considered to be well tolerated. In all single and multiple dose phase 1 studies in healthy volunteers, including a study with intravenous infusion up to 1.2 mg in volunteers, no changes in vital signs, electrocardiogram (ECG) or laboratory parameters assessed as clinically significant by the investigator were observed. No serious adverse events (SAEs) occurred.

Seven phase 2 studies have been completed in subjects with neurodegenerative diseases. Three 4-week studies used forced titration and included 62 subjects (60 to 80 years) with possible DAT and nine subjects with advanced PD. A total of 53 of them were exposed to tesofensine. Tesofensine was well tolerated at all doses, i.e., daily doses up to 2.0 mg for the first 3 days (loading doses) followed by daily doses up to 1.0 mg for up to 25 consecutive days. In four dose finding studies of 14 weeks' duration, 1036 subjects with DAT and PD were included and 796 of them were exposed to doses of 0.125-1.0 mg of tesofensine.

In obese subjects, one dose ranging study of 24 weeks' duration (NS2330-001, "TIPO-1") was conducted including 203 obese subjects, with 151 of them exposed to 0.25 to 1.0 mg tesofensine. The most frequent adverse events (AEs) in this study were insomnia, dry mouth, dizziness, and constipation. These events were dose-dependent and categorized as expected for drugs belonging to the same pharmacological class. Beyond that a long-term study, TIPO-4 (an extension study of the "TIPO-1"-study with subjects with uncomplicated obesity), over 48 weeks has been completed. In this study all subjects started on 0.5 mg tesofensine for the first 24 weeks and could be up-titrated to 1.0 mg. The last 24 weeks all subjects received 0.5 mg.

The emerging efficacy and safety profile of tesofensine from the studies in obese subjects has identified a clinically relevant, safe and well tolerated dose range of 0.25 mg up to 0.5 mg.

In total, tesofensine has been evaluated in approximately 170 subjects in studies examining the metabolic and weight loss effects in overweight and obese subjects and in approximately 900 subjects in other indications. Based on the pharmacological profile it can be assumed that tesofensine causes dopaminergic side effects such as insomnia, agitation, hallucinations, and psychoses including delusion, paranoid ideation and depression. The AEs, which were commonly reported in all investigated populations, were insomnia, dry mouth, dizziness, and constipation, which also expressed dose-dependency. In obese subjects the most frequent AEs were dry mouth, headache, nasopharyngitis, nausea, influenza, insomnia, diarrhoea, constipation, and back pain. Psychiatric side effects were more frequently reported in the elderly population (subjects with PD or DAT). Psychotic events, such as hallucinations, were also observed in this elderly population, mostly with high doses (> 0.75 mg/day).

Undesired effects, which have been observed up to now, comprise:

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

1.6 Overdose of Tesofensine

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

1.7 Safety of metoprolol

Metoprolol is a selective β_1 receptor blocker, used in the treatment of, e.g., hypertension, angina pectoris, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure and prevention of migraine headaches.
Metoprolol is available as IR and ER tablets and as solution for i.v. injection.
For further details refer to the SmPC of metoprolol (30).

1.8 Safety of co-administration of Tesofensine and metoprolol

To date, tesofensine tablet and metoprolol tablet have been co-administered to humans in three completed clinical studies. For more details please see section 1.2 in the DDI study (Q-21125), as well as in the TM003 and the phase 2 TM001 the co-administration of the drugs was generally well tolerated. No new or unexpected safety findings have been observed in the study compared to previous studies with tesofensine alone.

1.9 Risk-benefit assessment

The anticipated benefits are reduction in appetite and body weight, body fat, and increased satiety. In addition, attitude towards food and eating should be favourably influenced.

The TM005 protocol has been designed to minimize the risk to participating subjects: strict in- and exclusion criteria are implemented to minimize potential risks and subjects will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs. Metoprolol has already been approved for years, therefore side effects are well known. Subjects who are overweight with confirmed diagnosis of HIO will be eligible for the study only if they do not meet any contraindications or the listed special warnings from metoprolol Summary of Product Characteristics (SmPC). Subjects will only be eligible to participate if they do not have co-morbidities typical for obesity such as hypertension, diabetes or any cardiovascular conditions that are not under control.

Increases in HR and BP may occur due to tesofensine dosing and decreases in HR and BP may occur due metoprolol dosing, thus these effects should be mitigated following administration of Tesomet. Subjects with untreated hyper- or hypotension will not be eligible for the study. Vital signs will be measured at all visits and weekly home measures will be done. Home monitoring of 24H BP/48H HR will be done between screening and baseline, and at Day 84 (± 36) and at Day 168 (÷36/+3).

In the TM001 study 60 overweight or obese patients with T2DM were treated with for 3 months with either co-administration of tesofensine 0.5 mg/metoprolol 100 mg ER or matching placebo. In total one case of palpitations and one case of tachycardia were reported. None of the treatment emergent events were serious and no death occurred during the study.
In general, cardiovascular AEs were most frequently reported in the elderly population, which was characterized by significant co-morbidities, including cardiovascular conditions. Serious cardiovascular AEs were reported only in PD/DAT subjects, in 2% of the subjects in the tesofensine group and in 4% in the placebo group. No clear dose-dependency was observed for any of the cardiovascular events reported in any target population. No serious or severe cardiovascular AEs have been reported to date in obese subjects.

Psychiatric AEs appeared to be associated with high single doses or forced titration of tesofensine and, importantly, in an age group (elderly) and populations (subjects with Parkinson´s or Alzheimer´s disease) different from the population of this study. Insomnia occurred as most prominent psychiatric event but only at higher loading doses. Psychotic events seen in healthy volunteers were associated either with a single dose treatment with more than > 6 mg of tesofensine, or with multiple doses of more than 2 mg/day of tesofensine.
In obese subjects (TIPO-1), a dose ranging study of 24 weeks' duration was conducted including 203 obese subjects, with 151 of them exposed to 0.25 to 1.0 mg tesofensine. The most frequent AEs in these studies were insomnia, dry mouth, dizziness, and constipation. These events were dose-dependent and categorized as expected for drugs belonging to same pharmacological class.

In the TM001 a few cases of anxiety, insomnia, restlessness and sleep disorders were reported.

In conclusion, data from the clinical studies do not suggest that tesofensine 0.25 mg and 0.5 mg once daily in obese or obese subjects with diabetes or up to 2 mg/day (for 7 days) in healthy

volunteers will be associated with a clinically significant undesirable psychiatric adverse effect profile.
Also, no additional risks are expected by the co-administration compared to those known for dosing of tesofensine and metoprolol alone.

1.10 Current treatment strategies

Currently, there are no treatments approved for HIO. Various available strategies for weight loss are tried with mixed results.

1.11 Purpose of this study

The purpose of this study is to investigate the overall safety and tolerability as well as effect on satiety, appetite and weight loss of co-administration of tesofensine/metoprolol treatment in subjects with HIO.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary objectives:

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

Secondary objectives:

- To examine the effect on satiety and appetite from baseline to week 24, and from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on bodyweight from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on body composition from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on quality of life from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine effect on craving for something sweet, salty, savory and fatty from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on thirst from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine effect on glycemic control and lipid profile from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To examine the effect on HR and BP from baseline to week 24, from baseline to week 48 and from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO
- To establish profile of trough values of tesofensine, N-desmethyl-metabolite (NS2360) and metoprolol following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO:
    - Active arm: the first 24 weeks and then continuously up to week 48.
    - Placebo arm: start of treatment at week 25 and then continuously up to week 48.
- To evaluate the effect on BP and HR from baseline to week 24 by 24H home monitoring of BP and 48 H home monitoring of HR
- To evaluate overall safety and tolerability from week 24 to week 48 following co-administration of 0.5 mg tesofensine/50 mg metoprolol treatment in subjects with HIO

2.2 Endpoints

Primary endpoint

- Safety and tolerability will be judged from all safety data collected in the period, including Treatment Emergent Adverse Events (TEAEs), laboratory data, BP and HR measurements

Secondary efficacy endpoints

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

Secondary safety endpoints

- Change on HR and BP from baseline to week 24, from baseline to week 48 and from week 24 to week 48
- Trough values of tesofensine, metoprolol and N-desmethyl-metabolite (NS2360)
    - Active arm: the first 24 weeks and then continuously up to week 48.
    - Placebo arm: start of treatment at week 25 and then continuously up to week 48.
- Change of 24H BP/48H HR and QT from baseline to week 12 and week 24 and from week 12 to week 24 measured by home monitoring
- Number and frequency of AE's and SAE's from week 24 to week 48

3 OVERALL STUDY DESCRIPTION

This is a 24-week double-blind (DB), randomized, placebo-controlled, single-center, safety and efficacy study to evaluate overall safety and tolerability of co-administration of tesofensine/metoprolol in subjects with HIO with a 24-week open-label extension, in total 48 weeks. The study will have two parts:

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

- During part 1 subjects will be randomized to either treatment with co-administration of 0.5 mg tesofensine/50 mg metoprolol (active medication) or matching placebo in 2:1 ratio
- Subjects with T2DM will be stratified evenly to the two treatment arms during randomization
- As an integral part of the study all subjects will undergo regular lifestyle counseling, including guidance in diet, physical activity as well as behavioural modification, during both the part 1 and the part 2 portion of the study

Assessments conducted during each visit are described in the flow chart (FC). Subjects will be fasting for all visits, except the screening visit.

