CLINICAL STUDY PROTOCOL

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTIPLE-DOSE, MULTI-CENTER SAFETY AND EFFICACY STUDY OF CO-ADMINISTRATION OF TESOFENSINE/METOPROLOL IN SUBJECTS WITH PRADER-WILLI SYNDROME "SECOND 12 WEEKS OPEN LABEL EXTENSION"

Sponsor: Saniona, A/S
Baltorpvej 154
DK2750 Ballerup
Denmark

Protocol number: TM002
EudraCT number: 2016-003694-18

CLINICAL STUDY PROTOCOL SYNOPSIS

Study Title	A double-blind, randomized, placebo-controlled, multiple-dose, multi-centre safety and efficacy study of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome (PWS) "Second 12 weeks open label extension"
Study Sponsor	Saniona, A/S Baltorpvej 154 DK2750 Ballerup Denmark
Study Phase	2a
Number of sites	2 sites; one in Czech Republic and one in Hungary
Number of subjects	Subjects who completed the first open label phase (12 weeks) will be invited to participate in the second open label 12 weeks extension phase. • A subject's participation in the second 12 weeks open label extension (OLE) study will be based on the Investigators' judgment on whether or not it is safe for the subject to continue in the extension study.
Study design	Two-centre, multiple-dose clinical study. The second open label 12 weeks extension study will be initiated immediately during the Visit 17 (Day 180) of the first OLE part (12 weeks), which will then become the baseline visit of the second OLE, and study medication will be administered, without interruption, for another 90 days. • **Previously approved part:** Step 2 – 5-15 children with PWS. Study medication (0.125/25 mg) was administered for ninety one (91) days (+2 days after the final assessments with half-dose of metoprolol in those who did not continue in the OLE) and first OLE where all eligible patients have been receiving 0.125/25 mg). • **Second open label extension**: All subjects who completed the first OLE and are deemed eligible by the Investigators will be invited to participate in the second OLE for another 12 weeks followed by a final visit one month after the last dose of the study medication for a safety review and PK sampling. Those patients who refuse to participate in the second OLE, or are not deemed eligible by the Investigators, will complete the final visit (Visit 18) 1 month after the last dose in the first OLE

	is taken (Visit 17).
Study timelines	Q2 2019 – Q3 2019
Study treatment and Dosing schedule	In the second OLE all subjects deemed eligible by the PI will receive tesofensine 0.125 mg (0.25 mg every second day) + metoprolol ER 25 mg (Metoprolol Orion 25mg) administered once a day, in the morning with a meal. Those patients who tolerated the 0.125/25 mg tesofensine/metoprolol dose well in the first OLE will receive 0.25 mg of tesofensine with 25 mg of metoprolol ER. In case a patient, in the opinion of the PI, experiences an adverse event that by the PI is suspected to be potentially related to an undesirable drug concentration of the investigational medication, the investigators at each site, based on their discretion, can extend the period between dosages of the IMP or implement a drug holiday, or reduce the dose (those on 0.25 mg of tesofensine) in order to optimally manage the wellbeing and safety of the patient. Each of these cases should be discussed in advance with the Sponsor's medical monitor. Each tablet will be formulated separately; a currently available commercial formulation of extended-release metoprolol will be used.
Study objectives	Primary objective: • To examine the effect of co-administration of tesofensine/metoprolol on body weight in subjects with PWS in an open labeled extension study Secondary objectives: • To establish pharmacokinetic profile of tesofensine and metoprolol in subjects with PWS • To examine the change in hyperphagia-related behavior in subjects with PWS by use of the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) • To examine the effect of co-administration of tesofensine/metoprolol on glycaemic control and lipid profile in subjects with PWS • To examine the effect of co-administration of tesofensine/metoprolol on HR and BP in subjects with PWS • To examine the effects of co-administration of tesofensine/metoprolol on body composition in subjects with PWS • To evaluate overall safety and tolerability of co-administration of the tesofensine/metoprolol in subjects with PWS
Study population (inclusion/exclusion	All male and female pediatric subjects with confirmed diagnosis of PWS who completed the double blind phase (12

criteria)	weeks) and the first OLE, will be invited to participate in the second open label 12 weeks extension phase, if deemed eligible by the Investigators. If subject/parents decide to not participate in OLE, subject will finish the study based by completing the study as described previously.
Study procedures	Subjects who have completed the first OLE will continue in the second open label extension, starting on Visit 17 (Day 180) for another 12 weeks. Study procedures in the second OLE are the same as during the first OLE. Subjects will be invited for the monthly visits (30 days ± 3 days) to the site for safety evaluations, and some additional efficacy assessments and PK (see the schedule of events for details). (Visit 18 Day 210; Visit 19 Day 240) Between the on-site visits one phone call follow up will be performed once per month. On Day 270 (Visit 20) the 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 blood pressure. On Day 300 (Visit 21) the subjects will be invited for the final safety check, BP/HR assessment and PK sampling (30 days after last dose), which will conclude their participation in the study. Subjects who 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 schedule of events.
Statistics	The primary endpoint (percent change in body weight) will be summarized with mean estimate, standard deviation, range and 95% confidence interval for the mean. Impact of treatment allocation in the double-blind part will be checked graphically. Safety analyses will include all participants who took at least one dose of IMP and efficacy analyses all treated participants

	with post-dose data recorded (full analysis set). Continuous data will be summarized using non-missing counts, mean, standard deviation, median, minimum, maximum and, if appropriate, 95% confidence interval for the mean. Categorical data will be summarized using counts and percentages. Adverse events will be coded according to MedDRA. The number and percentage of subjects experiencing adverse events 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. Eligible patients are restricted to the completers from the first OLE.

INVESTIGATOR STATEMENT

TM002: A double-blind, randomized, placebo-controlled, multiple-dose, two-centre safety and efficacy study of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome "Second 12 weeks open label extension".

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

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

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

If required, I will also provide necessary protocol information to the responsible Ethics Committee and/or to the Regulatory Authorities 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.

_____

Principle Investigator Signature: Date:

SIGNATURE PAGE

TM002: A double-blind, randomized, placebo-controlled, multiple-dose, two-centre safety and efficacy study of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome "Second 12 weeks open label extension"**.**

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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2 ABBREVIATIONS INDEX

ADR	Adverse Drug Reaction	RA	Regulatory Authority
ALT	Alanine Aminotrasferase	kg	Kilogram
ANCOVA	Analysis of co-variance	l	Liter
AST	Aspartate Aminotrasferase	LDL	Low-density lipoprotein
ATC	Anatomical Therapeutic Chemical Classification	LPLV	Last Patient Last Visit
AUC	Area Under the Plasma Concentration	MedDRA	Medical Dictionary for Regulatory Activities
A/S	Aktieselskab	MDD	Major Depressive Disorder
BMI	Body Mass Index	mg	Milligram
BP	Blood Pressure	mL	Milliliter
Bpm	Beats per minute	mmHg	Millimeter of mercury
BMI	Body Mass Index	mmol	Millimol
CI	Confidence Interval	N	No
Cm	Centimeter	N (No)	Number
Cmax	Maximum measured plasma concentration	ng	Nanogram
CRF	Case Report Form	NYHA	New York Heart Association
CRO	Contract Research Organization	OLE	Open Label Extension
CYP	Cytochrome P450	OP	Out-patient
CV	Coefficient of Variation	OTC	Over the Counter
CV	Cardio Vascular	P	Phone
CVD	Cardio Vascular Disease	PK	Pharmacokinetic
°C	Degrees Celsius	PK/DM	Pharmacokinetics/Drug Metabolism
DBP	Diastolic Blood Pressure	PPP	Per-Protocol Population
DDI	Drug-drug Interaction	PWS	Prader Willi Syndrom
Dl	Deciliter	Q	Quarter
DMP	Data Management Plan	QA	Quality Assurance
DSMB	Data Safety Monitoring Board	QC	Quality Control
DXA	Dual X-ray absorptiometry	SAE	Serious Adverse Event
ECG	Electrocardiogram	SAP	Statistical Analysis Plan
EC	Ethic Committee	SBP	Systolic Blood Pressure
eCRF	Electronic Case Report Form	SD	Standard Deviation
EMEA	European Agency for the Evaluation of Medical Products	SOP	Standard Operating Procedure
EU	European Union	SUSAR	Suspected Unexpected Serious Adverse Reactions
FPG	Fasting Plasma Glucose	Tmax	Time of the maximum
GCP	Good Clinical Practice	TZD	Thiazolidinediones
HDL	High-density lipoprotein	T2MD	Type 2 diabetes mellitus
HbA1C	Hemoglobin A1c	ULN	Upper Limit of Normal range
HQCT	Hyperphagia Questionnaire for Clinical Trials	USA	United States of America
HR	Heart Rate	WHO DD	World Health Organization Drug Dictionary
IB	Investigator Brochures		
ICH	International Conference on Harmonization		
IEC	Independent Ethics Committee		
IMP	Investigation Medicinal Product		

3 INTRODUCTION AND STUDY RATIONALE

3.1 CLINICAL BACKGROUND

Etiology and treatment of Prader- Willi syndrome

Prader-Willi syndrome is a complex genetic condition caused by an abnormality on the long arm of chromosome 15 (q11-q13) that affects many parts and organ systems of the body. In infancy, this condition is characterized by weak muscle tone (hypotonia), feeding difficulties, poor growth, and delayed development. Beginning in childhood, affected individuals develop an insatiable appetite, which leads to chronic overeating (hyperphagia) and obesity. Many subjects with Prader-Willi syndrome, particularly those with obesity, also develop type 2 diabetes mellitus (T2DM) and other related co-morbidities early in life often leading to development of cardiovascular disease and early death.

Subjects with Prader-Willi syndrome typically have mild to moderate intellectual impairment and learning disabilities. Behavioral problems are common, including temper outbursts, stubbornness, and compulsive behavior such as picking at the skin. Sleep abnormalities can also occur. Additional features of this condition include distinctive facial features such as a narrow forehead, almond-shaped eyes, and a triangular mouth; short stature; and small hands and feet. Some people with Prader-Willi syndrome have unusually fair skin and light-colored hair. Both affected males and affected females have underdeveloped genitals. Puberty is delayed or incomplete, and most affected individuals are unable to have children (infertile). (1)

Prader-Willi syndrome affects an estimated 1 in 10,000 to 30,000 people worldwide. Most cases of Prader-Willi syndrome are not inherited, particularly those caused by a deletion in the paternal chromosome 15 or by maternal uniparental disomy. These genetic changes occur as random events during the formation of reproductive cells (eggs and sperm) or in early embryonic development. Affected subjects typically have no history of the disorder in their family.

Rarely, a genetic change responsible for Prader-Willi syndrome can be inherited. For example, it is possible for a genetic change that abnormally inactivates genes on the paternal chromosome 15 to be passed from one generation to the next. (1)

Current treatment strategies

There is currently no specific treatment for this syndrome. Growth hormone has been routinely used to help with growth and to increase muscle mass, which allows greater physical activity. As other diseases develop as the subjects age, eg, T2DM, hypertension, dyslipidemia or psychiatric disorders, these are managed per local practice and treatment standards.

Overview of tesofensine

Tesofensine was initially studied for the treatment of Parkinson and Alzheimer's diseases. However, clinical studies showed only a limited efficacy of tesofensine, but weight loss was noted in majority of participants, despite the fact that they did not attempt to lose weight. Tesofensine is an inhibitor of monoamine presynaptic reuptake of the neurotransmitters noradrenaline, dopamine and serotonin. This means it influences these chemicals in the brain

to suppress appetite. Tesofensine demonstrated strong weight reducing effects in Phase 2 clinical studies in obese subjects, exceeding benchmarks set by the regulatory agencies for approval of weight loss agents (2). Also, post-hoc analysis of the data from the Phase 2 obesity study showed that individuals with pre-diabetes in this study experienced a favorable reduction in body weight and glycaemic endpoints while on tesofensine.

In general, tesofensine was well tolerated in humans with the most commonly observed side effects of dry mouth, headache, insomnia, and nausea However, blood pressure and heart rate increase were observed. With the therapeutically relevant doses of tesofensine (0.25 mg and 0.5 mg) an increase in blood pressure (BP) of 1–3 mmHg and an increase in heart rate (HR) up to 8 bpm were seen (2). Currently, there are no data indicating that these effects of tesofensine would translate into increased risk of cardiovascular (CV) events; however, these increases could hypothetically have an adverse impact on the cardiovascular safety in certain individuals.. This lead to the addition of metoprolol to mitigate these effects and further ensure a favorable benefit/risk profile. For more information on tesofensine please see the Investigators' Brochure (Version 12).

Overview of metoprolol
Metoprolol is a $beta_1$-selective (cardio selective) adrenoceptor-blocking agent, for oral administration, which has been approved in the 70's and has been one of the most widely prescribed medicines to date. It is indicated for hypertension, angina pectoris and heart failure. It is now available as extended-release tablets. Metoprolol extended release, has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. This is also the formulation selected for this study (for more information please see the Summary of Product Characteristics of metoprolol).

Overview of tesofensine/metoprolol
In a pre-clinical study in rats the co-administration of tesofensine + metoprolol showed a HR and BP profile similar to placebo (vehicle) while the weight-reducing efficacy was maintained (3). In addition, in a drug-drug interaction study in healthy male subjects addition of short acting metoprolol on the background of chronic dosing with tesofensine showed a short term, but substantial, reduction in HR previously increased by tesofensine. Co-administration of tesofensine (0.5 mg qd) and metoprolol (100 mg qd) is currently being studied in a Phase 2a proof-of-concept study in 60 subjects with T2DM at two sites in Germany. Taken together, the available data support the concomitant use of tesofensine and a beta-blocker such as metoprolol as an investigational agent for the proposed indication of treatment of obesity and related co-morbidities in subjects with Prader-Willi syndrome.