Screening (visit 1, day -7 to -21): Subjects who give the written informed consent will be screened for the study. Subjects will be instructed in having home 24H BP/48H HR monitoring done, the devices will be put on, and instructions handed out.

Baseline (visit 2, Day 1): Blood will be drawn, BP, HR, weight and other endpoints will be collected. Fasting Plasma Glucose (FPG) will be measured on site to ensure eligibility for the study. The FPG measured at Klinisk Biokemisk Afdeling, RH will be the Baseline value. Devices for 24H BP/48H HR will be collected.

DEXA will need to be scheduled in advance so that it can be performed on Day 1.

Randomization (visit 2, Day 1): Following the completion of all Baseline assessments on Day 1, eligible subjects will be randomized to DB treatment with co-administration of tesofensine/metoprolol. The first dose of study medication will be administered on Day 1. Lifestyle counseling will be performed and subjects will receive sufficient study medication until next visits as well as BP meter, diaries and blood glucose (BG)-meter (if applicable).

Treatment period part 1 (visit 2-8): after the Day 1, subjects will visit the site on Days 28, 56, 84, 112, 140 and 168 (±3 days) for safety evaluations, efficacy, PK assessments and medication supply until Day 168 (visit 8). Assessment will include blood sampling, vital signs, weight and various questionnaires. Also, lifestyle counseling will be performed. The subjects will always receive sufficient study medication until next visit as well as a new diary at each visit. At visit 5, Day 84 (± 36) and at visit 8, Day 168 (÷36/+3) devices for home 24H BP/48H HR will be handed out and collected after mutual agreement between the individual subject and the investigator. A phone visit follow-up will be performed at Days 14, 42, 70, 98, 126, 154 and 182 to discuss status and experiences of AEs, hypoglyaemic events, 8-point BG measurements, BP and HR measurements.

Final visit part 1: Visit 8 will be the end of the DB part of the study and all assessments from the Baseline (visit 2) will be repeated.

Treatment period part 2 (visit 8-14, Day 168-336): On Day 168 (±3 days) (visit 8) all subjects still participating in the study if evaluated eligible by the investigator, will be invited for the open-label extension part where all subjects will be given the same dose of tesofensine and metoprolol. A phone visit follow-up will be performed at Days 210, 238, 266, 294 and 322 to discuss status and experiences of AEs, hypoglycaemic events, 8-point BG measurements, BP and HR measurements.

Subjects will be return monthly for evaluations as described in the FC as well as drug supply.

Final visit part 2: At visit 14 subjects will conclude their participation in the study. On that day safety and efficacy assessments will be performed and subjects will be given two days of half dose of metoprolol to take at home in order to gradually reduce the dose of metoprolol and avoid potential undesirable fluctuation in BP.

Follow-up: 45 days (+3 days) after end of treatment a follow-up visit (phone visit) must be performed to discuss experiences of AE's since last dose of trial product.

3.1 Flow chart: blinded treatment visits 1 - 8

	Screening	Randomization	Visit type											End of part 1
			Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	
Visit number	**1**	**2**	**2.1**	**3**	**3.1**	**4**	**4.1**	**5**	**5.1**	**6**	**6.1**	**7**	**7.1**	**8**
Days in relation to visit 2	**-21 to-7**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**
Visit window, days	**-3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
SUBJECT														
Informed Consent	X													
In/ Exclusion Criteria	X	X												
Subject Card dispensing	X													
Randomization		X												
Medical History	X													
Demographics[1]	X													
Concomitant illness	X													
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lifestyle counseling		X		X		X		X		X		X		X
ECG	X							X						X
DEXA		X												X
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X
Diabetes history and diabetes complications[2]		X												
Body examination														
Physical examination[3]	X	X						X						X
Vital signs	X	X		X		X		X		X		X		X
Height	X													
Body weight	X	X		X		X		X		X		X		X

	Screening	Randomization	Visit type											End of part 1
			Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	
Visit number	**1**	**2**	**2.1**	**3**	**3.1**	**4**	**4.1**	**5**	**5.1**	**6**	**6.1**	**7**	**7.1**	**8**
Days in relation to visit 2	**-21 to-7**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**
Visit window, days	**-3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
SUBJECT														
Waist circumference	X	X		X		X		X		X		X		X
Laboratory examination														
Hematology	X	X						X						X
Blood chemistry	X	X		X[9]		X[9]		X		X[9]		X[9]		X
Infectious serology	X	X						X						X
HbA_{1C}	X							X						X
Lipids	X	X						X						X
Endocrine examination[4]		X		X[10]		X[10]		X		X[10]		X[10]		X
Blood pregnancy test[5]	X	X		X		X		X		X		X		X
Fasting plasma glucose (FPG)		X[6]		X		X		X		X		X		X
Blood samples for future examination[7]		X						X						X
Blood samples for back-up		X						X						X
PK sample		X						X						X
Questionnaires														
Satiety and appetite Questionnaires		X		X		X		X		X		X		X
Assessment of craving		X		X		X		X		X		X		X
Assessment of thirst		X		X		X		X		X		X		X
SF-36 questionnaire		X		X		X		X		X		X		X
PHQ-9	X	X		X		X		X		X		X		X

	Screening	Randomization	Visit type											End of part 1
			Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	
Visit number	**1**	**2**	**2.1**	**3**	**3.1**	**4**	**4.1**	**5**	**5.1**	**6**	**6.1**	**7**	**7.1**	**8**
Days in relation to visit 2	**-21 to-7**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**
Visit window, days	**-3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
SUBJECT														
Medication														
Medication dispensing		X		X		X		X		X		X		X
Medication accountability				X		X		X		X		X		X
Dispense meters/ diaries, review of home measures														
Home monitoring of 24H BP/48H HR	X							X[8]						X[8]
Dispensation BP monitor		X												
Review of home measured BP and HR			X	X	X	X	X	X	X	X	X	X	X	X
Dispensing of BG meter[2]		X												
Review of home measured BG and Hypoglycaemic events[2]			X	X	X	X	X	X	X	X	X	X	X	X
Diary dispensation		X		X		X		X		X		X		X
Diary review				X		X		X		X		X		X
Diary collection				X		X		X		X		X		X
Open-Label Extension start														
Open-label extension														X

[1]: Demographics: Date of birth, sex and race

[2]:T2DM subjects only

[3]: Physical examination: Include heart, lung, head and neck exam, and abdominal, neurological and dermatological examination

[4]: Endocrine examination: IGF-1,, free T4, prolactin, LH, Follicle-stimulating hormone (FSH), testosterone (men), oestrodiol (women)

[5]: Female subjects of childbearing potential only

[6]: Plasma glucose at randomization: On site FPG is used for randomized. The FPG measured at Klinisk Biokemisk Afdeling, RH is the baseline value.

[7]: Blood samples for future examination: free fatty acid (FFA), Ghrelin, Glucagon Like Peptide 1 (GLP-1), Gastric inhibitory polypeptide (GIP), adiponectin, leptin

[8]: Devices for home monitoring of 24H BP/48H heart rate (HR) will be put on at Day 84 (± 36) and at Day 168 (÷36/+3) and collected after mutual agreement between the individual subject and the investigator.

[9]: Only creatinine and electrolyte

[10]: Only Thyroidea Stimulating Hormone (TSH) and free T4

3.2 Flow chart: open-label treatment visits 9-14

	Visit type											End of trial	Follow-up - Phone
	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone		
Visit number	**8.1**	**9**	**9.1**	**10**	**10.1**	**11**	**11.1**	**12**	**12.1**	**13**	**13.1**	**14**	**14.1**
Days in relation to visit 2	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**45[9]**
Visit window, days	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**
SUBJECT													
Lifestyle counseling		X		X		X		X		X		X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	
ECG						X						X	
DEXA												X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Body examination													
Physical examination[1]						X						X	
Vital signs		X		X		X		X		X		X	
Body weight		X		X		X		X		X		X	
Waist circumference		X		X		X		X		X		X	
Laboratory examination													
Hematology						X						X	
Blood chemistry		X[7]		X[7]		X		X[7]		X[7]		X	
Infectious serology						X						X	
HbA_{1C}						X						X	

	Visit type											End of trial	Follow-up - Phone
	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone		
Visit number	**8.1**	**9**	**9.1**	**10**	**10.1**	**11**	**11.1**	**12**	**12.1**	**13**	**13.1**	**14**	**14.1**
Days in relation to visit 2	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**45**[9]
Visit window, days	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**
SUBJECT													
Lipids						X						X	
Endocrine examination[2]		X[8]		X[8]		X		X[8]		X[8]		X	
Blood pregnancy test[3]		X		X		X		X		X		X	
FPG		X		X		X		X		X		X	
Blood samples for future examination[4]						X						X	
Blood samples for back-up						X						X	
PK sample						X						X	
Questionnaires													
Satiety and appetite Questionnaires		X		X		X		X		X		X	
Assessment of craving		X		X		X		X		X		X	
Assessment of thirst		X		X		X		X		X		X	
SF-36 questionnaire		X		X		X		X		X		X	
PHQ-9		X		X		X		X		X		X	
Medication													
Medication dispensing		X		X		X		X		X		X[6]	
Medication accountability		X		X		X		X		X		X	
Dispense diaries and review home measures													

	Visit type											End of trial	Follow-up - Phone
	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone	Site	Phone		
Visit number	**8.1**	**9**	**9.1**	**10**	**10.1**	**11**	**11.1**	**12**	**12.1**	**13**	**13.1**	**14**	**14.1**
Days in relation to visit 2	**182**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**45[9]**
Visit window, days	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**
SUBJECT													
Review of home measured BP and HR	X	X	X	X	X	X	X	X	X	X	X	X	
Review of home measured BG, Hypoglycaemic events[5]	X	X	X	X	X	X	X	X	X	X	X	X	
Diary dispensation		X		X		X		X		X			
Diary review		X		X		X		X		X		X	
Diary collection		X		X		X		X		X		X	
End of study													
End of Study Form												X	

[1]: Physical examination: Include heart, lung, head and neck exam, and abdominal, neurological and dermatological exam

[2]: Endocrine examination: IGF-1, TSH, free T4, prolactin, LH, FSH, testosterone (men), oestrodiol (women)

[3]: Female subjects of childbearing potential only

[4]: Blood samples for future examination: FFA, Ghrelin, GLP-1, GIP, adiponectin, leptin

[5]: T2DM subjects only, during the whole study subjects with T2DM will be asked to do 8-point home BG check once weekly

[6]: Dispensation of two half-doses of metoprolol

[7]: Only creatinine and electrolyte

[8]: Only TSH and free T4

[9]: After end of treatment (Last dose of Tesofensine/Tesofensine Placebo)

3.3 Study design

Visit 1 screening (Day -21 to -7)

Potentially eligible subjects will be given written and verbal information about the protocol, study design and potential risk and benefits according to procedures described in section 5. At screening, subjects will be provided with a subject card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

For other screening procedures Please see FC

Visit 2 baseline visit /randomization (Day 1):

On Day 1, following the completion of all baseline assessments, the investigator will randomize subject into one of the treatment arms. The first administration of study medication will be administered at site with investigator, and subject will receive sufficient study medication until next visit.

Given the value measured on site of the FPG ≥ 11.0 mmol/l and all other laboratory results are within the requested limits, the subjects can be invited for an unscheduled visit to have only the FPG re-tested, both on site and at Klinisk Biokemisk Afdeling, RH. Given the on site value of FPG is < 11.0 mmol/l, the subject can be randomized. The re-tested FPG value at Klinisk Biokemisk Afdeling, RH laboratory, should be entered into the electronic case report form (eCRF) as baseline.

Life style counseling including guidance in diet, physical activity and behavioural modification will be performed.

Subject will receive the BP meter and instruction for home measurements of BP and HR.
Subjects will be instructed to do home monitoring of BP and HR twice daily before breakfast and dinner (three measurements each time point), once weekly during the whole study. Subjects will receive a diary for BP and HR reporting.
On days where blood test for PK sampling is taken, time of last dose of study medication should be noted as well.

Subjects with T2DM will also receive BG meters and belonging auxiliaries as well as a diary for BG reporting. These subjects will be asked to do and record the following: once weekly 8-points BG measurements date and glucose level when experiencing hypoglycemia episodes.

A DEXA scan will also be performed at this visit.

For further procedures to be done at visit 2, please refer to the FC.

Treatment period part 1:

Visits 3, 4, 5, 6, 7 (Day 28, 56, 84, 112, 140 (±3 days))
For procedures to be done please see FC.

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 2.1; 3.1; 4.1;5.1;6.1;7.1- phone visits
A phone visits follow ups will be performed to discuss status and experiences of AEs, hypoglycemic events, 8-point BG measurements, BP and HR measurements, and to reinforce behavioural modifications discussed during the counseling sessions.

Visit 8 (Day 168 (±3 days))
Visit 8 is considered to be a more detailed visit for efficacy assessments – end of DB part. For procedures to be done please see FC.

Open-label extension part 2:

Visit 9, 10, 11, 12, 13 (Day 196, 224, 252, 280, 308 (±3 days)**)**
For procedures to be done please see FC.

Visit 8.1; 9.1;10.1;11.1;12.1;13.1- phone visits
A phone visit follow-up will be performed to discuss status and experiences of AEs, hypoglycemic events, 8-point BG measurements, BP and HR measurements.

Visit 14 end of part 2, end of study (Day 336 (±3 days))
Visit 14 is considered to be a final study visit, last patient last visit (LPLV). For procedures to be done please see FC. 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.

Follow-up: A follow-up phone visit must be performed 45 days (+3 days) after end of treatment to discuss experiences of AE's since last dose of trial product.
If the subjects withdraw treatment before visit 14, the follow-up must be made 45 days (+3 days) after the last day of administration of trial product.

3.4 End of study

The end of study is defined by LPLV for TM005. If a subject discontinues from the study medication during the treatment period, a visit will be organized at which the assessments planned for Day 336 will be performed. If a subject refuse to attend a visit, the investigator should make every effort to obtain the information over the telephone from the subject regarding safety.

3.5 Study participants

The target population is adult subjects suffering from HIO. Subjects will mainly be recruited from local population around the site. This study will be conducted at one investigational site in Denmark. Subjects who fulfill all of the following inclusion criteria and none of the exclusion criteria are eligible to enter the baseline phase of the study.

3.6 Inclusion criteria

1. Informed consent obtained before any trial-related activities
2. Males and females, aged 18-75
3. Confirmed diagnosis of HIO
4. BMI ≥27 kg/m^2 (where overweight is related to the HIO)
5. Well managed and stable substitution of hypopituitarism >2 months as judged by the investigator
6. Normal BP or well managed hypertension (only if dose of BP medication(s) has been stable for >2 months)
7. Type 2 diabetes is allowed, but the following criteria must be met:
    - Hemoglobin A1c (HbA1c) <86 mmol/mol
    - Subjects taking GLP-1 analogues must have been on stable dose for >3 months
    - FPG <11.0 mmol/l measured on site

3.7 Exclusion criteria

1. BP ≥160/90 mmHg
2. HR ≥ 90, <50 bpm
3. Hypersensitivity to tesofensine/metoprolol or any component of the products
4. Type 1 diabetes, Cushings disease, acromegaly, hypophysitis, infiltrative diseases or PWS
5. Heart failure New York Heart Association (NYHA) level II or greater, decompensated heart failure
6. Previous myocardial infarction or stroke within the last 5 years
7. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other DSM-III disorders, or any other psychiatric condition, which in the investigator's opinion will interfere significantly with study compliance
8. Physical impairment, which in the investigator's opinion will interfere significantly with study compliance
9. Any clinically significant cardiac arrhythmia
10. Treatment with calcium channel blockers and beta blockers
11. Concomitant use of monoaminooxidase inhibitors
12. Use of recreational medication
13. Bulimia or anorexia nervosa
14. Any agent used for weight loss in the past 3 months, except GLP-1 compounds
15. Untreated hypo- or hyperthyroidism
16. Clinically significant liver (>3x ULN) and/or kidney impairment
17. More than 5% weight loss within the last 3 months
18. Subject is pregnant or lactating or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive method (Spiral or hormonal contraception, birth control pills, implant, transdermal patch, vaginal ring or depot injection)
19. Male subjects not agreeing to use a condom without spermicide or oil-containing products (e.g., lubricants) during sexual activity with female partners of childbearing potential throughout the trial until at least 8 weeks after the last administration of IMP
20. Any contraindication for metoprolol according to the SmPC, e.g. severe peripheral arterial disease, untreated pheochromocytoma, concomitant intravenous administration of calcium antagonists of verapamil and diltiazem, due to the risk of

hypotension, AV conduction disturbances, or left ventricular insufficiency

21. Subject has lactose intolerance or a rare hereditary problem of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency
22. Subject is unable to understand and communicate in Danish language or to understand the protocol requirements, instructions and study-related restrictions, the nature, scope and possible consequences of the clinical study or is unlikely to comply with the study requirements; e.g., uncooperative attitude and improbability of completing the clinical study
23. PHQ-9 (Patient Health Questionnaire):
    a. If a score of at least 5 in question 1 and 2 coming from the area of "More than half the days" or Nearly every day"
       or
    b. PHQ-9 score ≥ 10 when counts from questions 3-5 have been subtracted
       or
    c. If a tic in question 6 in "More than half the days" or "Nearly every day"
       or
    d. Any score > 0 on question 9 at screening and baseline
24. Any suicidal behaviour within the past 30 days since screening
25. Subject has been enrolled in another clinical study within the past three months
26. Any other clinically meaningful condition, which in the opinion of the investigator, would make participation potentially unsafe

3.8 Screening failures

If a subject fails during the screening phase, before randomization, (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. Date of informed consent, reason for screen failure and any AE's before randomization will be entered in the eCRF.

3.9 Premature discontinuation of study medication

A subject may discontinue study medication for several different reasons and after different treatment durations.
The subject may also wish to discontinue study medication, irrespective meeting any criteria.
In the event of an early termination of study medication, all procedures described for a subject completing the study at visit 8 or visit 14 should be performed.
Subjects discontinuing due to AEs will be followed-up until complete resolution of the AE or until there is a satisfactory explanation of the changes observed.
Subjects discontinuing study medication for any reason will be offered to continue in the trial to receive the life style counseling and have the planned study assessments performed.
Subjects should stay in the trial regardless of adherence to randomized treatment, visit schedule or missing assessments. Efforts must be made so that subjects attend and complete all scheduled visit procedures.
Only subjects who decline any further contact with the site in relation to the trial or withdraw consent are considered as withdrawn from the trial.