Purpose of the Comparison to Placebo
Double blind, placebo-controlled design is the gold standard in evaluation of efficacy and safety of new drugs. It provides the most rigorous and unbiased evaluation of the true effects of an intervention. This design was chosen because it is critical to thoroughly assess the efficacy of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome.

Purpose of this study
The purpose of this study is to investigate the safety and efficacy of co-administration of tesofensine/metoprolol treatment versus placebo in adult and pediatric subjects with Prader-

Willi syndrome.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 OBJECTIVES

Primary objective:

- To examine the effect of co-administration of tesofensine/metoprolol on body weight in subjects with PWS in an open labeled extension

Secondary objectives:

- To establish pharmacokinetic profile of tesofensine and metoprolol in subjects with PWS
- To examine the change in hyperphagia-related behavior in subjects with PWS by use of the Hyperphagia Questionnaire for Clinical Trials (HQ-CT)
- To examine the effect of co-administration of tesofensine/metoprolol on glycemic control and lipid profile in subjects with PWS
- To examine the effect of co-administration of tesofensine/metoprolol on HR and BP in subjects with PWS
- To examine the effects of co-administration of tesofensine/metoprolol on body composition in subjects with PWS
- To evaluate overall safety and tolerability of co-administration of the tesofensine/metoprolol in subjects with PWS

4.2 ENDPOINTS (Baseline = Day 0; End of double-blind treatment = Day 90, end of first OLE = Day 180, end of second OLE = Day 270)

Primary endpoint

- Percent change from baseline to end of treatment periods in mean body weight

Secondary endpoints

- Steady state concentrations of tesofensine and metoprolol as measured by trough values
- Uptake and initial plateau concentrations of metoprolol as measured by samples taken 2 and 4 hours after dose administration
- Change from baseline to end of the treatment periods in total HQCT score
- Change from baseline to end of treatment periods in mean body weight (kg)
- Change from baseline to end of treatment periods in fat- and fat-free mass (%) by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment periods in HR (bpm), SBP (mmHg), DBP (mmHg)
- AEs, clinical labs, ECG

Exploratory endpoints:

- Change from baseline to end of treatment periods in FPG, insulin
- Change from baseline to end of treatment periods in lipid profile
- Change from baseline to end of treatment periods in waist circumference (cm)

5 OVERALL STUDY DESCRIPTION

This is a second open label extension study of the double-blind, randomized, placebo-controlled, multiple-dose, multi-centre, safety and efficacy study of co-administration of tesofensine/metoprolol treatment in subjects with Prader-Willi syndrome. This open label extension is a follow up of the first OLE, which included 8 children with PWS (Protocol Amendment 1.5).

Subjects who complete first OLE (12 weeks) will be invited to participate in the second open label extension phase. Participation will be based on the judgment of the Investigators whether or not it is safe for the subject to continue in the extension study. Study medication will be administered for ninety (90) days (+2 days after the final assessments with half-dose of metoprolol).
In the second OLE all subjects deemed eligible by the PI will receive tesofensine 0.125 mg (0.25 mg every second day) + metoprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, in the morning with a meal. Those patients who tolerated the 0.125/25 mg tesofensine/metoprolol dose well in the first OLE will receive 0.25 mg of tesofensine with 25 mg of metoprolol ER.

In case a patient, in the opinion of the PI, experiences an adverse event that by the PI is suspected to be potentially related to an undesirable drug concentration of the investigational medication, the investigators at each site, based on their discretion, can extend the period between dosages of the IMP or implement a drug holiday, or reduce the dose (those on 0.25 mg of tesofensine) in order to optimally manage the wellbeing and safety of the patient. Each of these cases should be discussed in advance with the Sponsor's medical monitor.

Subjects (together with their parents/guardians/caregivers (where applicable according to existing country legislation)) who give the written informed consent for the second open label extension part will continue in the study. If not, subject will finish the study based on the Protocol Amendment 1.5.

Opel label period: after the Day 180 (Visit 17), subjects will visit the site every month for efficacy and safety evaluations and medication supply (in total 4 personal visits at the site are requested). Study procedures in the second extension part are the same as in the first OLE.
If possible subjects will be asked to stay at the site for the collection of blood for PK of metoprolol 2 and 4 hours after dose administration – the blood for these samples will be collected once from each patient (only if it hasn't been collected during the first OLE), but to allow for greater flexibility accounting for their unstable and unpredictable nature, it is included during every on site visit.

End of treatment visit: On Visit 20 (Day 270) subjects will come for the final treatment visit. During the Visit 20 the blood will be collected for metabolic endpoint as well as safety measurements. Subjects will also receive two days of half-dose dose of metoprolol to take at home in order to gradually reduce the dose of metoprolol to avoid potential undesirable fluctuation in blood pressure.

End of study: On Visit 21 (Day 300) the subjects will be invited for the final safety check, BP/HR assessment and PK sampling (30 days after last dose), which will conclude their participation in the study.

Phone calls in-between the onsite visits will be used to provide additional reassurance regarding the safety of the subjects and collect adverse events.

Subjects who exceed predefined values of HbA1c>10%, FPG >11.0 mmol/l or BP>160/110 mmHg will be treated at the discretion of the investigator per established guidelines to improve the patients glycaemic/BP control while remaining in the study.

Assessments conducted during each visit are described in the schedule of events, Appendix 16.2.

5.1 STUDY VISIT DESCRIPTION

Visit 17, Day 180 – Last visit of the first OLE and first visit of the second OLE:

The following procedures will be performed:

- Signing the Addendum to double blind ICF for the second open label extension
- Conducting physical examination
- Measurement of vital signs
- Measurement of body weight and waist circumference
- Measurement of height, calculation of BMI
- Obtaining ECG
- Performing routine hematology, blood chemistry assessment
- Collection of blood for efficacy (HbA1c, FPG, lipids, insulin)
- Collection of blood for PK of steady state concentrations of tesofensine and metoprolol as measured by trough values
- Collection of blood for PK of metoprolol taken 2 and 4 hours after dose administration (only if not done already– during the first OLE)
- Performing the urinary pregnancy test
- DEXA
- HQCT
- AEs assessment
- Psychiatric examination
- Assessment of concomitant medications
- Dispensing the subject diary for the open label extension, study card for second OLE
- Dispensation of study medication

- Scheduling the next on-site visit and phone call

All diabetic subjects (together with their parents/guardians/caregivers) will be again instructed to closely follow the dietary instruction and medical treatment for their diabetes. Subjects (together with their parents/guardians/caregivers) will be again educated in and again asked to watch for any symptoms or signs of hypoglycemia. Hypoglycaemic episodes must be reported to investigator during the phone call visits or personal visit at the site. In case of an unexplained hypoglycaemic event (no extra exercise, skipping a meal or alike) the subjects (together with their parents/guardians/caregivers) should contact the site. Information about providing instruction regarding hypoglycaemic episodes must be recorded in the subject's source data.

Visit 18, 19 (Day 210, 240 (30 ±3 days**) – personal visits:**
The following assessments will be done:

- Measurement of vital signs
- Measurement of body weight and waist circumference
- Collection of blood for efficacy (HbA1c, FPG, lipids, insulin)
- Collection of blood for PK of steady state concentrations of tesofensine and metoprolol as measured by trough values
- Collection of blood for PK of metoprolol taken 2 and 4 hours after dose administration (only if not done already)
- HQCT
- AEs assessment
- Psychiatric examination
- Assessment of concomitant medications
- Review of subject diary
- Medication accountability check
- Scheduling the phone call and subject personal visit

Visit 20 (Day 270 (30±3 days**) – End of treatment visit**
The following assessments will be done:

- Conducting physical examination
- Measurement of vital signs
- Measurement of body weight and waist circumference
- Obtaining ECG
- Performing routine hematology, blood chemistry assessment
- Collection of blood for efficacy (HbA1c, FPG, lipids, insulin)
- Collection of blood for PK of steady state concentrations of tesofensine and metoprolol as measured by trough values
- Collection of blood for PK of metoprolol taken 2 and 4 hours after dose administration (only if not done already)
- Performing the urinary pregnancy test
- DEXA
- HQCT
- AEs assessment

- Psychiatric examination
- Assessment of concomitant medications
- Medication accountability check
- Dispense of two half-doses of active / placebo medication
- Collection and review of subject diary
- Dispensing a follow up diary lists for recording AE and concomitant medication between last subject visit and a phone call on Day 300
- Scheduling Final follow up visit on Day 300

Day 270 (morning) will be the last day when subjects receive the study medication.

On Day 270 subjects will receive a half-dose of the metoprolol dose to take at home, one dosage over the next two days in order to gradually reduce the dose of metoprolol and avoid potential undesirable fluctuation in blood pressure.

Phone calls between the on-site visit
Phone calls in between the onsite visits will be used to provide additional reassurance regarding the safety of the subjects and to collect adverse events. Subjects (parents/guardians/caregivers) will be asked the following:

- Since your last visit, have you experienced or do you currently experience any symptoms that are not associated with your disease?
- Any change in concomitant medications
- Any Hypoglycemic episodes

Visit 21 (Day 300 (30±3 days) Final follow-up — personal visit
The following assessments will be done:

- AEs
- Measurement of vital signs
- Measurement of body weight and waist circumference
- HQCT
- Psychiatric examination
- Concomitant medications
- Collection of blood for PK
- Review of subject diary
- Collection of subject follow up diary

End of study (Day 300)
Visit 21 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.

Unscheduled visit – if applicable:
The following assessments will be done:

- Conducting physical examination
- Measurement of vital signs
- Measurement of body weight and waist circumference

- Performing routine hematology, blood chemistry assessment
- AEs assessment
- Assessment of concomitant medications

5.2 END OF STUDY

The end of study (Day 300) is defined by LPLV for TM002, including the second OLE. If a subject withdraws from the study during the treatment period, or has to discontinue for any reason, a visit will be organized at which the assessments planned for Visit 20 will be performed. If a subject refuses to attend a visit, the investigator should make every effort to obtain the information over the telephone from the subject regarding the safety.

5.3 STUDY PARTICIPANTS

All male and female pediatric subjects with confirmed diagnosis of PWS who completed the first OLE (12 weeks), will be invited to participate in the second open label extension phase, if deemed eligible by the Investigators.

5.4 DISCONTINUATION CRITERIA

The subject or her/his parents/guardians/caregivers has a right to discontinue subject's study participation at any time for any reason. The reason for discontinuation will be documented in the subject's source documents and in the eCRF. In the event of an early termination, all procedures described for a subject completing the study as planned for Visit 20 (Day 270) should be performed. Subjects discontinuing due to adverse events will be followed-up until complete resolution of the adverse event or until there is a satisfactory explanation of the changes observed.

5.5 WITHDRAWAL CRITERIA

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

- Request by subject (withdrawal of informed consent)
- Request by parents/guardians/caregivers
- Investigator's decision
- Pregnancy
- Acute allergic reaction to study medication
- HbA1c $\geq$ 10%
- FPG>13.3 mmol/l (repeated on 2 days)
- Subjects who during the treatment period exceed BP systolic values >160, <100 mmHg, or diastolic >110, <60 mmHg on two consecutive mornings and confirmed at the investigational site
- Any event, including hospitalization of the subject in another location where the investigator will not be able to follow the subject
- Evidence of the use of recreational medications or prohibited medications during the study
- Failure to comply with the study stipulations
- Severe symptomatic bradycardia (heart rate < 50 bpm) during the study
- Lost to follow-up. Subjects will be deemed lost to follow-up if they do not return for scheduled visits without giving a reason, and if the investigator is unable to contact the

subject directly or indirectly (e.g. via the subject's family). If a subject does not attend a scheduled visit, the investigator will make best efforts to obtain information about the subject before considering the subject lost to follow up

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviation, administrative or any other valid and ethical reason. If an investigator judges a subject to be at medical risk by complying with the protocol, he or she may discontinue the participation of the subject. The circumstances surrounding the decision must be discussed with the sponsor and recorded in the subject's source documents and eCRF.

5.6 PREMATURE STUDY DISCONTINUATION

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

Reasons for terminating the study may include the following:

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

5.7 EARLY TERMINATION OF A STUDY SITE

The sponsor may close the site if severe protocol deviations are observed.

5.8 STUDY SITES

The study will be conducted at two sites, one in Czech Republic and one in Hungary.

5.9 STUDY DURATION

The expected start date for the inclusion of study subjects is March/April 2019. The individual study duration for one subject is up to 16 weeks including treatment period (12 weeks of the open label period) and the final visit (30 days after the last treatment visit). The end of second open label is defined by the Last Visit of the Last pediatric subject, which is likely to occur in June/July 2019.

5.10 TOTAL STUDY DURATION

The projected duration of the whole study (including Step 2 and both OLEs) is ~15 months. The end of TM002 is defined as Last Visit of the Last Pediatric Patient in the second open label extension.

5.11 BENEFITS AND RISKS FOR STUDY PARTICIPANTS

It is expected that tesofensine and metoprolol combination will be well tolerated. This assessment is based on the comprehensive experiences from previous preclinical and clinical studies of tesofensine, the availability of metoprolol on the market for many years and the present tesofensine/metoprolol investigation in subjects with T2DM. All subjects will receive diet consulting, and it is expected that subjects on active treatment will see a reduction in their hunger, food craving and body weight. 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, and will have weekly contact (personal or telephone contact) to the site throughout the study.