3.10 Discontinuation

The subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.
If a subject meets a discontinuation criterion, the study medication must be immediately discontinued and the date should be noted in the medical records and eCRF.

Discontinuation criteria
Subjects may be discontinued from study medication if any of the following items is met and documented:

- Pregnancy or not using a reliable method of birth control or breastfeeding
- Investigator's decision
- Acute allergic reaction to study medication
- PHQ-9 (Patient Health Questionnaire):
    a) If a score of at least 5 in question 1 and 2 coming from the area of "More than half the days" or Nearly every day"
    or
    b) PHQ-9 score ≥ 10 when counts from questions 3-5 have been subtracted
    or
    c) If a tic in question 6 in "More than haft the days" or "Nearly every day"
    or
    d) Any score > 0 on question 9 at screening and baseline
- 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 of prohibited medications during the study
- Failure to comply with the study stipulations
- Subject has alanine aminotrasferase (ALT) or aspartate aminotrasferase (AST) ≥ 3 × ULN (confirmed by repeat) with
    a) Total bilirubin ≥ 2 × ULN without simultaneous ALP ≥ 2 times the ULN (confirmed by repeat)
    or
    b) International Normal Ration (INR) (will be assessed, if the above criteria are reached) > 1.5 times the ULN without simultaneous ALP ≥ 2 times the ULN (confirmed by repeat)
    or
    c) The appearance or worsening of symptoms potentially related to hepatic inflammation, e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia in two consecutive measurements within 24 hours
- Subject shows dopaminergic side effects such as agitation, hallucinations, psychoses including delusion, paranoid ideation and depression of moderate to severe intensity, jeopardizing subject safety and requiring medical intervention and supervision

3.11 Withdrawal

The subject may withdraw consent at will at any time. The subject's request to withdraw from the trial must always be respected. Reason for withdrawal will be documented in the subject's source documents and the eCRF.

The end of study form in the eCRF must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. The case book must be signed. Although a subject is not obliged to give his/her reason(s) for withdrawing consent, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

Where the reasons are obtained, the primary reason for withdrawing consent must be specified in the eCRF.

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 case report form (CRF).

3.12 Replacement of withdrawn subjects

Enrolment will continue until a minimum of 12 and a maximum of 25 adult subjects are randomized. Subjects excluded during the screening period (Day -21 to -7) may be considered for another selection visit at a later date but will need to undergo complete rescreening, except if the reason is a FPG > 11.0 mmol/l.

Randomized subjects who withdraw or are withdrawn from the study for any reason will not be replaced.

3.13 Lost to follow-up

If a subject loses contact with the study staff or does not come for the visits, attempts must be made to locate the subject and obtain relevant safety information. A subject cannot be deemed lost to follow-up until at least substantial contacts with family/relatives/family physician have been attempted. Subject information may be retrieved from other health care professionals, medical records or publicly available records. A subject will only be considered lost to follow-up in case vital status cannot be determined at the time of day 336 for that subject.

3.14 Premature study discontinuation

The sponsor has the right to terminate this study at any time. If the sponsor, the investigators, or the CA 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. The following event shall result in an immediate stop to dosing of all subjects and a re-evaluation of the risk-benefit profile:

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

3.15 Study site

The study will be conducted at one site in Denmark

3.16 Study duration

The projected start date for the inclusion of study subjects is:

- Q1 2019 – Q2 2020 – the double-blind part

- Q3 2019 – Q1 2021 – the open-label extension part

The individual study duration for one subject is up to 357 days including screening period (21 days), baseline, together with the blinded treatment part 1 and the open-label treatment part 2 (336 days). The projected duration of the study is ~12-18 months. The end of study is defined by the Last Visit of the Last Subject for TM005.

3.17 Benefits and risks for study participants

It is expected that the combination of tesofensine and metoprolol will be well tolerated. This assessment is based on a large body of experiences from previous pre-clinical 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 site.

Tesofensine

The majority of treatment related AEs 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 AEs in clinical studies in the obese population was 13% with tesofensine and 6% with placebo. BP and HR 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.

Metoprolol adverse reactions – post marketing experience

Please see the SmPC of metoprolol succinate "Orion" 50 mg retard (30).

It is anticipated that subject receiving the study medication will experience a reduction in their body weight and appetite and improvement in their glycaemic control and/or other clinical parameters, beyond what can be achieved by receiving regular dietary and physical activity counseling during the study. That could require change in concomitant medication.

4 TREATMENT OF STUDY PARTICIPANTS

4.1 Description of study medication

IMP

Tesofensine is a serotonin-noradrenaline-dopamine re-uptake 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.

Metoprolol is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration. It has been formulated into ER tablets to provide a controlled and predictable release of metoprolol for once daily administration

For the DB part (part 1), the IMP consists of one carton for each visit containing one bottle of tesofensine 0.5 mg and one bottle of metoprolol 50 mg, both formulated for oral use once a day. For the open-label extension part (part 2), the IMP consists of one carton for each visit containing one bottle of tesofensine 0.5 mg and four blister sheets of 10 tablets of metoprolol 50 mg each.

Placebo

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

4.2 Identity of investigational products

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

ER = extended release

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

4.3 Supply, packaging, labelling and storage

IMPs will be supplied by a third party (KLIFO A/S, Smedeland 36, Glostrup, 2600, Denmark) contracted by Saniona A/S. Tesofensine, metoprolol and placebo tablets will be packaged, labelled and Qualified Person (QP)-certified according to applicable local and regulatory requirements by KLIFO A/S. All supplies of IMPs must be stored in accordance with the manufacturer's instructions. The IMPs will be stored at the study site in a securely locked area, with the temperature monitored, accessible to authorized persons only, until needed for dosing. Tesofensine for home-dosing days will be dispensed to the subjects in appropriately labelled containers together with instructions of use.

4.4 Procedures to assure double blinding

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

- The IMP will look similar to placebo with regard to size, colour and general appearance
- The labelling of the IMP will identify the study and the investigational product but will not indicate the contents. When a patient is ready for randomization, the investigator pick the lowest available randomization number from one of two lists; one list for patients with Drug Metabolism (DM) and one list for patients without DM

4.5 IMP handling procedures at the site

The designated site personnel at the investigational site are responsible for storage of received study medication, 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 site in a secured area with restricted access as instructed on the study kits labels
- Dispensing IMP according to the protocol

An IMP kit will be provided for each patient with a randomization number and enough medication for the initial 24 weeks (+ extra). The patient should be supplied form this kit during participation in the 24 weeks DB treatment.

Another IMP kit will be provided for each patient with a randomization number and enough medication for the open labelled 24 weeks (+ extra) extension period (part 2). The patient should be supplied form this kit during participation in the 24 weeks open labelled extension part.

The investigator and designated site personnel are responsible for study medication kits accountability. The investigator and designated site personnel are 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 designated site personnel in writing. Upon receipt, and as instructed, the investigator or designated site personnel should immediately contact any study subject in possession of the corresponding study medication kits.

4.6 Labels for study medication

The label texts will be translated or adjusted as necessary so that they comply with Annex 13, Danish laws and regulatory requirements and trial requirements.

4.7 Packaging and destruction

Medication will be distributed to the subjects in plastic bottles labelled with the appropriate randomization number for the DB part (part 1) and study medication number for the open-label part. Bottles for the respective IMPs will be identical in colour, size and shape to preserve the blinding of the study during part 1. Unused study medication will be collected by the investigator and designated site personnel. KLIFO is responsible for central destruction of all study medication (partially used and unused).

4.8 Handling of the study medication

Study medication will be distributed to the subjects during the visits 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 at the site. First administration will be done on Day 1, at the site. Subjects will be asked to use study medication every morning, preferably with the breakfast, and not to crush or chew the tablets. Subject will be asked to store the medication at room temperature (15 - 25 °C) and protected from light and return the unused study medication on each in-person (IP) visit at the site.

4.9 Supply and storage of the study medication

Study medication supplies

Tesofensine, tesofensine placebo and metoprolol placebo will be supplied by the sponsor. Commercially available metoprolol 50 mg retard will be purchased directly by KLIFO. IMP will be shipped to the site under temperature control and monitoring. The receiving site 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 site, the following essential documents must be available:

- IEC and CA approval
- IEC and CA approved subject information/informed consent form (ICF)
- Clinical Study Protocol signed by the principal investigator (PI)
- Study agreement/contract signed by the PI

4.10 Study medication compliance

The IMPs 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.

In case a subject, in the opinion of the investigator, experiences an AE that by the investigator is suspected to be potentially related to an undesirable drug concentration of the IMP, the period between dosages can be extended or a drug holiday can be implemented in order to optimally manage the well-being and safety of the subject. Each of these cases should if possible be discussed in advance with the sponsor's medical expert.

4.11 Screening and randomization

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
TM005	01	001

Randomization of eligible subjects to one of the study medication groups will be done at baseline visit Day 1, following successful completion of all baseline assessments, using a study medication number defined by the center-specific assignment list.
Subjects will be randomly allocated to either study medication group in a 2:1 randomization by selecting the lowest available randomization number at the time of randomization. The randomization codes will be generated within the Biometrics Department of the sponsor's Contract Research Organization (CRO) by a statistician and IMP kits for patients will be packaged according to this list. The randomization codes and the complete generation procedure will be filed at a secure place by sponsor's CRO statistician until the study database is closed. The only person on site with access to the code break sealed envelopes will be the principle investigator. The study medication number consists of four digits. In part 1, all kits assigned to a subject will have the same randomization number. In part 2, kits assigned to a subject will have different study medication numbers between visits. This procedure will be checked by the monitor.