There were adverse events observed in Step 1 of this study, which lead to premature discontinuation of several patients. It is anticipated that these adverse events were driven by unexpected high concentration of tesofensine and that the proposed changes in the dosing of the IMP in the study protocol proposed for Step 2 and both OLEs should keep the overall risk/benefit balance favorable.

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

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

Metoprolol adverse reactions – post marketing experience

- Blood and lymphatic system: thrombocytopenia, leukopenia, agranulocytosis
- Cardiovascular: cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension
- Respiratory: wheezing (bronchospasm), dyspnea, rhinitis
- Central Nervous System: confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia
- Psychiatric: changes in personality, depression
- Gastrointestinal: nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting, abdominal pain, retroperitoneal fibrosis
- Hypersensitive Reactions: pruritus
- Miscellaneous: fatigue, hyperhidrosis, hepatitis, increased liver enzymes, musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, dry eyes, psoriasis-like dermatitis, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance, gangrene

For more information regarding the adverse events please see the Summary of Product Characteristics of metoprolol.

It is anticipated that the subject receiving the study medication will experience a reduction in their body weight and improvement in their glycaemic control (if diabetic or pre-diabetic). Although tesofensine has not been previously investigated in adult and pediatric subjects with Prader-Willi syndrome, based on the highly statistically and clinically meaningful degree of weight loss seen in the available literature it is anticipated that participants in this study will experience improvement in their glycaemic control (also including those on placebo who will receive diet, exercise and lifestyle modification guidance). In addition, all patients will have access to a state-of-the-art clinical care that they will receive for the duration of the study. Subjects randomized to the placebo arm will receive state of the art clinical study for almost 4 months with regular visits and multiple sophisticated assessment of their health status, including their diabetes, as well as lifestyle guidance from a dietician. Pediatric subjects with PWS will be included only after the received positive opinion from respective regulatory authorities and ethics committees, which concludes that that no safety concerns arose from IMP application in adult PWS patients in Step 1 and TM001.

6 TREATMENT OF STUDY PARTICIPANTS= identical to the first OLE

6.1 DESCRIPTION OF STUDY MEDICATION

Investigational Medicinal Product

Tesofensine is a serotonin-noradrenaline-dopamine reuptake inhibitor, for oral administration, which is manufactured, packed and labeled by Delpharm in Reims (France). Its chemical name (IUPAC) is (1R,2R,3S,5S)-2-Ethoxymethyl-3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane,2-hydroxy-1,2,3-propanetricarboxylate (1:1). Designated contractors will supply study medications directly.

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

In the first OLE tesofensine 0.125 mg (0.25 mg every second day) + metoprolol 25 mg was administered once a day, in the morning with a meal. In the second OLE all subjects deemed eligible by the PI will receive tesofensine 0.125 mg (0.25 mg every second day) + metoprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, in the morning with a meal. Those patients who tolerated the 0.125/25 mg tesofensine/metoprolol dose well in the first OLE will receive 0.25 mg of tesofensine with 25 mg of metoprolol ER.

In case a patient, in the opinion of the PI, experiences an adverse event that by the PI is suspected to be potentially related to an undesirable drug concentration of the investigational medication, the investigators at each site, based on their discretion, can extend the period between dosages of the IMP or implement a drug holiday, or reduce the dose (those on 0.25

mg of tesofensine) in order to optimally manage the wellbeing and safety of the patient. Each of these cases should be discussed in advance with the Sponsor's medical monitor.

6.2 IMP BLINDING AND HANDLING PROCEDURES - KLIFO

The contracted CRO Klifo (Denmark) is responsible for the IMP management.

6.3 IMP HANDLING PROCEDURES – STUDY SITE

- Klifo is responsible for transferring the IMP to assigned and contracted study site pharmacies in Czech Republic and Hungary
- The site pharmacists (at the both sites) are responsible for acknowledgment of receipt of the of IMP by signing the receipt forms
- Storing the IMP on site pharmacy in a secured area with restricted access under the controlled temperature conditions
- Dispensing IMP to site staff according to the protocol

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

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

The investigator is responsible for study medication kits accountability. The site pharmacist is responsible for maintaining accurate records of all information relating to the management of the study medication. If any quality issues are noticed on receipt or use of the IMP (e.g. damaged condition, faults in appearance, errors in the documentation, incorrect labeling, 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 study medication made by the study subjects.
In the event of a batch recall, the sponsor or its representative will inform the investigator or site pharmacist in writing. Upon receipt, and as instructed, the investigator or site pharmacist should immediately contact any study subject in possession of the corresponding study medication kits.

6.4 LABELS FOR STUDY MEDICATION

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

- Name of Sponsor
- Name of CRO or Investigator
- Protocol number
- Subject screening number
- Dosing instructions
- Batch number
- Expiry date
- The words 'For clinical study use only'
- The words 'Keep out of reach of children'

- Storage conditions

6.5 PACKAGING AND DESTRUCTION

Medication will be distributed to the subjects in plastic bottle (tesofensine) and in blisters (metoprolol) labeled with the appropriate study medication number. The investigator and site pharmacists will collect unused study medication. Klifo is responsible for central destruction of all study medication (partially used and unused).. Subjects will be asked to use study medication every morning with or right after a meal and not to crush or chew the tablets. Metoprolol every morning with or right after a meal and not to crush or chew the tablets and Tesofensine every second day. Subject will be asked to store the medication at room temperature (15 - 25 °C) and return the unused study medication on visit 20 at the site.

6.6 STUDY MEDICATION COMPLIANCE

The investigational medicinal products will be self-administered by the subjects or parents/guardians/caregivers at home. For the monitoring of study medication, subjects or parents/guardians/caregivers will be instructed to return bottle and blisters with study medication at visit 20, whether full, partially empty, or empty.

6.7 OPEN LABEL SUBJECT NUMBER

Subjects who sign the informed consent (together with signed informed consent form by subject's parents/guardians/caregivers where applicable according to existing country legislation) will keep at Visit 17 their unique screening number consisting of a two (2) digit site number and three (3) digit subject number and country abbreviation.

6.8 UNBLINDING

Not applicable, it is an open label study.

6.9 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 or subject's parents/guardians/caregivers, including empty bottles/blisters will be accounted for and returned to the investigator and destroyed by the Klifo.

6.10 ACCOUNTABILITY OF THE STUDY MEDICATION

The investigators will make every effort to encourage subjects together with help of subject's parents/guardians/caregivers 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/blisters on-site. The delivery to, use by and return from the subject or subject's parents/guardians/caregivers must be documented. All opened and unopened bottles/blisters together with remaining contents will be returned by the subject or subject's caregiver/guardian/parents 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 bottles/blisters that is missing. It is the investigator's responsibility to instruct the subjects and subject's parents/guardians/caregivers about using and returning of study medication.

6.11 CONCOMITANT MEDICATION

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

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

6.12 PROHIBITED MEDICATIONS

For prohibited concomitant medications, please refer to Appendix 1 and Exclusion criteria.
Paracetamol is an exception and may occasionally be taken by the subjects in the treatment of acute pain (e.g. headache or toothache). In such case, the subjects will be asked to keep record in the diary.

6.13 STUDY PROCEDURES AND OTHER EXAMINATIONS

Informed Consent for the second OLE

It is the responsibility of the investigator to give each subject (or, if the subjects do not have legal authority to provide consent for themselves their legally appointed parents/guardians/caregivers where applicable according to existing country legislation) full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. In pediatric subjects the patient information and informed consent forms will be prepared per local legislative requirements.

The OLE ICF, approved by the RA/EC, must be given to each subject or parents/guardians/caregivers before any study-related procedure is undertaken. The subjects must be informed about their right to withdraw from the study at any time. The written subject/parents/guardians/caregivers information cannot be changed without prior approval by Sponsor and the RA/EC. Furthermore, it is the responsibility of the investigator to obtain signed informed consent from all subjects (or the parents/guardians/caregivers) prior to undertaking any study-related procedure. Two original forms for written informed consent will be given to the subject/parents/guardian/caregivers for signature. One is to be kept by the subject/parents/guardians/caregivers and one is to be filled in the Investigator's Study File.

Due to the special nature of this population, it is possible that they will have caregivers (i.e. a person caring for the subject but who is not authorized to provide legally relevant consent in relation to the subject' participation in the study) but who, in the course of the clinical study, will help the subject and the study team in administering the treatment, travelling to the site, and conduct at home subject' assessments in compliance with the rules of the clinical study. A separate written information sheet for caregivers will be prepared specifying all of the

important pieces of information for this person; the document will also explain the role of the caregiver in detail. By signing the informed consent the caregiver agrees that the child under his/her care will participate in the OLE and he/she will become involved in the clinical trial as well, but with limited rights.

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

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

Blood pressure measurement

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

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

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

Urinary pregnancy test will be done only for any women of childbearing potential at the site at the Day 180 and on Day 270.

DEXA will be done using standardized protocol while the subjects wear light clothing at the Day 180 and on Day 270.

HQCT - parents/guardian/caregivers will be asked during each personal visit to evaluate the food-seeking behavior of the subject with PW. Subjects with PWS are themselves unable to consistently and reliably report the severity of their hyperphagia, due to their intellectual

limitations. In case that the subject is not at home during the week (for ex. at boarding school), parents/guardian/caregivers should ask the teacher or the relevant person about subject's eating behavior during the week and based on the received information, the HQCT should be completed.

6.14 LABORATORY EVALUATIONS

Laboratory samples will be collected from subjects at the site, and will be shipped to the local laboratory for analysis in ambient conditions.

The investigator will receive the data from local laboratory. Laboratory results will be reviewed, evaluated, signed and dated by the investigator. 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 in subject's medical file.

The investigator´s evaluation (´normal´, ´abnormal and not clinically significant´ or ´abnormal and clinically significant´) will be entered into the eCRF.

If a laboratory result is considered clinically significant and it fulfills the criteria for a clinical laboratory AE, it should be reported in accordance with section 6. Clinically significant laboratory findings from the screening visit before the randomization should be recorded as concomitant illness.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the study database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

- **Hematology**: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets, will be analyzed by local laboratory
- **Blood chemistry**: creatinine, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, GFR and urea will be analyzed by local laboratory
- **HbA1c** will be analyzed by local laboratory
- **Lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), serum insulin** will be analyzed by local laboratory
- **Fasting plasma glucose** - will be analyzed by local laboratory

PK – plasma concentrations of tesofensine/metoprolol will be measured. Each PK blood sample must have time of draw attached to it as well as timing of the last dose of the study mediation taken prior to the blood draw. The analyses will be done by sponsor selected external laboratory: Bioanalytical and ADME Labs. Q2 Solutions, 19 Brown Rd, Ithaca, NY 14850, USA.

6.15 SUBJECTS' DIARIES /CARDS

Subject diaries for the second OLE on Day 180 (Visit 17) and cards will be provided. Subject's caregiver/guardian/parents will be asked on behalf of subject to record in the diary the following: date, taking of the study medication, AEs, concomitant medication hypoglycemic episodes.

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7 SAFETY REPORTING

All AEs occurring after the randomization of the subject will be reported as AE (if any AEs occurred between screening and randomization will be reported in medical history, but not as a AE). The report will include information on onset and stop dates, nature, severity (=grading, see below), seriousness, interventions and medications required, and outcome. SAEs will be reported to the regulatory authorities and Independent Ethics Committees (IECs) according to local regulations, and will be followed-up until the resolution of the event.

At each visit, subject together with help of subject's parents/guardians/caregivers will be asked: "Do you currently (or did you) experience any symptoms that are not associated with your disease (since the last visit)?" Any symptom is to be entered into the Adverse Event eCRF.

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.

7.1 DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes all unintended or unforeseeable signs and symptoms, and addition:

- All suspected IMP adverse reactions
- Psychological symptoms (including aggressive behavior 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)
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory]

test)

- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event

Each adverse event is to be classified by the investigator as serious or non-serious.

7.2 ADVERSE EVENT

All AEs encountered after the randomization will be recorded in detail indicated in the eCRF, regardless of their relationship to the investigational study product as assessed by the investigator. The investigator must record all directly observed adverse events and all adverse events spontaneously reported by the subject or parents/guardians/caregivers during the study. AEs will be coded by use of an internationally recognized dictionary (MedDRA). Details are described in the study specific Data Management Plan.

7.3 GRADING OF ADVERSE EVENT SEVERITY

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of each adverse event. For purposes of consistency, these intensity grades are defined as follows:

Mild	Does not interfere with subject's usual age-appropriate instrumental* activities of daily life (ADL)
Moderate	Interferes with subject's usual age-appropriate instrumental* activities of daily life (ADL)
Severe	Interferes with subject's usual age-appropriate self care** activities of daily life (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.4 CAUSALITY OF AE

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

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely or Unrelated: A clinical event, including a laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

or

The event may or may not follow a reasonable temporal sequence from administration of the investigational study medication and is clearly related to other factors, such as other drugs, chemicals, underlying disease, therapeutic intervention, or concomitant therapy.

Actual changes in severity or causal relationship of a medical occurrence require the completion of a new line in the AE form in the CRF.

7.5 OUTCOME OF AE

The outcome type and the follow-up of subjects with AEs should be specified. Outcome of adverse event may include at time of last observation: Recovered / resolved; Not recovered / not resolved; Recovered / resolved with squeal; Fatal; Unknown.

AEs requiring therapy must be treated by recognized standards of medical care to protect the health and welfare of the subject. Appropriate equipment and medicines must be available to ensure the best possible treatment of emergency situations. Action(s) taken: Study treatment withdrawn; Dose reduced; Dose increased; Dose not changed; Unknown; Not applicable.

7.6 UNEXPECTED ADVERSE REACTION

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

7.7 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is any adverse event that at any dose is

- Fatal
- Life-threatening
- Results in a persistent disability or incapacity
- Results in a congenital abnormality or birth-defect
- Results in or prolongs in-patient hospitalization; or
- Is otherwise classified as medically significant

Elective surgeries are not considered as SAEs and do not have to be reported as such.

In this context, the term life threatening refers to an event in which the subject was at immediate risk of death at the time of the event; it does NOT refer to an event, which might have caused death if it would have been more severe.

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 outpatient 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.

Any important medical event that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above should also be reported as a SAE. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

Hospitalization for diagnostic or therapeutic procedures in the absence of any associated AE will not be considered as a SAE, except when otherwise required by Regulatory Authorities.

7.8 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

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

7.9 RECORDING OF ADVERSE EVENTS

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

Pre-existing Conditions

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

Overdose

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

Pregnancy

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the study. Pregnancies occurring during the study must be reported by the investigational staff within 24 hours of their knowledge. Study medications will be immediately discontinued and study medications will not be tapered. Follow-up information

regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Pregnancy will be recorded as an AE in all cases. It will be classified as an SAE only if it fulfills SAE criteria. eCRF will be completed and pregnant subjects will be follow-up until the outcome of the pregnancy has been determined.

7.10 REPORTING PROCEDURE OF SERIOUS ADVERSE EVENTS

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

Any serious AE must be reported by investigator to the Sponsor´s delegate for Pharmacovigilance within 24 hr by fax or email:

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

Care should be taken to ensure that the subject's identity is protected and the subject's identifiers in the clinical study are not included on any copy of source documents provided to the sponsor. Post-study SAEs may be reported in an expedited manner to the sponsor at the investigator´s discretion.

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

The sponsor's delegate for pharmacovigilance will make expedited reports of all SAEs that are both unexpected and causally related to the IMP, to the Regulatory Authorities, IECs as appropriate and to the investigators at other investigational sites. In addition, the sponsor's delegate for pharmacovigilance may make expedited reports of all SAEs that are expected and causally related to the IMPs to the Competent Authorities, according to the European directive 2001/20/EC and the local regulations. The sponsor's delegate for pharmacovigilance will report all safety observations made during the conduct of the study in the clinical study report. Details of SAE case exchange between the Sponsor´s delegate for pharmacovigilance, the Sponsor, National Competent Authorities and Ethics Committees will be set forth in a separate Safety Management Plan.

7.11 FOLLOW-UP OF ADVERSE EVENTS

The investigator must ensure that follow-up of the subject is appropriate to the nature of the event, and that follow-up continues until the event is stabilized or resolved. The investigator

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

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

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

7.12 ANNUAL SAFETY REPORTS

Once yearly or upon request by the National Competent Authorities the Sponsor's delegate for pharmacovigilance will write down an Annual Safety Report, which will adhere to the Development Safety Update Report (DSUR) format (ICH E2F guideline) and contain a list of Serious Adverse Events an analysis of the study's subjects' safety. This report will be sent to Regulatory Authorities and to the IECs in the 60 days after the anniversary of the first inclusion. Details of DSUR preparation, review and submission will be set forth in a separate Safety Management Plan.

When the Step 2 double-blind part is completed, it will be unblinded and reported, even though the OLE will still be ongoing.

8 DESCRIPTION OF STATISTICAL METHODS

8.1 DESCRIPTION OF STATISTICAL METHODS

CRO selected and designated by the Sponsor 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 CRO's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this chapter, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before data base lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.4 or later.

8.2 SAMPLE SIZE CALCULATION

As this is an explorative study no formal sample size calculation was done. Eligible patients are restricted to completers from step 2 in the double-blind part of the study.

8.3 SELECTION OF SUBJECTS FOR ANALYSES

The following analysis sets are defined in accordance with the ICH-E9 guidance (5):

Full Analysis Set (FAS)
Includes all randomized and treated subjects with post-dose data collected. Subjects in the FAS will contribute to the evaluation 'as treated'

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

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

The primary analyses of primary and secondary endpoints will be based on the FAS. Sensitivity analyses will be based on the PPP. The analyses of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. Furthermore, outliers will be identified by data review according to ICH-E9 (5). In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis. Obviously erroneous data points may be excluded from the analyses. The decision to exclude data points from the statistical analysis is the joint responsibility of the sponsor, the investigator and the CRO statistician.

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

8.4 STATISTICAL METHODS

All primary and secondary endpoints will be summarized by treatment and visit using descriptive statistics. Continuous endpoints are summarized by the arithmetic mean, geometric mean (when applicable), median, standard deviation, coefficient of variation (CV when applicable), minimum and maximum value. If appropriate 95% confidence intervals for the mean will be given in addition Categorical endpoints are summarized by the number (N) and percentage (%). 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 FAS, PPP and Safety Analysis Set. Subjects withdrawn from the study will be listed including the primary reason for withdrawal.

8.5 ANALYSIS OF THE PRIMARY ENDPOINT

Primary endpoint will be summarized with mean estimate, standard deviation, range and 95% confidence interval for the mean. The impact of treatment allocation in the double-blind part will be checked graphically.

8.6 ANALYSIS OF THE SECONDARY & EXPLORATORY ENDPOINTS

Continuous data will be summarized using non-missing counts, mean, standard deviation, median, minimum, maximum and 95% confidence interval for the mean when appropriate. Categorical data will be summarized using counts and percentages. The impact of treatment allocation in the double-blind part will be checked graphically.

Tesofensine and metoprolol concentration will be summarized for each assessment point including measures of geometric means and coefficient of variation. The individual PK data collected during the double-blind (Step 2) and the open extension phases will further be presented graphically
Adverse events will be coded according to MedDRA. The number and percentage of subjects experiencing adverse events in each treatment group will be tabulated by MedDRA system organ class and preferred term.

Secondary endpoints evaluated will be (not a complete list):

- Change from baseline to end of treatment in mean HR
- Change from baseline to end of treatment in mean SBP
- Change from baseline to end of treatment in mean DBP
- Change from baseline to end of treatment in HQCT
- Change from baseline to end of treatment in HbA1c
- Change from baseline to end of treatment in insulin
- Change from baseline to end of treatment in lipids
- Change from baseline to end of treatment in FPG
- Change from baseline to end of treatment in fasting insulin
- Change from baseline to end of treatment in waist circumference
- Change from baseline to end of treatment in fat- and fat-free mass
- PK levels collected for tesofensine and metoprolol

Other secondary endpoints may be added and will be described in the SAP.

8.7 SAFETY CRITERIA

- AEs
- Clinical labs (Hematology, Blood Chemistry)
- ECG
- Vital signs
- Physical examination

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

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

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

Permission for direct access to subject's data will be sought in writing by the investigator and from the subject or parents/guardians/caregivers 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 Regulatory Authorities, study monitor and auditors) with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subject's identities and sponsor's proprietary information. It is the monitor's responsibility to verify that each subject has consented, in writing, to direct access. It is to be ensured by the investigator that documents that are given to Saniona A/S or its representatives do not contain the name or address of the subject, or other information that would affect the anonymity of the subject.

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

9.1 SOURCE DATA

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

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

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

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

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

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

9.2 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 Randomization List". For completeness the monitor will review this document. A "Screening Log" that reports all subjects that were seen to determine eligibility for inclusion in the clinical study also has to be completed by the investigator. The Subject Screening Log and Subject Randomization Log may be combined in one list.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 DEFINITIONS

Quality Assurance

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

Quality Control

The monitor will visit the 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.

10.2 AUDITS AND INSPECTIONS

An independent quality control unit may audit the study protocol, the documentation and, if applicable, the performance of the study and the clinical study report to ensure that the study will be performed in accordance with ICH-GCP guidelines, FDA requirements and other regulatory requirements. The investigator will make all study-related source data and records available to a medically qualified quality assurance auditor mandated by the sponsor, or to regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the investigational medicinal product have been reported to the sponsor.

11 ETHICS

11.1 BASIC PRINCIPLES AND ETHICAL CONSIDERATIONS

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

11.2 APPROVALS

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

11.3 ETHICS COMMITTEE

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

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

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

11.4 REGULATORY AUTHORITY

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

11.5 PROTOCOL MODIFICATIONS

If it turns out during the study that some procedures cannot be conducted according to the clinical study protocol, the principal investigator has to be informed immediately by the study personnel. The principal investigator will be responsible for informing the clinical monitor or the clinical project manager of the issue. It will then be decided if a protocol amendment has to be written and approved by the RA/IEC before the study can continue. Any amendment becomes part of the clinical study protocol.

The amended protocol will be approved and signed by the relevant personnel at Saniona A/S and by the principal investigator. 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/favorable opinion of the appropriate IEC and, if legally required, Regulatory Authority, except where necessary to eliminate an immediate hazard to the subjects, or when the change(s) that were approved by Saniona A/S involve only logistical or administrative aspects of the study.

11.6 SUBJECT INFORMATION AND INFORMED CONSENT

RA/IEC approval of the written Subject Information and Informed Consent (for subjects/ parents/guardians/caregivers where applicable according to existing country legislation) must be obtained prior to their use. This consent form contains a phrase by which consent is given for the access to the non-personalized data by the sponsor, national and regulatory authorities. In addition, it states that the subject is free to withdraw from the study at any time without any negative consequences. The Subject Information gives a complete and comprehensive explanation of the significance, nature, extent and possible risks of the study.
The informed consent form must be signed, with name and date noted by the subject and/or parents/guardians/caregivers where applicable according to valid country legislation. The investigator will complete the informed consent section of the eCRF for each subject enrolled.
If new information becomes available that potentially affects the subject's safety or willingness to continue in the study, or if a protocol amendment is issued that affects subject's safety, study procedures or any aspects of the study that may influence the subject's willingness to continue in the study, the subject information leaflet and informed consent form will be revised. After the new documents have received approval from the RA/IEC in accordance with applicable regulations, the subject/parents/guardians/caregivers where applicable according to existing country legislation will be asked to sign the new consent form to confirm his or her willingness to continue in the study.

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

11.7 PARTICIPANT CONFIDENTIALITY

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

12 DATA HANDLING AND RECORD KEEPING

12.1 DATA COLLECTION AND DOCUMENTATION

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

12.2 STUDY MONITORING, SOURCE DATA VERIFICATION AND DATA MANAGEMENT

Clinical Data Management is the responsibility of the CRO. All Data Management procedures will be detailed in a separate document known as the Data Management Plan (DMP). The DMP will also describe the Clinical Data Management System (CDMS) that will be used to collect data with an electronic Case Report Form (eCRF) in detail. For each enrolled study participant an eCRF will be maintained. ECRFs must be kept current to reflect subject status at each phase during the course of study. Data on subjects collected on eCRFs during the study will be documented in an anonymous fashion and contains an electronic audit trail.

In compliance with 21 CRF part 11 each user of the CDMS will be assigned a unique user name and will be allocated to a special user role. This special user role controls the user's permissions in the electronic data capture system depending on the function within the study. All staff involved in the study in each site has to be instructed how to maintain the eCRF and therefore be able to edit eCRF entries. 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 eCRF 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. Once eCRFs are completed, they will be available for review by the study monitor and CRO Clinical Data Management. Completed eCRFs will be reviewed remotely for logical discrepancies. The study monitor will ensure that all data queries and subsequent amendments in the eCRF documentation are made according to GCP guidelines.

12.3 DATA MANAGEMENT PLAN

The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this study.

12.4 CASE REPORT FORMS (CRFS)

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

Database Lock

After all data are entered, all queries are solved and quality control procedures have been completed respectively each subject's evaluability is determined, the database will be authorized for lock. Electronic case report form data per site will be provided to the responsible investigator at the end of the study and will need to be retained by the investigator. The complete data will be provided to the sponsor at the close of the study for archiving.

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.

12.5 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.

12.6 LOGS

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

12.7 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.

12.8 RECORD KEEPING

To enable evaluations and/or audits from regulatory authorities or Sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient

information to link records, e.g., case report forms and hospital records), all original signed informed consent forms, copies of all case report forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to Sponsor. The investigator must obtain Sponsor's written permission before disposing of any records.

13 FINANCE AND INSURANCE

13.1 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.

13.2 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 A/S together with help of the contracted CRO.

14 PUBLICATION POLICY

14.1 REPORTING AND PUBLICATION

CRO will prepare a study report after the completion of the study. The sponsor representative will sign the final study report intended to be submitted to Regulatory Authorities.

The results of this study may be published or presented at scientific meetings. The sponsor will be responsible for publication of all the data generated in this study. In accord with standard editorial and ethical practice, the sponsor will support publication of multicentre studies only in their entirety and not as individual site data. Sites or investigators must not publish any data from this study without obtaining prior written permission from the Sponsor.

15 REFERENCES

1. https://ghr.nlm.nih.gov/condition/prader-willi-syndrome

2. Astrup A, Madsbad S, Breum L, et al. Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1916-1913.

3. Bentzen BH, Grunnet, M, Hyveled-Nielsen, L. Anti-Hypertensive Treatment Preserves Appetite Suppression While Preventing Cardiovascular Adverse Effects of Tesofensine in Rats. Obesity 2013;21:985-992.