4.12 Un-blinding

The part 1 of the study will be DB. Neither the investigators nor the subjects will be informed about the type of subject´s medication. In general, emergency un-blinding is to be done only when absolutely necessary for the clinical management of an individual subject and where stopping the blinded medication is not sufficient in the opinion of the investigator. If possible, the justification for the un-blinding should be discussed with the sponsor prior to un-blinding to ensure that un-blinding is truly necessary and that appropriate steps for subject's welfare and management are being taken.
When un-blinding for the purpose of expedited safety reporting is required by the CA, this will be performed by KLIFO Pharmacovigilance.

<u>Emergency un-blinding:</u>
Emergency un-blinding can be performed using sealed envelopes. The randomization code may only be un-blinded in case of an emergency situation as described above. Whenever a code is broken, the person breaking the code must sign and date the code envelope. The reason for breaking the code must be documented in the subject's medical record. The investigator must immediately inform the sponsor about any un-blinding. The information will be forwarded to the CA and IEC, if necessary, and the principal PI and the sponsor must 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 un-blinding:
After terminating the study, establishing the statistical analysis plan (SAP), 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 un-blinding. Formal records will be kept on measures and dates of each step.

4.13 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 KLIFO.

4.14 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.

4.15 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 CRF indicating the:

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

Any medicinal product, prescribed or over the counter (OTC), including herbal and other nontraditional remedies, is considered a concomitant medication. Prior and concomitant medication use will be recorded for the 30 days prior to screening until Day 336. Prior and concomitant medication use is not permitted from 2 weeks before admission until discharge (occasional use of paracetamol up to 2 g/day or other Non-Steroide Anti-Inflammatoriske Drugs (NSAIDs) and hormonal contraception is permitted). However, concomitant medication use may be warranted for the treatment of AEs, a list of prohibited medication is provided in Appendix 8.7, with emergencies being the exemption.

4.16 Prohibited medication

Please refer to Exclusion Criteria and to Appendix 8.7

5 STUDY PROCEDURES

5.1 Site procedures

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, one original forms for written informed consent will be given to the subjects for signature. One copy 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.

Demography will be recorded at screening and consists of:

- Date of birth
- Sex
- Race

Medical history

Medical history is a medical event that the subject has experienced in the past. Only relevant and significant medical history as judged by the investigator should be recorded. Findings of specific medical history described below should be entered on the specific forms.

ECG

An ECG will be performed at the visits specified in the FC.
The investigator or delegate must sign, date and interpret the ECG by using the following categories:

- Normal
- Abnormal: Diagnose and statement of whether the result is clinically significant? (Yes/No)

Clinically significant is an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example, change of medicine dose or more frequent follow-up due to the abnormality. If the result is clinically significant, the investigator must report such an abnormal finding as an AE or SAE.

ECG performed at screening will be considered as baseline.

Concomitant illness

A concomitant illness is any illness that is present at the start of the trial (i.e., at the screening visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.
Any change to a concomitant illness should be recorded during the trial. Any clinically significant worsening of a concomitant illness must be reported as an AE.

Concomitant medication
A concomitant medication is any medication, other than the trial product, which is taken during the trial, including the screening and follow-up periods. Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each visit as they occur. The investigator must assess the concomitant medication at every visit for any changes.
The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.
If a change in concomitant medication is due to an AE, then this must be reported according to Section 6.2 .

Vital signs
Vital signs include body temperature, pulse rate and BP.

BP
For BP, measurement with a precision of minimum 2 mmHg must be performed. The value must be used to evaluate eligibility of the subject in relation to exclusion criterion no 1. This means, that if the BP value obtained at visit 1 and/or visit 2 exceed BP>160/90 mmHg, the mean value from the 24H BP measurements between visit 1 and 2 can be used to evaluate eligibility of the subject in relation to exclusion criterion no 1. The method for measuring systolic and diastolic BP needs to follow the standard clinical practice at site, but as a minimum, the following guideline must be adhered to:
Avoid caffeine, smoking and exercise at least 30 minutes prior to measuring the BP. BP should be measured in a sitting position, with the legs uncrossed, the back and arms supported. The subject should be sitting for five minutes before the measurement is taken. The same arm and an appropriate cuff size should be used for BP measurements at all visits.
Subjects who during the study exceed predefined values BP>160/100 mmHg will be treated at the discretion of the investigator per established guidelines to improve the subjects BP control while remaining in the study.

Physical examination
Physical examination will be performed at the visits specified in the FC. Physical examination should include heart, lung, head and neck exam, and abdominal, neurological and dermatological exam, and must be recorded in the subject's medical record and eCRF. Any abnormal, clinically significant findings at screening (visit 1) must be recorded as a concomitant illness.

Body weight
The body weight should be measured at all site visits without shoes, on an empty bladder and only wearing light clothing. It should be measured on a digital scale to the nearest 0.1 kg using the same scale throughout the trial. The scale must be calibrated yearly as a minimum.
BMI will be calculated according to below equation with weight assessment from visit 1 data and must be in accordance with inclusion criterion 2.
BMI will be calculated as follows:
BMI = weight (kg)/height2 (m^2)
Height is measured at screening without shoes to the nearest cm with one decimal.

Waist circumference

Will be measured at the specified visits (see FC) and is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest. Waist circumference is measured in the horizontal plane and rounded to the nearest cm using a non-stretchable measuring tape. The same measuring tape should be used throughout the trial. The subject should be measured in a standing position and wearing light clothing. The subject should be standing, feet together with arms at the side and waist accessible. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The subject should be asked to breathe normally.

Pregnancy test
Female subjects of childbearing potential must be instructed to use adequate contraceptive methods (please see below) throughout the trial and until 8 weeks after end of treatment.
Blood pregnancy test will be done for any woman of childbearing potential at the site at every visit.
Further, urine stick pregnancy tests will be performed before every DXA scan, if applicable by local procedures.

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

Female subjects:
Women of childbearing potential must be using highly effective methods of birth control (Spiral or hormonal contraception, birth control pills, implant, transdermal patch, vaginal ring or depot injection).
The subjects should be using the same method for 3 months prior to screening and continued until at least 8 weeks after the last administration of IMP.

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

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

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

DEXA for determination of body composition
Fat mass of abdomen and liver will be determined non-invasively using DEXA. The DEXA machine will be operated according to local specifications.

Diabetic history and diabetes complications:
For T2DM subjects the following information must be collected regarding their diabetes history and related complications.

- History of hypoglycemic events:

  - Awareness hypoglycaemia (yes / no)
  - Type (minor/major/nocturnal)
  - Frequency
- Date of diagnosis of T2DM
- Information regarding diabetes complications including date of onset in case of:
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Macroangiopathy (including peripheral vascular disease)

Diabetes history and diabetes complications, must be recorded on the designated form in the eCRF.

HbA_1C
Blood samples will be drawn at the specified visits (see flowchart) for measurement of HbA_1c. Subjects who during the study exceed predefined values of HbA1c (>10%) and FPG >11.0 mmol/l) will be treated at the discretion of the investigator per established guidelines to improve the subjects glycaemic control while remaining in the study.

Fasting plasma glucose
FPG is measured at specified visits (see flowchart) in order to evaluate metabolic control. The subject must attend these visits fasting.
FPG measured at visit 2 will be considered as baseline.

Fasting requirements
The subjects should be fasting when attending some visits, please see FC.
Fasting is defined as at least 8 hours without food and drink intake, except water and other prescribed medication. Trial product and other glucose lowering agents should be withheld on the day of the visit until blood sampling has been performed. If the subject attends a fasting visit in a non-fasting state, the blood sampling should be re-scheduled within the visit window.

Study questionnaires and VAS scales:
Study questionnaires are used to collect clinical data for all subjects enrolled in the study at the visits specified in the FC. The questionnaires are linguistically validated to fluent language of all subjects participating. The VAS scales are psychometric measuring instruments designed to document the characteristics of disease-related symptom. The questionnaires and VAS scales must be completed by the subject and should preferably be completed after conclusion of all fasting-related activities, but before any other visit-related activities. Subjects should be given the opportunity to complete the questionnaires by themselves without interruption.

Questionnaires and VAS scales used in the study:

- The CSS = (satiety + fullness + (100−prospective food intake) + (100−hunger))/4. VAS scales (satiety, fullness, prospective food intake and hunger) are used to examine the effects on satiety and appetite
- VAS scales measurements of craving on something sweet, salty, savory and fatty (mean of the four) to examine the effects on craving
- VAS scale to examine the effects on thirst
- SF-36: To examine the effects on quality of life
- PHQ-9 (Patient Health Questionnaire) score to assess development of depression.

Short Form 36 v2.0 acute
Short Form 36 v2.0 acute (SF-36) is a 36-item, patient-reported survey of patient health. SF-36 measures the subject's overall HRQoL (health related quality of life) on eight domains: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

PHQ-9:
The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression.

- The PHQ-9 incorporates DSM-IV depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow-up, non-scored question on the PHQ-9 screens and assigns weight to the degree to which depressive problems have affected the patient's level of function.

In addition, great care will be exerted during the course of obtaining medical history, particularly focusing on psychiatric diseases and should any signs of on-going depression be found, these subjects will not be included into the study, as in accordance with exclusion criteria 7 and 23.