4. ICH Harmonised Tripartite Guideline. Good Clinical Practice [Internet]. 1996 [cited 2015 Oct 28]. Available from: https://firstclinical.com/regdocs/doc/?db=ICH_E6_Good_Clinical_Practice

16 Appendices

16.1 Appendix I: table of recommended concomitant medication use

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	Y	N	Prohibited for 2 weeks prior to randomisation, however, hypnotics and/or anxiolytics at a stable dose for at least 4 weeks prior to screening and up to the follow-up visit could be allowed, i.e.up to zolpidem (10 mg/day), choral hydrate (1 g/day), triazolam (0.5 mg/day), or lorazepam (1 mg/day)
Beta- blockers	N	N	Per protocol
Buproprion (non-SSRI antidepressant)	N	N	Strong inhibitor of CYP2D6
Calcium channel blockers	N	N	Per protocol
Carbonic anhydrase inhibitors (e.g., acetazolamide, dichlorphenamide, dorzolamide, methazolamide)	N	N	
Cinacalcet (calcimimetic)	N	N	Strong inhibitor of CYP2D6
Dopamine reuptake inhibitors (e.g. bupropion)	N	N	
Glucocorticoids	Y	N	
Hypnotic sedative (glutethimide)	N	N	Strong inducer of CYP2D6
H2-receptor antagonist (cimetidine)	N	N	Weak inhibitor of CYP2D6
Immunosuppressives	N	N	
Insulin and/or other injectable anti-diabetic medications, or TZDs	N	N	Per protocol
Lithium	N	N	
Monoamine oxidase (MAO) inhibitors	N	N	
Opioids, cannabinidiols	N	N	
Oral hypoglycemic	-	-	Per protocol
Orlistat	N	N	
Phenothiazines	N	N	
Selective serotonin reuptake inhibitors (SSRIs)	N	N	
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	N	N	

Drug Class	Episodic Use	Chronic Use	Comment
Tricyclic antidepressants	N	N	
Drug inducing ocular toxicity Chloroquine Hydrochloroquine	N	N	
Non-drugs			

Weight loss supplements	N	N	
Anti-depression, anxiety, epilepsy, psychotics OTC, supplements	N	N	

16.2 STUDY FLOW CHART: VISITS 17 - 21 (all visits are ±3 day)

Visit	17 Equal to last visit of first OLE Treatment	18 Treatment	19 Treatment	20 End of Treatment	21 End of study
Day	**180**	**210 (30 days ± 3 days)**	**240 (30 days ± 3 days)**	**270 (30 days ± 3 days)**	**300 (30 days ± 3 days)**
Obtaining second Addendum to double blind ICF for the second OLE part	x				
Subject screening number (keeping the same as in Step 2 and the first OLE)	x				
Psychiatric examination	x	x	x	x	x
Physical examination	x			x	
Vital signs	x	x	x	x	x
Weight, waist circumference	x	x	x	x	x
Height, calculation of BMI	x				
HQCT	x	x	x	x	x
ECG	x			x	
Hematology	x			x	
Blood chemistry	x			x	
FPG, HbA1c	x	x	x	x	
Lipids, insulin	x	x	x	x	
DEXA	x			x	
PK sample	x**	x**	x**	x**	x
Drug dispensation and accountability	x	x	x	*x	

AEs	x	x	x	x	x
Concomitant medication	x	x	x	x	x
Urinary pregnancy test	x			x	
Diary dispensation, Subject card for OLE dispensation	x				
Diary review		x	x	x	x
Diary collection				x	x
Dispense Follow-up diary list				x	
End of study form					x

***two half doses of metoprolol should be dispensed**
**** Blood samples of metoprolol taken 2 and 4 hours after dose administration – to be done only once in each patient during the study, if not done during the first OLE. Time point for dosing and the two blood samples should be noted!**

Phone calls in-between the onsite visits will be used to provide additional reassurance regarding the safety of the subjects and collect adverse events.

Visit	**17.1 Phone call**	**18.1 17 Phone call**	**19.1 Phone call**	**20.1 Phone call**
Frequency	Once per month	Once per month	Once per month	Once per month
AEs	X	X	X	X
Hypoglycemic episodes (at DM subjects)	X	X	X	X
Concomitant medication	X	X	X	X

17.1 Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

Instructions:
The following items refer to the person in your care and assessment of his/her food-related behavior during the past 2 weeks.

(1) During the past 2 weeks, how upset did the person generally become when denied a desired food?

□ Not at all upset
□ A little upset
□ Moderately upset
□ Very upset
□ Extremely upset

(2) During the past 2 weeks, how often did the person try to bargain or manipulate to get more food at meals?

□ Never
□ Up to 2 times a week
□ 3 to 6 times a week
□ Every day
□ Several times a day

(3) During the past 2 weeks, how often did the person forage through trash for food?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(4) During the past 2 weeks, how often did the person get up at night to food seek?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(5) During the past 2 weeks, how persistent was the person in asking or looking for food after being told “no” or “no more”?

□ Not at all persistent
□ A little persistent
□ Moderately persistent
□ Very persistent
□ Extremely persistent

(6) During the past 2 weeks, outside of normal meal times, how much time did the person generally spend asking or talking about food?

□ Less than 5 minutes a day
□ 5 to 15 minutes a day
□ 15 to 30 minutes a day
□ 30 minutes to 1 hour a day
□ More than 1 hour a day

(7) During the past 2 weeks, how often did the person try to sneak or steal food (that you are aware of)?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(8) During the past 2 weeks, when others tried to stop the person from asking about food, how distressed did he or she generally appear?

□ Not at all distressed
□ A little distressed
□ Moderately distressed
□ Very distressed
□ Extremely distressed

(9) During the past 2 weeks, how often did food-related behavior interfere with the person’s normal daily activities, such as self-care, recreation, school, or work?

□ Never
□ Up to 2 times a week
□ 3 to 6 times a week
□ Every day
□ Several times a day

CLINICAL STUDY PROTOCOL

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTIPLE-DOSE, MULTI-CENTER SAFETY AND EFFICACY STUDY OF CO-ADMINISTRATION OF TESOFENSINE/METOPROLOL IN SUBJECTS WITH PRADER-WILLI SYNDROME "SECOND 12 WEEKS OPEN LABEL EXTENSION"

Sponsor:	Saniona, A/S Baltorpvej 154 DK2750 Ballerup Denmark
Protocol number:	TM002
EudraCT number:	2016-003694-18

CLINICAL STUDY PROTOCOL SYNOPSIS

Study Title	A double-blind, randomized, placebo-controlled, multiple-dose, multi-center safety and efficacy study of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome "Second 12 weeks open label extension"
Study Sponsor	Saniona, A/S Baltorpvej 154 DK2750 Ballerup Denmark
Study Phase	2a
Number of sites	2 sites; one in Czech Republic and one in Hungary
Number of subjects	Subjects who completed the first open label phase phase (12 weeks) will be invited to participate in second open label 12 weeks extension phase. A subject's participation in the second 12 weeks open label extension (OLE) study will be based on the Investigators' judgment on whether or not it is safe for the subject to continue in the extension study.
Study design	Two-centre, multiple-dose clinical study. The second open label 12 weeks extension study will be initiated immediately during the Visit 17 (Day 180) of the first OLE part (12 weeks), which will then become the baseline visit of the second OLE, and study medication will be administered, without interruption, for another 90 days. • **Previously approved part:** Step 2 – 5-15 children with PWS. Study medication (0.125/25 mg) was administered for ninety one (91) days (+2 days after the final assessments with half-dose of metoprolol) in those who did not continue in the OLE) and first OLE where all eligible patients have been receiving 0.125/25 mg). • **Second open label extension**: All subjects who completed the first OLE and are deemed eligible by the Investigators will be invited to participate in the second open label extension for another 12 weeks followed by a final visit one month after the last dose of the study medication for a safety review and PK sampling. • Those patients who refuse to participate in the second OLE, or are not deemed eligible by the Investigators, will complete the final visit (Visit 18) 1 month after the

	last dose in the first OLE is taken (Visit 17).
Study timelines	Q3 2018 – Q2 2019
Study treatment and Dosing schedule	**In the second open label extension all subjects** deemed eligible by the PI **will receive:** tesofensine 0.125 mg (0.25 mg every second day) + metoprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, in the morning with a meal. Those patients who tolerated the 0.125/25 mg tesofensine/metoprolol dose well in the first OLE will receive 0.25 mg of tesofensine with 25 mg of metoprolol ER. In case a patient, in the opinion of the PI, experiences an adverse event that by the PI are suspected to be potentially related to an undesirable drug concentration of the investigational medication, the investigators at each site, based on their discretion, can extend the period between dosages of the IMP or implement a drug holiday, or reduce the dose (those on 0.25 mg of tesofensine) in order to optimally manage the wellbeing and safety of the patient. Each of theses cases should be discussed in advance with the Sponsor's medical monitor. Each tablet will be formulated separately; a currently available commercial formulation of extended-release metoprolol will be used.
Study objectives	<u>Primary objective:</u> • To examine the effect of co-administration of tesofensine/metoprolol on body weight in subjects with PWS in an open labeled extension study <u>Secondary objectives:</u> • To establish pharmacokinetic profile of tesofensine and metoprolol in subjects with PWS • To examine the change in hyperphagia-related behavior in subjects with PWS by use of the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) • To examine the effect of co-administration of tesofensine/metoprolol on glycaemic control and lipid profile in subjects with PWS • To examine the effect of co-administration of tesofensine/metoprolol on HR and BP in subjects with PWS • To examine the effects of co-administration of tesofensine/metoprolol on body composition in subjects with PWS • To evaluate overall safety and tolerability of co-administration of the tesofensine/metoprolol in subjects with PWS
Study population (inclusion/exclusion criteria)	All male and female pediatric subjects with confirmed diagnosis of PWS who completed the double blind phase (12

	weeks) and the first OLE, will be invited to participate in the second open label 12 weeks extension phase, if deemed eligible by the Investigators. If subject/parents decide to not participate in OLE, subject will finish the study based by completing the study as described previously.
Study procedures	Subjects who have completed the first OLE will continue in the second open label extension, starting on Visit 17 (Day 180) for another 12 weeks. Study procedures in the second OLE are the same as during the first OLE. Subjects will be invited for the monthly visits (30 days ± 3 days) to the site for safety evaluations, and some additional efficacy assessments and PK (see the schedule of events for details). (Visit 18 Day 210; Visit 19 Day 240) Between the on-site visits one phone call follow up will be performed once per month. On Day 270 (Visit 20) the 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 blood pressure. On Day 300 (Visit 21) the subjects will be invited for the final safety check, BP/HR assessment and PK sampling (30 days after last dose), which will conclude their participation in the study. Subjects who 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 schedule of events.
Statistics	The primary endpoint (percent change in body weight) will be summarized with mean estimate, standard deviation, range and 95% confidence interval for the mean. Impact of treatment allocation in the double-blind part will be checked graphically. Safety analyses will include all participants who took at least one dose of IMP and efficacy analyses all treated participants with post-dose data recorded (full analysis set). Continuous data will be summarized using non-missing counts, mean,

	standard deviation, median, minimum, maximum and, if appropriate, 95% confidence interval for the mean. Categorical data will be summarized using counts and percentages. Adverse events will be coded according to MedDRA. The number and percentage of subjects experiencing adverse events 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. Eligible patients are restricted to the completers from the first OLE.

INVESTIGATOR STATEMENT

TM002: A double-blind, randomized, placebo-controlled, multiple-dose, multi-center safety and efficacy study of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome "Second 12 weeks open label extension".

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

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

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

If required, I will also provide necessary protocol information to the responsible Ethics Committee and/or to the Regulatory Authorities 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.

_____

Principle Investigator Signature: Date:

SIGNATURE PAGE

TM002: A double-blind, randomized, placebo-controlled, multiple-dose, multi-center safety and efficacy study of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome "Second 12 weeks open label extension".

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

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

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_____

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2 ABBREVIATIONS INDEX

ADR	Adverse Drug Reaction	RA	Regulatory Authority
ALT	Alanine Aminotrasferase	kg	Kilogram
ANCOVA	Analysis of co-variance	l	Liter
AST	Aspartate Aminotrasferase	LDL	Low-density lipoprotein
ATC	Anatomical Therapeutic Chemical Classification	LPLV	Last Patient Last Visit
AUC	Area Under the Plasma Concentration	MedDRA	Medical Dictionary for Regulatory Activities
A/S	Aktieselskab	MDD	Major Depressive Disorder
BMI	Body Mass Index	mg	Milligram
BP	Blood Pressure	mL	Milliliter
Bpm	Beats per minute	mmHg	Millimeter of mercury
BMI	Body Mass Index	mmol	Millimol
CI	Confidence Interval	N	No
Cm	Centimeter	N (No)	Number
Cmax	Maximum measured plasma concentration	ng	Nanogram
CRF	Case Report Form	NYHA	New York Heart Association
CRO	Contract Research Organization	OLE	Open Label Extension
CYP	Cytochrome P450	OP	Out-patient
CV	Coefficient of Variation	OTC	Over the Counter
CV	Cardio Vascular	P	Phone
CVD	Cardio Vascular Disease	PK	Pharmacokinetic
°C	Degrees Celsius	PK/DM	Pharmacokinetics/Drug Metabolism
DBP	Diastolic Blood Pressure	PPP	Per-Protocol Population
DDI	Drug-drug Interaction	PWS	Prader Willi Syndrom
Dl	Deciliter	Q	Quarter
DMP	Data Management Plan	QA	Quality Assurance
DSMB	Data Safety Monitoring Board	QC	Quality Control
DXA	Dual X-ray absorptiometry	SAE	Serious Adverse Event
ECG	Electrocardiogram	SAP	Statistical Analysis Plan
EC	Ethic Committee	SBP	Systolic Blood Pressure
eCRF	Electronic Case Report Form	SD	Standard Deviation
EMEA	European Agency for the Evaluation of Medical Products	SOP	Standard Operating Procedure
EU	European Union	SUKL	State Institute for Drug Control
FPG	Fasting Plasma Glucose	SUSAR	Suspected Unexpected Serious Adverse Reactions
GCP	Good Clinical Practice	Tmax	Time of the maximum
HDL	High-density lipoprotein	TZD	Thiazolidinediones
HbA1C	Hemoglobin A1c	T2MD	Type 2 diabetes mellitus
HQCT	Hyperphagia Questionnaire for Clinical Trials	ULN	Upper Limit of Normal range
HR	Heart Rate	USA	United States of America
IB	Investigator Brochures	WHO DD	World Heath Organization Drug Dictionary
ICH	International Conference on Harmonization		
IEC	Independent Ethics Committee		
IMP	Investigation Medicinal Product		

3 INTRODUCTION AND STUDY RATIONALE

3.1 CLINICAL BACKGROUND

Etiology and treatment of Prader- Willi syndrome

Prader-Willi syndrome is a complex genetic condition caused by an abnormality on the long arm of chromosome 15 (q11-q13) that affects many parts and organ systems of the body. In infancy, this condition is characterized by weak muscle tone (hypotonia), feeding difficulties, poor growth, and delayed development. Beginning in childhood, affected individuals develop an insatiable appetite, which leads to chronic overeating (hyperphagia) and obesity. Many subjects with Prader-Willi syndrome, particularly those with obesity, also develop type 2 diabetes mellitus (T2DM) and other related co-morbidities early in life often leading to development of cardiovascular disease and early death.

Subjects with Prader-Willi syndrome typically have mild to moderate intellectual impairment and learning disabilities. Behavioral problems are common, including temper outbursts, stubbornness, and compulsive behavior such as picking at the skin. Sleep abnormalities can also occur. Additional features of this condition include distinctive facial features such as a narrow forehead, almond-shaped eyes, and a triangular mouth; short stature; and small hands and feet. Some people with Prader-Willi syndrome have unusually fair skin and light-colored hair. Both affected males and affected females have underdeveloped genitals. Puberty is delayed or incomplete, and most affected individuals are unable to have children (infertile). (1)

Prader-Willi syndrome affects an estimated 1 in 10,000 to 30,000 people worldwide. Most cases of Prader-Willi syndrome are not inherited, particularly those caused by a deletion in the paternal chromosome 15 or by maternal uniparental disomy. These genetic changes occur as random events during the formation of reproductive cells (eggs and sperm) or in early embryonic development. Affected subjects typically have no history of the disorder in their family.

Rarely, a genetic change responsible for Prader-Willi syndrome can be inherited. For example, it is possible for a genetic change that abnormally inactivates genes on the paternal chromosome 15 to be passed from one generation to the next. (1)

Current treatment strategies

There is currently no specific treatment for this syndrome. Growth hormone has been routinely used to help with growth and to increase muscle mass, which allows greater physical activity. As other diseases develop as the subject's age, eg, T2DM, hypertension, dyslipidemia or psychiatric disorders, these are managed per local practice and treatment standards.

Overview of tesofensine

Tesofensine was initially studied for the treatment of Parkinson and Alzheimer's diseases. However, clinical studies showed only a limited efficacy of tesofensine, but weight loss was noted in majority of participants, despite the fact that they did not attempt to lose weight. Tesofensine is an inhibitor of monoamine presynaptic reuptake of the neurotransmitters noradrenaline, dopamine and serotonin. This means it influences these chemicals in the brain to suppress appetite. Tesofensine demonstrated strong weight reducing effects in Phase 2

clinical studies in obese subjects, exceeding benchmarks set by the regulatory agencies for approval of weight loss agents (2). Also, post-hoc analysis of the data from the Phase 2 obesity study showed that individuals with pre-diabetes in this study experienced a favorable reduction in body weight and glycaemic endpoints while on tesofensine.

In general, tesofensine was well tolerated in humans with the most commonly observed side effects of dry mouth, headache, insomnia, and nausea However, blood pressure and heart rate increase were observed. With the therapeutically relevant doses of tesofensine (0.25 mg and 0.5 mg) an increase in blood pressure (BP) of 1–3 mmHg and an increase in heart rate (HR) up to 8 bpm were seen (2). Currently, there are no data indicating that these effects of tesofensine would translate into increased risk of cardiovascular (CV) events; however, these increases could hypothetically have an adverse impact on the cardiovascular safety in certain individuals.. This lead to the addition of metoprolol to mitigate these effects and further ensure a favorable benefit/risk profile. For more information on tesofensine please see the Investigators' Brochure (Version 13).

Overview of metoprolol
Metoprolol is a $beta_1$-selective (cardio selective) adrenoceptor-blocking agent, for oral administration, which has been approved in the 70's and has been one of the most widely prescribed medicines to date. It is indicated for hypertension, angina pectoris and heart failure. It is now available as extended-release tablets. Metoprolol extended release, has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. This is also the formulation selected for this study (for more information please see the Summary of Product Characteristics of metoprolol).

Overview of tesofensine/metoprolol
In a pre-clinical study in rats the co-administration of tesofensine + metoprolol showed a HR and BP profile similar to placebo (vehicle) while the weight-reducing efficacy was maintained (3). In addition, in a drug-drug interaction study in healthy male subjects addition of short acting metoprolol on the background of chronic dosing with tesofensine showed a short term, but substantial, reduction in HR previously increased by tesofensine. Co-administration of tesofensine (0.5 mg qd) and metoprolol (100 mg qd) is currently being studied in a Phase 2a proof-of-concept study in 60 subjects with T2DM at two sites in Germany. Taken together, the available data support the concomitant use of tesofensine and a beta-blocker such as metoprolol as an investigational agent for the proposed indication of treatment of obesity and related co-morbidities in subjects with Prader-Willi syndrome.

Purpose of the Comparison to Placebo
Double blind, placebo-controlled design is the gold standard in evaluation of efficacy and safety of new drugs. It provides the most rigorous and unbiased evaluation of the true effects of an intervention. This design was chosen because it is critical to thoroughly assess the efficacy of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome.

Purpose of this study
The purpose of this study is to investigate the safety and efficacy of co-administration of tesofensine/metoprolol treatment versus placebo in adult and pediatric subjects with Prader-Willi syndrome.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 OBJECTIVES

Primary objective:

- To examine the effect of co-administration of tesofensine/metoprolol on body weight in subjects with PWS in an open labeled extension

Secondary objectives:

- To establish pharmacokinetic profile of tesofensine and metoprolol in subjects with PWS
- To examine the change in hyperphagia-related behavior in subjects with PWS by use of the Hyperphagia Questionnaire for Clinical Trials (HQ-CT)
- To examine the effect of co-administration of tesofensine/metoprolol on glycemic control and lipid profile in subjects with PWS
- To examine the effect of co-administration of tesofensine/metoprolol on HR and BP in subjects with PWS
- To examine the effects of co-administration of tesofensine/metoprolol on body composition in subjects with PWS
- To evaluate overall safety and tolerability of co-administration of the tesofensine/metoprolol in subjects with PWS

4.2 ENDPOINTS (Baseline = Day 0; End of double-blind treatment = Day 90, end of first OLE = Day 180, end of second OLE = Day 270)

Primary endpoint

- Percent change from baseline to end of treatment periods in mean body weight

Secondary endpoints

- Steady state concentrations of tesofensine and metoprolol as measured by trough values
- Uptake and initial plateau concentrations of metoprolol as measured by samples taken 2 and 4 hours after dose administration
- Change from baseline to end of the treatment periods in total HQCT score
- Change from baseline to end of treatment periods in mean body weight (kg)
- Change from baseline to end of treatment periods in fat- and fat-free mass (%) by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment periods in HR (bpm), SBP (mmHg), DBP (mmHg)
- AEs, clinical labs, ECG

Exploratory endpoints:

- Change from baseline to end of treatment periods in FPG, insulin
- Change from baseline to end of treatment periods in lipid profile
- Change from baseline to end of treatment periods in waist circumference (cm)

5 OVERALL STUDY DESCRIPTION

This is a second open label extension study of the double-blind, randomized, placebo-controlled, multiple-dose, multi-centre, safety and efficacy study of co-administration of tesofensine/metoprolol treatment in subjects with Prader-Willi syndrome. This open label extension is a follow up of the first OLE, which included 8 children with PWS (Protocol Amendment 1.6).

Subjects who complete first OLE (12 weeks) will be invited to participate in the second open label extension phase. Participation will be based on the judgment of the Investigators whether or not it is safe for the subject to continue in the extension study. Study medication will be administered for ninety (90) days (+2 days after the final assessments with half-dose of metoprolol).
In the second OLE all subjects deemed eligible by the PI will receive tesofensine 0.125 mg (0.25 mg every second day) + metoprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, in the morning with a meal. Those patients who tolerated the 0.125/25 mg tesofensine/metoprolol dose well in the first OLE will receive 0.25 mg of tesofensine with 25 mg of metoprolol ER.

In case a patient, in the opinion of the PI, experiences an adverse event that by the PI is suspected to be potentially related to an undesirable drug concentration of the investigational medication, the investigators at each site, based on their discretion, can extend the period between dosages of the IMP or implement a drug holiday, or reduce the dose (those on 0.25 mg of tesofensine) in order to optimally manage the wellbeing and safety of the patient. Each of these cases should be discussed in advance with the Sponsor's medical monitor.

Subjects together with their parents/guardians/caregivers (where applicable according to existing country legislation) who give the written informed consent for the second open label extension part will continue in the study. If not, subject will finish the study based on the Protocol Amendment 1.6.

Opel label period: after the Day 180 (Visit 17), subjects will visit the site every month for efficacy and safety evaluations and medication supply (in total 4 personal visits at the site are requested). Study procedures in the second extension part are the same as in the first OLE.
If possible subjects will be asked to stay at the site for the collection of blood for PK of metoprolol 2 and 4 hours after dose administration – the blood for these samples will be collected once from each patient (only if it hasn't been collected during the first OLE), but to allow for greater flexibility accounting for their unstable and unpredictable nature, it is included during every on site visit.

End of treatment visit: On Visit 20 (Day 270) subjects will come for the final treatment visit. During the Visit 20 the blood will be collected for metabolic endpoint as well as safety measurements. Subjects will also receive two days of half-dose dose of metoprolol to take at home in order to gradually reduce the dose of metoprolol to avoid potential undesirable fluctuation in blood pressure.

End of study: On Visit 21 (Day 300) the subjects will be invited for the final safety check, BP/HR assessment and PK sampling (30 days after last dose), which will conclude their participation in the study.

Phone calls in-between the onsite visits will be used to provide additional reassurance regarding the safety of the subjects and collect adverse events.

Subjects who exceed predefined values of HbA1c>10%, FPG >11.0 mmol/l or BP>160/110 mmHg will be treated at the discretion of the investigator per established guidelines to improve the patients glycaemic/BP control while remaining in the study.

Assessments conducted during each visit are described in the schedule of events, Appendix 16.2.

5.1 STUDY VISIT DESCRIPTION

Visit 17, Day 180 – Last visit of the first OLE and first visit of the second Open label extension study:

The following procedures will be performed:

- Signing the Addendum to double blind ICF for the second open label extension
- Conducting physical examination
- Measurement of vital signs
- Measurement of body weight and waist circumference
- Measurement of height, calculation of BMI
- Obtaining ECG
- Performing routine hematology, blood chemistry assessment
- Collection of blood for efficacy (HbA1c, FPG, lipids, insulin)
- Collection of blood for PK of steady state concentrations of tesofensine and metoprolol as measured by trough values
- Collection of blood for PK of metoprolol taken 2 and 4 hours after dose administration (only if not done already)
- Performing the urinary pregnancy test
- DEXA
- HQCT
- AEs assessment
- Psychiatric examination
- Assessment of concomitant medications
- Dispensing the subject diary for the open label extension, study card for second OLE
- Dispensation of study medication
- Scheduling the next on-site visit and phone call

All diabetic subjects (together with their parents/guardians/caregivers) will be again instructed to closely follow the dietary instruction and medical treatment for their diabetes. Subjects (together with their parents/guardians/caregivers) will be again educated in and again asked to watch for any symptoms or signs of hypoglycemia. Hypoglycaemic episodes must be reported to investigator during the phone call visits or personal visit at the site. In case of an unexplained hypoglycaemic event (no extra exercise, skipping a meal or alike) the subjects (together with their parents/guardians/caregivers) should contact the site. Information about providing instruction regarding hypoglycaemic episodes must be recorded in the subject's source data.