Home monitoring of 24H BP/48H HR
Home monitoring of 24H BP/48H HR will be done between screening and baseline, and at Day 84 (± 36) and at Day 168 (÷36/+3).

Subjects will be instructed in having home 24H BP monitoring done, the devices will be put on at the Medical Endocrinology Department, RH, and a written instruction will be handed out.

The result of 24H BP home monitoring will be evaluated by the investigators at the Medical Endocrinology Department, RH.

The device for 48H HR home monitoring will be put on at the Cardiology department B, RH, instruction will be provided and a written instruction handed out.

The result of the 48H home monitoring will be evaluated by a cardiologist from Cardiology department B, RH, and the result provided as in a PDF document.

Data from the 24H BP/48H HR home monitoring will be evaluated blinded before database release (DBR) and be kept blinded until after DBR.

Lifestyle counseling
All subjects will receive a written guide in diet modification, physical activity and behavioural modifications, but also a verbal guidance in connection to the visit by a qualified dietician. For further instructions, please refer to Appendix 8.8.

<u>Diet modifications</u>
Subjects will receive guidance to follow an energy reduced and moderate low fat diet. The goal is a macronutrient distribution in the diet of app 30% energy from fat, app 20% energy from protein and app 50% energy from carbohydrates.

An energy restriction of app -300 kcal/day =4,2 kilojoule (KJ) will be based on a calculation of body composition and hereafter be multiplied by 1.3-1.5 PAL (Physical Activity Level) dependent of the subject's physical activity level)

Physical activity:
All subjects will receive guidance in physical activity. The subject will be guided to 30 min physical activity pr day.

Behavioural modification:
Subjects will receive guidance in behavioural modifications including techniques for sticking to their life style change.

5.2 Laboratory evaluations

Laboratory samples will be collected from subjects at the site, and will be shipped to the Klinisk Biokemisk department at RH for analysis in ambient conditions, except samples for PK, future tests and back-up.
The investigator will receive the data from laboratory safety analyzes from Klinisk Biokemisk department at RH and will review, evaluate, sign and date the laboratory report and enter the data into the eCRFs. 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.
The investigator´s evaluation will be entered in the eCRF 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 analyzes not requested in the protocol but produced automatically in connection with the requested analyzes 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 (except for samples for future tests and back-up samples) 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 analyzed by Klinisk Biokemisk department at RH.
- **Blood chemistry**: creatinine, electrolyte, gamma glutamyl transferase, aspartate aminotransferase, ALT, alkaline phosphatase, GFR and urea will be analyzed by Klinisk Biokemisk department at RH.
- **Infectious serology:** Hepatitis B surface antigen, Hepatitis C antibodies, HIV-1/2 combi will be analyzed by Klinisk Biokemisk department at RH.
- **HbA1c** will be analyzed by Klinisk Biokemisk department at RH.
- **Lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides),** will be analyzed by Klinisk Biokemisk department at RH.
- **FPG test** before taking the BG test, subject will not be allowed to eat anything for at least eight hours. FPG will be measured on site to ensure eligibility for the study. The FPG measured by Klinisk Biokemisk department at RH will be the baseline value.
- **Endocrine examination**: IGF-1, TSH, free T4, prolactin, LH, FSH, testosterone (men),

oestradiol (women) will be analyzed by Klinisk Biokemisk department at RH.

- **Blood samples for future tests**: free fatty acid (FFA), Ghrelin, GLP-1, GIP, adiponectin, leptin. The evaluation will be done by investigator selected external laboratory. The samples will be stored in a coded research biobank in Endokrinologisk laboratory at RH until analysis.
- **Blood samples for back-up**: Samples are collected to ensure back-up material for" future tests", or to evaluate new ideas in a later research project. Research of new ideas will have to await accept from the IEC of a new research project and permission from the individual subjects. The samples will be stored in a coded research biobank in Endokrinologisk laboratory at RH until analysis.
- **PK Sampling** will be evaluated for presence/absence of tesofensine/metoprolol and N-desmethyl-metabolite (NS2360). The evaluation will be done by sponsor selected external laboratory Covance. The samples should be stored at site until further instructions are provided by sponsor.

5.3 Total amount of blood

Each subject will have less than 400 ml of blood collected over the course of the entire study (from Screening to End of Study, but not including repeat or additional tests ordered by the investigator), which presents no undue risk to the subjects.

Approximate total amount of blood for each subject

Assessment	Sample Volume (ml)	Number of Samples	Total Blood Volume (ml)
Pharmacokinetics (tesofensine, N-desmethyl-metabolite (NS2360) metoprolol)	7.5	5	37.5
Lipids	4.0	5	24
Hematology and infectious serology[1]		5	0
HbA1c	3.0	5	15
FPG	2.0	13	
Blood chemistry and blood pregnancy test	3	14	42
Endocrine examination	12.0	5	60
TSH and free T4[1]	0	8	0
Blood samples for future tests	17.0	5	85
Blood samples for back-up	24.0	5	120
Total Blood Volume[2] per Subject in entire study			**383.5 ml**

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

[2] Excluding repeat laboratory investigations.

5.4 Home measurements by subjects

Subjects will be asked to perform several procedures at home and will be asked to record the following in the diary:

- BP and HR

- Subjects will carry devices for Home monitoring of 24H BP/48H HR between screening and baseline, and at Day 84 (± 36) and at Day 168 (÷36/+3)
- Date and time for taking study medication the day before a visit where PK samples are taken

T2DM subjects will be requested to further record the following;

- 8-point BG profile
- Hypoglycemic events

The subjects should be clearly instructed in the procedures and this should be documented in the subject's medical records.

BP and HR

Subject will receive a BP meter for measuring BP and HR at home. Subjects will be instructed to measure their BP and HR two times a day, before breakfast and before dinner (three measurements each time point), ones weekly during the whole study. The subject must note down the three values for each measurement for respectively BP and HR. The subjects will be instructed in how to use the device and the instruction should be repeated at regular intervals as needed and documented in the medical record. Subjects should also be instructed in how to record the results of the BP and HR measurements correctly in the diaries. Data must be transcribed into the eCRF during or following the site visit.

The subject must be instructed to follow below procedure:

- Subject should avoid food immediately before the measurement. Subject should go to the toilet before BP measurement. A full bladder can increase BP 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 BP and pulse, 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 BP. 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 appropriately sized cuff should be always used!
- Three measurements should be performed
- The subject must note down the three measurements in the diary

Date and time for taking study medication before a visit

The day before a visit, the subject must note down in the diary, the date and time for taking study medication. This must be entered into the eCRF during or following the visit.

8-point BG measurement

T2DM subjects will be provided with a BG meter including auxiliaries. The subjects will be instructed in how to use the device and the instruction should be repeated at regular intervals as needed and documented in the medical record for the subject.

Subjects should be instructed in how to record the results of the 8-point BG measurements in

the diaries. The record of each BG value should include date, time and value.

Subjects will be instructed to perform 8-point BG measurement once weekly.
The BG measurement should be measured and recorded in the diary at the time points listed below. The record of each BG measurement must include date, actual time point and the plasma glucose value.

Time points for 8-point BG measurement

- Before breakfast
- 90 min after start of breakfast
- Before lunch
- 90 minutes after start of lunch
- Before dinner
- 90 min after start of dinner
- At bedtime
- Before breakfast

Data must be transcribed into the eCRF during or following the site visit.

Hypoglycemic events
If the subject experiences a hypoglycemic event, the following should be recorded in the diary:

- 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

This information must be entered into the eCRF during or following the visit.

Home monitoring of 24H BP/48H HR
Home monitoring of 24H BP/48H HR will be done between screening and baseline, and at Day 84 (± 36) and at Day 168 (÷36/+3).

Subjects will be instructed in having home 24H BP monitoring done, the devices will be put on at the Medical Endocrinology Department, RH, and a written instruction will be handed out.

The device for 48H HR home monitoring will be put on at the Cardiology department B, RH, instruction will be provided and a written instruction handed out.

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. SUSARs will be reported to the CA and IECs according to local regulations, and will be followed-up until the resolution of the event.

6.1 Definitions

An 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 and first doses of IMP given (treatment emergent AE) 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 (DMP).

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 AE 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 related	The AE is clearly related to the study treatment – i.e. an event that 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 AE 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 with the study treatment/IMP 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 stopped/withdrawn
Decreased frequency of dosing (or drug holiday)
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 (IB) for an unauthorized study treatment, or SmPC for an authorized product.

6.4 Serious adverse event

A 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- 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 everyday 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

The suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction, whose nature or severity is not consistent with the applicable product information.

6.6 Procedures for recording adverse events

AEs will be collected with a non-leading question at each clinic visit and at phone visits: "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 fulfill 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 AEs, 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 CRF.

7.7.1 Adverse events of Special Interest and Reporting Procedures

Adverse Event of Special Interest (AESI) is a noteworthy event for a product or class of products that a sponsor wants to monitor carefully. It can be serious or non-serious, or it be a potential precursor or prodrome for more serious medical conditions in susceptible individuals. AESI have been identified based upon mode of action for the investigational product and previous experience with the investigational product and falls into the categories of psychiatric disorders and cardiovascular disorders.
In case of an AESI sponsor advice investigator to consider to make a timely referral to psychiatrist or cardiologist as appropriate, pending on the patient's clinical condition and the type of AESI.