Visit 18, 19 (Day 210, 240 (30±3 days**) – personal visits:**

The following assessments will be done:

- Measurement of vital signs
- Measurement of body weight and waist circumference
- Collection of blood for efficacy (HbA1c, FPG, lipids, insulin)
- Collection of blood for PK of steady state concentrations of tesofensine and metoprolol as measured by trough values
- Collection of blood for PK of metoprolol taken 2 and 4 hours after dose administration (only if not done already)
- HQCT
- AEs assessment
- Psychiatric examination
- Assessment of concomitant medications
- Review of subject diary
- Medication accountability check
- Scheduling the phone call and subject personal visit

Visit 20 (Day 270, (30±3 days**)) – End of treatment visit**
The following assessments will be done:

- Conducting physical examination
- Measurement of vital signs
- Measurement of body weight and waist circumference
- Obtaining ECG
- Performing routine hematology, blood chemistry assessment
- Collection of blood for efficacy (HbA1c, FPG, lipids, insulin)
- Collection of blood for PK of steady state concentrations of tesofensine and metoprolol as measured by trough values
- Collection of blood for PK of metoprolol taken 2 and 4 hours after dose administration (only if not done already)
- Performing the urinary pregnancy test
- DEXA
- HQCT
- AEs assessment
- Psychiatric examination
- Assessment of concomitant medications
- Medication accountability check

- Dispense of two half-doses of metoprolol medication
- Collection and review of subject diary
- Dispensing a follow up diary lists for recording AE and concomitant medication between last subject visit on Day 300
- Scheduling Final visit on Day 300

Day 270 (morning) will be the last day when subjects receive the study medication.

On Day 270 subjects will receive a half-dose of the metoprolol dose to take at home, one dosage over the next two days in order to gradually reduce the dose of metoprolol and avoid potential undesirable fluctuation in blood pressure.

Phone calls between the on-site visit
Phone calls in between the onsite visits will be used to provide additional reassurance regarding the safety of the subjects and to collect adverse events. Subjects (parents/guardians/caregivers) will be asked the following:

- Since your last visit, have you experienced or do you currently experience any symptoms that are not associated with your disease?
- Any change in concomitant medications
- Any Hypoglycemic episodes

Visit 21 (Day 300 (30±3 days))) Final follow-up –– personal visit
The following assessments will be done:

- AEs
- Measurement of vital signs
- Measurement of body weight and waist circumference
- HQCT
- Psychiatric examination
- Concomitant medications
- Collection of blood for PK
- Review of subject diary
- Collection of subject follow up diary

End of study (Day 300)
Visit 21 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.

Unscheduled visit – if applicable:
The following assessments will be done:

- Conducting physical examination
- Measurement of vital signs
- Measurement of body weight and waist circumference
- Performing routine hematology, blood chemistry assessment
- AEs assessment
- Assessment of concomitant medications

5.2 END OF STUDY

The end of study (Day 300) is defined by LPLV for TM002, including the second OLE. If a subject withdraws from the study during the treatment period, or has to discontinue for any reason, a visit will be organized at which the assessments planned for Visit 20 will be performed. If a subject refuses to attend a visit, the investigator should make every effort to obtain the information over the telephone from the subject regarding the safety.

5.3 STUDY PARTICIPANTS

All male and female pediatric subjects with confirmed diagnosis of PWS who completed the first OLE (12 weeks), will be invited to participate in the second open label extension phase, if deemed eligible by the Investigators.

5.4 DISCONTINUATION CRITERIA

The subject or her/his parents/guardians/caregivers has a right to discontinue subject's study participation at any time for any reason. The reason for discontinuation will be documented in the subject's source documents and in the eCRF. In the event of an early termination, all procedures described for a subject completing the study as planned for Visit 20 (Day 270) should be performed. Subjects discontinuing due to adverse events will be followed-up until complete resolution of the adverse event or until there is a satisfactory explanation of the changes observed.

5.5 WITHDRAWAL CRITERIA

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

- Request by subject (withdrawal of informed consent)
- Request by parents/guardians/caregivers
- Investigator's decision
- Pregnancy
- Acute allergic reaction to study medication
- HbA1c ≥ 10%
- FPG>13.3 mmol/l (repeated on 2 days)
- Any event, including hospitalization of the subject in another location where the investigator will not be able to follow the subject
- Evidence of the use of recreational medications or prohibited medications during the study
- Failure to comply with the study stipulations
- Severe symptomatic bradycardia (heart rate < 50 bpm) during the study
- Lost to follow-up. Subjects will be deemed lost to follow-up if they do not return for scheduled visits without giving a reason, and if the investigator is unable to contact the subject directly or indirectly (e.g. via the subject's family). If a subject does not attend a scheduled visit, the investigator will make best efforts to obtain information about the subject before considering the subject lost to follow up

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviation, administrative or any other valid and ethical reason. If an investigator judges a subject to be at medical risk by complying with the protocol, he or she may discontinue the participation of the subject. The circumstances surrounding the decision must be discussed with the sponsor and recorded in the subject's source documents and eCRF.

5.6 PREMATURE STUDY DISCONTINUATION

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

Reasons for terminating the study may include the following:

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

5.7 EARLY TERMINATION OF A STUDY SITE

The sponsor may close the site if severe protocol deviations are observed.

5.8 STUDY SITES

The study will be conducted at two sites, one in Czech Republic and one in Hungary.

5.9 STUDY DURATION

The expected start date for the second open label part is planned for March/April 2019. The individual study duration for one subject is up to 16 weeks including treatment period (12 weeks of the open label period) and the final visit (30 days after the last treatment visit). The end of second open label is defined by the Last Visit of the Last pediatric subject, which is likely to occur in June/July 2019.

5.10 TOTAL STUDY DURATION

The projected duration of the whole study (including Step 2 and both OLEs) is ~15months. The end of TM002 is defined as Last Visit of the Last Pediatric Patient in the second open label extension.

5.11 BENEFITS AND RISKS FOR STUDY PARTICIPANTS

It is expected that tesofensine and metoprolol combination will be well tolerated. This assessment is based on the comprehensive experiences from previous preclinical and clinical studies of tesofensine, the availability of metoprolol on the market for many years and the present tesofensine/metoprolol investigation in subjects with T2DM. All subjects will receive diet consulting, and it is expected that subjects on active treatment will see a reduction in their hunger, food craving and body weight. 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, and will have weekly contact (personal or telephone contact) to the site throughout the study.

There were adverse events observed in Step 1 of this study, which lead to premature discontinuation of several patients. It is believed these adverse events were driven by unexpectedly high concentration of tesofensine and that the proposed changes in the dosing of the IMP in the study protocol proposed for Step 2 and both OLEs should keep the overall risk/benefit balance favorable.

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

Due to the CNS-located mechanism of action of tesofensine, a monoamine reuptake inhibitor, there could be a concern regarding psychiatric side effects. In obese subjects dosed for up to 24 weeks, common psychiatric symptoms were insomnia and depressed mood. Occurrence of insomnia displayed a clear dose-dependency with the highest incidence on the highest dose (1 mg). Psychotic phenomena, like those encountered in patients with dementia of the Alzheimer's type or Parkinson's disease, were not registered in the population of obese subjects. Pooled data from studies NS2330-001 and NS2330-004 did not reveal an increased incidence of psychiatric events following long-term extension study, i.e. 18 months of treatment. Current data from the clinical studies with obese patients do not suggest that tesofensine at doses of 0.25 mg and 0.5 mg once daily are associated with any clinically significant undesirable psychiatric profile. (IB version 13 and any updates thereof).

Metoprolol adverse reactions – post marketing experience
- Blood and lymphatic system: thrombocytopenia, leukopenia, agranulocytosis
- Cardiovascular: cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension
- Respiratory: wheezing (bronchospasm), dyspnea, rhinitis
- Central Nervous System: confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia
- Psychiatric: changes in personality, depression
- Gastrointestinal: nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting, abdominal pain, retroperitoneal fibrosis
- Hypersensitive Reactions: pruritus
- Miscellaneous: fatigue, hyperhidrosis, hepatitis, increased liver enzymes, musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, dry eyes, psoriasis-like dermatitis, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance, gangrene

For more information regarding the adverse events please see the Summary of Product Characteristics of metoprolol.

It is anticipated that the subject receiving the study medication will experience a reduction in their body weight and improvement in their glycaemic control (if diabetic or pre-diabetic). Although tesofensine has not been previously investigated in adult and pediatric subjects with Prader-Willi syndrome, based on the highly statistically and clinically meaningful degree of weight loss seen in the available literature it is anticipated that participants in this study will experience improvement in their glycaemic control (also including those on placebo who will receive diet, exercise and lifestyle modification guidance). In addition, all patients will have access to a state-of-the-art clinical care that they will receive for the duration of the study.

Subjects randomized to the placebo arm will receive state of the art clinical study for almost 4 months with regular visits and multiple sophisticated assessment of their health status, including their diabetes, as well as lifestyle guidance from a dietician. Pediatric subjects with PWS are being included only after the Sponsor received positive opinion from SUKL, which concludes that that no safety concerns arose from IMP application in adult PWS patients in Step 1 and TM001.

6 TREATMENT OF STUDY PARTICIPANTS= identical to the first OLE

6.1 DESCRIPTION OF STUDY MEDICATION

Investigational Medicinal Product

Tesofensine is a serotonin-noradrenaline-dopamine reuptake inhibitor, for oral administration, which is manufactured, packed and labeled by Delpharm in Reims (France). Its chemical name (IUPAC) is（1R,2R,3S,5S)-2-Ethoxymethyl-3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane,2-hydroxy-1,2,3-propanetricarboxylate (1:1). Designated contractors will supply study medications directly.

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

In the first Open label (children with PWS), tesofensine 0.125 mg (0.25 mg every second day) + metoprolol 25 mg was administered once a day, in the morning with a meal. In the second OLE all subjects deemed eligible by the PI will receive tesofensine 0.125 mg (0.25 mg every second day) + metoprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, in the morning with a meal. Those patients who tolerated the 0.125/25 mg tesofensine/metoprolol dose well in the first OLE will receive 0.25 mg of tesofensine with 25 mg of metoprolol ER.

In case a patient in the opinion of the PI experience an adverse event that by the PI are suspected to be potentially related to an undesirable drug concentration of the investigational medication the investigators at each site, based on their discretion, can extend the period between dosages of the IMP or implement a drug holiday or reduce the dose (those on 0.25 mg of tesofensine) in order to optimally manage the wellbeing and safety of the patient. Each of theses cases should be discussed in advance with the Sponsor's medical monitor.

6.2 IMP HANDLING PROCEDURES - KLIFO

The contracted CRO Klifo (Denmark) is responsible for the IMP management.

6.3 IMP HANDLING PROCEDURES – STUDY SITE

- Klifo is responsible for transferring the IMP to assigned and contracted study site pharmacies in Czech Republic and Hungary
- The site pharmacists (at both sites) are responsible for acknowledgment of receipt of the of IMP by signing the receipt forms
- Storing the IMP on site pharmacy in a secured area with restricted access under the

controlled temperature conditions
- Dispensing IMP to site staff according to the protocol

Prior to the initial shipment of the study medication to the site(s), the following essential documents must be available in the Study Master File:
- EC/RA approval
- EC/RA approved subject information/informed consent form
- Clinical study protocol signed by the principal investigator
- Study agreement/contract signed by the principal investigator

The investigator is responsible for study medication kits accountability. The site pharmacist is responsible for maintaining accurate records of all information relating to the management of the study medication. If any quality issues are noticed on receipt or use of the IMP (e.g. damaged condition, faults in appearance, errors in the documentation, incorrect labeling, 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 study medication made by the study subjects.
In the event of a batch recall, the sponsor or its representative will inform the investigator or site pharmacist in writing. Upon receipt, and as instructed, the investigator or site pharmacist should immediately contact any study subject in possession of the corresponding study medication kits.

6.4 LABELS FOR STUDY MEDICATION

The label texts will be translated or adjusted as necessary so that they comply with the applicable national laws and regulatory requirements of the country in which the study will be conducted. The label text will include the following information as minimum:
- Name of Sponsor
- Name of CRO or Investigator
- Protocol number
- Subject screening number
- Dosing instructions
- Batch number
- Expiry date
- Visit number
- The words ‘For clinical study use only’
- The words ‘Keep out of reach of children’
- Storage conditions

6.5 PACKAGING AND DESTRUCTION

Medication will be distributed to the subjects in plastic bottle (tesofensine) and in blisters (metoprolol) labeled with the appropriate study medication number. The investigator and site pharmacists will collect unused study medication. Klifo is responsible for central destruction of all study medication (partially used and unused). Subjects will be asked to use Metoprolol every morning with or right after a meal and not to crush or chew the tablets and Tesofensine every second day. Subject will be asked to store the medication at room temperature (15 - 25 °C) and return the unused study medication on visit 20 at the site.

6.6 STUDY MEDICATION COMPLIANCE

The investigational medicinal products will be self-administered by the subjects or parents/guardians/caregivers at home. For the monitoring of study medication, subjects or parents/guardians/caregivers will be instructed to return bottle and blisters with study medication at visit 20, whether full, partially empty, or empty.

6.7 OPEN LABEL SUBJECT NUMBER

Subjects who sign the informed consent (together with signed informed consent form by subject's parents/guardians/caregivers where applicable according to existing country legislation) will keep at the Visit 17 their unique screening number consisting of a two (2) digit site number and three (3) digit subject number and country abbreviation.

6.8 UNBLINDING

Not applicable, it is an open label study.

6.9 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 or subject's parents/guardians/caregivers, including empty bottles/blisters will be accounted for and returned to the investigator and destroyed by the Klifo.