For **Psychiatric disorders** the AESI areas is listed below

- **Mood disorders and disturbances including various types of depressions**, where the patient may present affect alterations, emotional and mood disturbances such as anger and mood swings as well as depressive disorders including major or suicidal depression

- **Dissociative disorders**, where the patient may present various forms such as dissociative amnesia, identity disorder or de-personalization/ de-realization disorder

- **Disturbances in thinking and perception**, where the patient may present delusional symptoms, thinking disturbances, hallucinations and perception disturbances

- **Manic and bipolar mood disorders and disturbances,** where the patient may present various forms of bipolar disorders and various mood alterations such as hypomania/mania

- **Schizophrenia and other psychotic disorders**, where the patient may present various forms of psychotic disorders, delusional disorders as well as Schizoaffective and schizophreniform disorders

- **Suicidal and self-injurious behaviors, where** patient may present suicidal ideation, suicide attempt, suicide threat or other forms

For **Cardiovascular** disorders the AESI areas is listed below

- **Cardiac arrhythmias,** the patient may present rate and rhythm disorders including but not limited to supraventricular arrhythmias, ventricular arrhythmias including cardiac arrest

- **Cardiac disorders, signs and symptoms,** where the patient may present various cardiac hypertensive complications such as hypertensive heart disease or cardiomegaly

- **Vascular hypertensive disorders,** where the patient may present malignant hypertension complications including hypertension complications such as cardiomegaly and other types of hypertension such as procedural hypertension or essential hypertension

Reporting: The investigator must complete and submit an AESI report and in any case within 72 hours of having received information on the AESI. The initial report can be followed by a follow-up report as soon as the investigator obtains more specific information on the event. All AESIs must be reported by investigator to the KLIFO Pharmacovigilance within 72 hr. Such events will be documented in the best possible detail on the AESI Report Form and can also be transmitted to the sponsor by email within 72hr. The contact information of the KLIFO Pharmacovigilance department is as follows:
Email: pharmacovigilance@klifo.com
or fax: +45 39 209 045

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.
If the investigator learns of an AESI occurring to a subject after the treatment of that subject has ended, this should be reported to the sponsor within 72 hours from the investigator becoming aware of the event. AESIs identified by the investigator after the end of the trial should be reported to the sponsor within 72 hours from the investigator becoming aware of the event.

7.7.2 Pre-existing conditions

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

7.7.3 Overdose

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

should be considered. 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 KLIFO Pharmacovigilance using the same expedited reporting timelines as for SAEs (within 24 hours).

7.7.4 Pregnancy

Any pregnancy that occurs in a female subject or the female partner of a male subject during trial participation until at least 8 weeks after the last administration of IMP must be reported to KLIFO Pharmacovigilance on a pregnancy report form using the same expedited reporting timelines as for SAEs (within 24 hours). The investigator will arrange for the pregnant person to be counseled by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant person should continue until the outcome of the pregnancy is known. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study medication. All data related to pregnancy, pregnancy outcome, and SAE associated with pregnancy will also be recorded in a safety database maintained by KLIFO Pharmacovigilance Service. Consent to report information regarding pregnancy outcomes has to be obtained from the mother and the (where possible) the father.

7.7.5 Water retention and/or hyponatremia

Patients with hypothalamic obesity may take medication such as desmopressin and precautions to avoid hyponatremia must be taken in case of concomitant treatment with drugs which are known to induce syndrome of inappropriate antidiuretic hormone secretion (SIADH) such tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, carbamazepine and NSAIDs.
Additive antidiuretic effect between Tensofensine and desmopressin has not been confirmed but based on mechanism of action, as a non-selective inhibitor of serotonin reuptake, it may be anticipated that an additive antidiuretic effect of Tensofensine may lead to increased risk of water retention and/or hyponatremia.
Patients should carefully have the serum sodium monitored and in case of decreasing values, patients should be called for unscheduled visits.

7.7.6 Hypoglycemic events in subjects with T2DM

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

All plasma glucose values:

- ≤ 3.9 mmol/l (70 mg/dl) or
- > 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

- ≤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 administrated to the subject by another person

Nocturnal hypoglycaemic episode

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

7.7.7 Development of depression

In case of depression or suicidal ideation/behaviour, it should be evaluated if the subject fulfils the criteria for discontinuation from the trial (section 4.10.1). The event must be reported as an AE. Appropriate treatment and careful monitoring of the subject should be initiated as per local clinical practice. A subject should be referred to a Mental Health Practitioner (MHP) if he/she has:
1. symptoms of moderate or more severe depression,
2. or any suicidal behaviour,
3. or any suicidal thoughts with some intent to act, irrespective of whether accompanied by a specific plan.

In case the subject refuses to consult the MHP, the investigator must state in the medical records whether it is considered safe for the subject to stay in the trial.

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. All SAEs must be reported by investigator to the KLIFO Pharmacovigilance within 24 hr. Such events will be documented in the best possible detail on the SAEs Report Form and can be also transmitted to the sponsor by email within 24hr. The contact information of the KLIFO Pharmacovigilance department is as follows:

Email: pharmacovigilance@klifo.com
or fax: +45 39 209 045

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. If the investigator learns of a SAE occurring to a subject after the treatment of that subject has ended, 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. SAEs identified by the investigator after the end of the trial should be reported to the sponsor within 24 hours from the investigator becoming aware of the event, if the causality to the investigational study product cannot be excluded.

All data updates should be recorded in the CRF as appropriate, and further documentation as well as additional information (e.g. laboratory data, concomitant medication, subject status) should be sent (by email) 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.

KLIFO will make expedited reports of all SAEs that are both unexpected and causally related to the IMP, to the CA, IECs as appropriate and to the investigators.

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.

7 DESCRIPTION OF STATISTICAL METHODS

7.1 Description of statistical methods

KLIFO 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 KLIFO'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 SAP, which will be prepared before data base lock after DB part. Should any changes of the statistical analysis be implemented, they will be described in the corresponding section of the final study report. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.3 or later.

7.2 Sample size calculation

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

7.3 Selection of subjects for analyses

The following analysis sets are defined in accordance with the ICH-E9 guidance (10):

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

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

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

The analyses of the primary and secondary safety endpoints will be based on the Safety Analysis Set.
Analyses of secondary efficacy endpoints will be based on the mITT Population. Additionally, sensitivity analysis may be performed on the PPP in case mITT and PPP differ.
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 treatment group the subjects are assigned to. The blinding of the treatment groups will be maintained for those involved in allocating subjects to the analysis sets (including, but not limited to: Statistician, Statistical Programmers, Data Managers, and Medical Expert of Saniona) until data are released for statistical analysis. The results of the PK measurements must not be entered in the database prior to database lock (DBL). Furthermore, outliers will be identified by data review according to ICH-E9 (10), and a dummy-randomization. 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 DBR. 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 (CSR). The un-blinding will take place after the last subject last visit (LSLV) of the double blinded part.

7.4 Statistical methods

All analyses will be performed in two steps – first after the completion of the DB part, then following the completion of the open-label extension part. As the primary endpoint is at week 24, no data will be changed that could affect the endpoints after un-blinding.
All primary and secondary endpoints will be summarized by treatment and visit using descriptive statistics. Continuous endpoints will be summarized by non-missing counts, mean, median, standard deviation, minimum and maximum value. Categorical endpoints will be summarized by frequency counts (N) and percentages (%). Moreover, complete listings of individual values for all endpoints will be provided.
Individual and mean curves for the 24 h. 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 mITT population, PPP and Safety Analysis Set. Subjects withdrawn from the study will be listed including the primary reason for withdrawal. The primary reasons for withdrawal will be summarized.

7.5 Analysis of the primary endpoint

No inferential statistical test will be performed for the primary endpoint.
Safety and tolerability will be judged based on the following:

- The number and type of TEAEs during the first 24 weeks
- Change in laboratory data (hematology and blood chemistry) from Baseline to week 24
- Change in BP and HR from Baseline to week 24

Each TEAE will be evaluated for duration, severity, seriousness, and causal relationship to the study drug. The action taken and the outcome will also be reported.
The TEAEs will be summarized overall. The number and percentage of subjects experiencing any TEAE will be summarized and presented by system organ class and preferred term. The TEAEs will also be presented by severity, by relationship to study drug, and by seriousness.
Laboratory data, BP and HR will be listed. Any abnormalities will be reported, clinically relevant or significant abnormalities will be additionally flagged.
Changes in Laboratory data, BP and HR from baseline to week 24 will be summarized descriptively by treatment arms. Shift tables will also be provided.

A more detailed description will be provided in the SAP.

7.6 Analysis of the secondary endpoints

Continuous secondary efficacy endpoints will be compared between treatment arms by means using analysis of covariance (ANCOVA) including treatment as fixed factor and baseline value as covariate. Estimates and 95% confidence intervals (CIs) of treatment differences will be calculated.

First, changes from baseline to week 48 will be compared between treatment arms. Additionally, changes from week 24 to week 48 may be compared between treatment arms. When comparing changes from week 24 to week 48 the baseline value will still be Day 1 value.

7.7 Safety criteria

Addition to analyzes related to the primary endpoint the following safety criteria will be analyzed:

- AEs
- Clinical labs (Hematology, Blood Chemistry)
- ECG
- Vital signs
- Physical examination
- Home monitoring 24H BP/48H HR

All safety analyses will be based on the Safety Analysis Set.
Continuous data will be summarized separately for DB and open-label parts using non-missing counts, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized separately for DB and open-label parts using counts and percentages.

7.8 Handling of missing and doubtful data

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

7.9 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. Patients will get direct access to the eCRF to answer the electronic questionnaires and VAS scales; the eCRF will therefore contain source data for these questionnaires and VAS scales. 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, analyze, verify and reproduce any records and reports that are important to the evaluation of the study. Any party (e.g., domestic and foreign CA, 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 medical record for 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 AEs.

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 CA. 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. The eCRF can be used as source data for data not required to the written the patient medical records at site e.g. drug accountability and questionnaires. The investigator will complete a source data location list defining where the source of each data point is recorded. Source data will be archived for the maximum period of time permitted by local requirements.

<u>The following documentation is considered as source documentation for this study:</u>

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

<u>The following information must be entered in the subject's source documents:</u>

- Subject identification number
- Gender, body measurement
- Medical history and concomitant illness

- Known duration of HIO
- 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.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Definitions

Quality assurance (QA)

A 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 IMP were reported to the sponsor. The involved CRO will implement a QA system for their respective study-related activities.

Quality control (QC)

The monitor will visit the site 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 CRF 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 QA 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 IMP 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 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 CA.

10.3 Ethics committee

This protocol, a sample subject information sheet and ICF, 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 IB
- Reports of AEs that are serious, unlisted and associated with the IMP
- All protocol amendments and revised ICFs (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 and CA about the study completion. Furthermore, he/she will provide the synopsis of the final report to the IEC and CA 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 CA 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 CA. 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, CA, 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 CRF 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 QA auditor or an IEC/CA 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 CRFs 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 CRFs 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 and randomization 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 site to ensure quality of data and subject safety. Data entered in the eCRFs will be available for review by the study monitor and KLIFO Clinical Data Management. The eCRF data will be reviewed remotely for logical discrepancies, missing values and trends. 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 Clinical Research Associate (CRA) will review data remotely as preparation for onsite visits. 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 QA 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. Details regarding monitoring are included in the Study Monitoring Plan.

In general, during monitoring visits the monitor will ensure that the study is being conducted according to the protocol, 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 the CRO KLIFO. The complete Data Management process will be described in detail and agreed on in the DMP for this study.

11.4 Case report forms

The Data Management Department of KLIFO will provide the eCRFs. All further information regarding the eCRFs and the data flow will be described and agreed on in the DMP for this study.

DBL
When the last patient has completed week 24, all data entry, validation and medical encoding activities will be finalized before the database will be locked. All data pertaining to the first 24 weeks will be locked before un-blinding the treatment for analysis.
When the last patient has completed week 48, all data will be cleaned all unnecessary user privileges to the study will be removed, except for the data manager who will perform the DBL. The audit trail report will be reviewed to ensure that no data pertaining to the first 24 weeks have been changed and if this is the case, each change will be described on the CSR for week 48.

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 CRF for the sponsor. The investigator will ensure that this secret list is maintained securely for a period of 25 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, ICG 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 Saniona.

13 PUBLICATION POLICY

13.1 Reporting and publication

KLIFO will prepare a study report after completion of the DB 24-week treatment and another study report after the completion of the entire 48 weeks. The sponsor representative will sign the final study report intended to be submitted to the CA.

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.

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8. APPENDICES

8.7 Appendix 1 - List of prohibited medication

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

8.8 Appendix 2 – Instruction in diet and physical activity

All patients will receive written instructions in exercise, behaviour modification and dietary instruction, but they will also careful instructions at frequent visits by a registered dietician.

See below for description of the exercise, behaviour modification and dietary instruction.

Physical activity
All participants will receive instructions to be physically active at least 30 minutes per day.

www.bevaegdigforlivet.dk, www.altomkost.dk (de 10 kostråd)

Behaviour modification
All participants will receive instruction on behavioural modification. The behavioural modification involves techniques to change unhealthy lifestyle

Material:
www.altomkost.dk: de 10 kostråd,
https://ernaeringsfokus.dk/materialer-og-links/materialer-til-bestilling-og-dowload/vidste-du-at https://hjerteforeningen.dk

Dietary intervention
All participants will be instructed to follow a low-calorie, moderately low fat diet. The target macronutrient composition of the diet is: Approx. 30% of total energy from fat, approx. 20 % from protein and approx. 50% from carbohydrate.

The diet is designed to provide -300 kcal/d (1 kilocalorie (kcal) = 4.2 kilo joule (kJ)) less than the individually estimated energy requirement based on an initial estimated resting metabolic rate based on estimates of body composition, and subsequently multiplied by 1.3 -1.5 (PAL).

Subjects are given oral and written instructions relating to these targets, using individually tailored diet prescription plans [example below]. The subjects themselves purchase all food items

Calculation of total energy expenditure
Harris Benedict equation for calculation of total energy expenditure (TEE) using basal energy expenditure (BEE) and physical activity level (PAL):

TEE = BEE * PAL

BEE

For men,
BEE = 66 + (13.8 x weight/kg) + (5 x height/cm) - (6.8 x age/years)

For women,
BEE = 655 + (9.5 x weight/kg) + (1.8 x height/cm) - (4.7 x age/years)

Physical activity level (PAL)

PAL is estimated at 1.3 for most participants

PAL is estimated at 1.5 for very active participants (> 2 hours a week of high intensity sport, e.g., cycling, spinning, running, rowing, etc.)

Calorie-restricted diet

Calorie-restricted diet = TEE – 300 kcal

Example:

70-year-old man

Weight 90 kg

Height 170 cm (BMI: 31 kg/m^2)

PAL: 1.3

BEE = 66 + (13.8 x 90) + (5 x 170) – (6.8 x 70)

= 1682 kcal/d

TEE = BEE * PAL

= 1682 x 1.3

= 2187 kcal/d

Calorie-restricted diet: 2187 kcal – 300 kcal

= **1887 kcal** (~8 MJ)

Dietary counseling

The first meeting: The dietitian will ask the participant about dietary habits, patterns and preferences for food etc. The participants' answers will be used to prepare a personal diet plan that furthermore meets the macronutrient distribution of approx. 30 E% from fat, about 20 E% from protein and about 50 E% from carbohydrate and -300 kcal less than the individually estimated energy requirement per day.

The diet plan is prepared in such a way that it is possible for the participant to choose for example different breakfast suggestions, so the participant has the opportunity to choose for example bread one day and oatmeal the next.

Additional guidance material

In combination with the diet plan, the participants will be guided to follow the official Danish dietary advice and recipes from the Danish Heart Association and the like.

www.altomkost.dk, www.hjerteforeningen.dk, www.ernaeringsfokus.dk.

Example of a diet plan of 8000 kJ

Morning:	1 slice of	Rye bread
	1 slice of	wholemeal bread
	Scraped	Butter/margarine
	1 slice of	Cheese 30+
	2 teaspoon	Jam
	1 glass	Milk (max. 0,5 %)
Snack:	1	Fruit
	10 pieces	Almonds/nuts
Lunch:	2 slices of	Rye bread
	Scraped	Butter/margarine
	4 x	Cold cuts: ex: egg, fish, lean meat, cottage cheese
	2 teaspoon of	Mayonnaise or similar
	½ plate of	Vegetables
Snack:	2 slices of	Whole grain crispbread OR
	1 slice of	Rye bread/wholemeal bread
	2 slices of	Cheese 30+
	1	Fruit
Dinner:	3 medium	Potatoes OR
	2½ dl	Boiled rice/pasta
	150 gram	Meat/fish/poultry
	½ plate of	Vegetables
	½ dl	Low fat sauce
Snack:	1½ dl	Yogurt natural 0,5%
	3 table spoon	Muesli

Beverages: Water, sparkling water, sugar-free lemonade and soft drinks, coffee, tea

8.9 Appendix 3 – PHQ9 questionnaire

SPØRGESKEMA OM DIT HELBRED-9 (PHQ-9)

Inden for de seneste 2 uger, hvor ofte har du været generet af følgende problemer? *(Marker dit svar med "x")*	Slet ikke	Flere dage	Mere end halvdelen af dagene	Næsten hver dag
1. Lille interesse i eller glæde ved at gøre ting	0	1	2	3
2. Følt dig nedtrykt, håbløs eller været deprimeret	0	1	2	3
3. Problemer med at falde i søvn eller sove, eller med at sove for meget	0	1	2	3
4. Følt dig træt eller har kun haft lidt energi	0	1	2	3
5. Ringe appetit eller spist for meget	0	1	2	3
6. Haft det dårligt med dig selv – eller følt, at du er en fiasko eller har skuffet dig selv eller din familie	0	1	2	3
7. Problemer med at koncentrere dig om ting, såsom at læse avisen eller se TV	0	1	2	3
8. Har bevæget dig eller talt så langsomt, at andre kunne have bemærket det? Eller det modsatte – været så rastløs eller hvileløs, at du har bevæget dig mere omkring end sædvanligt	0	1	2	3
9. Tanker om, at det ville være bedre, hvis du var død eller om at gøre skade på dig selv på en eller anden måde	0	1	2	3

For office coding: 0 + _____ + _____ + _____

=Total Score: _____

Hvis du har afkrydset mindst ét af de ovenstående problemer, hvor besværligt har disse problemer gjort det for dig at arbejde, klare tingene i hjemmet eller komme overens med andre?

Slet ikke besværligt	Lidt besværligt	Meget besværligt	Ekstremt besværligt
☐	☐	☐	☐

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