6.10 ACCOUNTABILITY OF THE STUDY MEDICATION

The investigators will make every effort to encourage subjects together with help of subject's parents/guardians/caregivers 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/blisters on-site. The delivery to, use by and return from the subject or subject's parents/guardians/caregivers must be documented. All opened and unopened bottles/blisters, together with remaining contents, will be returned by the subject or subject's caregiver/guardian/parents 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/blister that is missing. It is the investigator's responsibility to instruct the subjects and subject's parents/guardians/caregivers about using and returning of study medication.

6.11 CONCOMITANT MEDICATION

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

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

- Reason for administration

6.12 PROHIBITED MEDICATIONS

For prohibited concomitant medications, please refer to Appendix 1 and Exclusion criteria. Paracetamol is an exception and may occasionally be taken by the subjects in the treatment of acute pain (e.g. headache or toothache). In such case, the subjects will be asked to keep record in the diary.

6.13 STUDY PROCEDURES AND OTHER EXAMINATIONS

Informed Consent for the second OLE

It is the responsibility of the investigator to give each subject (or, if the subjects do not have legal authority to provide consent for themselves their legally appointed parents/guardians/caregivers where applicable according to existing country legislation) full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. In pediatric subjects the patient information and informed consent forms will be prepared per local legislative requirements.

The OLE ICF, approved by the RA/EC, must be given to each subject or parents/guardians/caregivers before any study-related procedure is undertaken. The subjects must be informed about their right to withdraw from the study at any time. The written subject/parents/guardians/caregivers information cannot be changed without prior approval by Sponsor and the RA/EC. Furthermore, it is the responsibility of the investigator to obtain signed informed consent from all subjects (or the parents/guardians/caregivers) prior to undertaking any study-related procedure. Two original forms will be given to the subject/parents/guardian/caregivers for signature. One is to be kept by the subject/parents/guardians/caregivers and one is to be filed in the Investigator's Study File.

Due to the special nature of this population, it is possible that they will have caregivers (i.e. a person caring for the subject but who is not authorized to provide legally relevant consent in relation to the subject' participation in the study) but who, in the course of the clinical study, will help the subject and the study team in administering the treatment, travelling to the site, and conduct at home subject' assessments in compliance with the rules of the clinical study. A separate written information sheet for caregivers will be prepared specifying all of the important pieces of information for this person; the document will also explain the role of the caregiver in detail. By signing the informed consent the caregiver agrees that the child under his/her care will participate in the OLE and he/she will become involved in the clinical trial as well, but with limited rights.

Vital Signs

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

Physical Examination

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

Blood pressure measurement

- Subject should avoid food immediately before the measurement
- Subject should go to the toilet before BP measurement. A full bladder can increase blood pressure slightly

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

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

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

Urinary pregnancy test will be done only for any women of childbearing potential at the site at the Day 180 and on Day 270.

DEXA will be done using standardized protocol while the subjects wear light clothing at the Day 180 and on Day 270

HQCT - parents/guardian/caregivers will be asked during each personal visit to evaluate the food-seeking behavior of the subject with PW. Subjects with PWS are themselves unable to consistently and reliably report the severity of their hyperphagia, due to their intellectual limitations. In case that the subject is not at home during the week (for ex. at boarding school), parents/guardian/caregivers should ask the teacher or the relevant person about subject's eating behavior during the week and based on the received information, the HQCT should be completed.

6.14 LABORATORY EVALUATIONS

Laboratory samples will be collected from subjects at the site, and will be shipped to the local laboratory for analysis in ambient conditions.

The investigator will receive the data from local laboratory. Laboratory results will be reviewed, evaluated, signed and dated by the investigator. 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 in subject's medical file.

The investigator´s evaluation (´normal´, ´abnormal and not clinically significant´ or ´abnormal and clinically significant´) will be entered into the eCRF.

If a laboratory result is considered clinically significant and it fulfills the criteria for a clinical laboratory AE, it should be reported in accordance with section 6. Clinically significant laboratory findings from the screening visit before the randomization should be recorded as concomitant illness.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the study database, but abnormal values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

- **Hematology**: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets, will be analysed by local laboratory
- **Blood chemistry**: creatinine, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, GFR and urea will be analyzed by local laboratory
- **HbA1c** will be analyzed by local laboratory
- **Lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), serum insulin** will be analyzed by local laboratory
- **Fasting plasma glucose** - will be analyzed by local laboratory

PK – plasma concentrations of tesofensine/metoprolol will be measured. Each PK blood sample must have time of draw attached to it as well as timing of the last dose of the study mediation taken prior to the blood draw. The analyses will be done by sponsor selected external laboratory: Bioanalytical and ADME Labs. Q2 Solutions, 19 Brown Rd, Ithaca, NY 14850, USA.

6.15 SUBJECTS' DIARIES

Subject diaries for the second open label extension on Day 180 (Visit 17) will be provided. Subject's caregiver/guardian/parents will be asked on behalf of subject to record in the diary the following: date, taking of the study medication, AEs, concomitant medication, hypoglycemic episodes.

7 SAFETY REPORTING

All AEs occurring after the randomization of the subject will be reported as AE (if any AEs occurred between screening and randomization will be reported in medical history, but not as a AE). The report will include information on onset and stop dates, nature, severity (=grading, see below), seriousness, interventions and medications required, and outcome. SAEs will be reported to the regulatory authorities and Independent Ethics Committees (IECs) according to local regulations, and will be followed-up until the resolution of the event.

At each visit, subject together with help of subject's parents/guardians/caregivers will be asked: "Do you currently (or did you) experience any symptoms that are not associated with your disease (since the last visit)?" Any symptom is to be entered into the Adverse Event eCRF.

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.

7.1 DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes all unintended or unforeseeable signs and symptoms, and addition:

- All suspected IMP adverse reactions
- Psychological symptoms (including aggressive behavior 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)
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event

Each adverse event is to be classified by the investigator as serious or non-serious.

7.2 ADVERSE EVENT

All AEs encountered after the randomization will be recorded in detail indicated in the eCRF, regardless of their relationship to the investigational study product as assessed by the investigator. The investigator must record all directly observed adverse events and all adverse events spontaneously reported by the subject or parents/guardians/caregivers during the study. AEs will be coded by use of an internationally recognized dictionary (MedDRA). Details are described in the study specific Data Management Plan.

7.3 GRADING OF ADVERSE EVENT SEVERITY

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of each adverse event. For purposes of consistency, these intensity grades are defined as follows:

Mild	Does not interfere with subject's usual age-appropriate instrumental* activities of daily life (ADL)
Moderate	Interferes with subject's usual age-appropriate instrumental* activities of daily life (ADL)

Severe	Interferes with subject's usual age-appropriate self care** activities of daily life (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.4 CAUSALITY OF AE

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

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely or Unrelated: A clinical event, including a laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

or

The event may or may not follow a reasonable temporal sequence from administration of the investigational study medication and is clearly related to other factors, such as other drugs, chemicals, underlying disease, therapeutic intervention, or concomitant therapy.

Actual changes in severity or causal relationship of a medical occurrence require the completion of a new line in the AE form in the CRF.

7.5 OUTCOME OF AE

The outcome type and the follow-up of subjects with AEs should be specified. Outcome of adverse event may include at time of last observation: Recovered / resolved; Not recovered / not resolved; Recovered / resolved with squeal; Fatal; Unknown.

AEs requiring therapy must be treated by recognized standards of medical care to protect the health and welfare of the subject. Appropriate equipment and medicines must be available to ensure the best possible treatment of emergency situations. Action(s) taken: Study treatment withdrawn; Dose reduced; Dose increased; Dose not changed; Unknown; Not applicable.

7.6 UNEXPECTED ADVERSE REACTION

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

7.7 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is any adverse event that at any dose is

- Fatal
- Life-threatening
- Results in a persistent disability or incapacity
- Results in a congenital abnormality or birth-defect
- Results in or prolongs in-patient hospitalization; or
- Is otherwise classified as medically significant

Elective surgeries are not considered as SAEs and do not have to be reported as such.

In this context, the term life threatening refers to an event in which the subject was at immediate risk of death at the time of the event; it does NOT refer to an event, which might have caused death if it would have been more severe.
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 outpatient 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.

Any important medical event that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above should also be reported as a SAE. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

Hospitalization for diagnostic or therapeutic procedures in the absence of any associated AE will not be considered as a SAE, except when otherwise required by Regulatory Authorities.

7.8 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

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

7.9 RECORDING OF ADVERSE EVENTS

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

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

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

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

7.10 REPORTING PROCEDURE OF SERIOUS ADVERSE EVENTS

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

Any serious AE must be reported by investigator to the Sponsor´s delegate for Pharmacovigilance within 24 hr by fax or email:

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

Care should be taken to ensure that the subject's identity is protected and the subject's identifiers in the clinical study are not included on any copy of source documents provided to the sponsor. Post-study SAEs may be reported in an expedited manner to the sponsor at the investigator´s discretion.

All data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (e.g. laboratory data, concomitant medication, subject status) should be sent (by e-mail) to the sponsor within 24 hours of knowledge. In addition, every

effort should be made to document further any SAE that is fatal or life threatening within 1 week (7 days) following initial notification.

The sponsor's delegate for pharmacovigilance will make expedited reports of all SAEs that are both unexpected and causally related to the IMP, to the Regulatory Authorities, IECs as appropriate and to the investigators at other investigational sites. In addition, the sponsor's delegate for pharmacovigilance may make expedited reports of all SAEs that are expected and causally related to the IMPs to the Competent Authorities, according to the European directive 2001/20/EC and the local regulations. The sponsor's delegate for pharmacovigilance will report all safety observations made during the conduct of the study in the clinical study report. Details of SAE case exchange between the Sponsor´s delegate for pharmacovigilance, the Sponsor, National Competent Authorities and Ethics Committees will be set forth in a separate Safety Management Plan.

7.11 FOLLOW-UP OF ADVERSE EVENTS

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

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

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

7.12 ANNUAL SAFETY REPORTS

Once yearly or upon request by the National Competent Authorities the Sponsor's delegate for pharmacovigilance will write down an Annual Safety Report, which will adhere to the Development Safety Update Report (DSUR) format (ICH E2F guideline) and contain a list of Serious Adverse Events an analysis of the study's subjects' safety. This report will be sent to Regulatory Authorities and to the IECs in the 60 days after the anniversary of the first inclusion. Details of DSUR preparation, review and submission will be set forth in a separate Safety Management Plan.

When the Step 2 double-blind part is completed, it will be unblinded and reported, even though the OLE will still be ongoing.

8 DESCRIPTION OF STATISTICAL METHODS

8.1 DESCRIPTION OF STATISTICAL METHODS

CRO selected and designated by the Sponsor 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 CRO's biostatistical standard operating procedures (SOPs). A general description of the statistical methods to be used is given in this chapter, specific details will be provided in the Statistical Analysis Plan (SAP), which will be prepared before data base lock. All statistical analyses will be performed using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.4 or later.

8.2 SAMPLE SIZE CALCULATION

As this is an explorative study no formal sample size calculation was done. Eligible patients are restricted to completers from step 2 in the double-blind part of the study.

8.3 SELECTION OF SUBJECTS FOR ANALYSES

The following analysis sets are defined in accordance with the ICH-E9 guidance (5):

Full Analysis Set (FAS)
Includes all randomized and treated subjects with post-dose data collected. Subjects in the FAS will contribute to the evaluation 'as treated'.

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

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

The primary analyses of primary and secondary endpoints will be based on the FAS. Sensitivity analyses will be based on the PPP. The analyses of the safety endpoints will be based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. Furthermore, outliers will be identified by data review according to ICH-E9 (5). In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis. Obviously erroneous data points may be excluded from the analyses. The decision to exclude data points from the statistical analysis is the joint responsibility of the sponsor, the investigator and the CRO statistician.

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

8.4 STATISTICAL METHODS

All primary and secondary endpoints will be summarized by treatment and visit using descriptive statistics. Continuous endpoints are summarized by the arithmetic mean, geometric mean (when applicable), median, standard deviation, coefficient of variation (CV, when applicable), minimum and maximum value. If appropriate 95% confidence intervals for the mean will be given in addition. Categorical endpoints are summarized by the number (N) and percentage (%). 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 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 FAS, PPP and Safety Analysis Set. Subjects withdrawn from the study will be listed including the primary reason for withdrawal.

8.5 ANALYSIS OF THE PRIMARY ENDPOINT

Primary endpoint will be summarized with mean estimate, standard deviation, range and 95% confidence interval for the mean. The impact of treatment allocation in the double-blind part will be checked graphically.

8.6 ANALYSIS OF THE SECONDARY & EXPLORATORY ENDPOINTS

Continuous data will be summarized using non-missing counts, mean, standard deviation, median, minimum, maximum and 95% confidence interval for the mean when appropriate. Categorical data will be summarized using counts and percentages. The impact of treatment allocation in the double-blind part will be checked graphically.

Tesofensine and metoprolol concentration will be summarized for each assessment point including measures of geometric means and coefficient of variation. The individual PK data collected during the double-blind (Step 2) and the open extension phase will further be presented graphically.

Adverse events will be coded according to MedDRA. The number and percentage of subjects experiencing adverse events in each treatment group will be tabulated by MedDRA system organ class and preferred term.

Secondary endpoints evaluated will be (not a complete list):

- Change from baseline to end of treatment in mean HR
- Change from baseline to end of treatment in mean SBP
- Change from baseline to end of treatment in mean DBP
- Change from baseline to end of treatment in HQCT
- Change from baseline to end of treatment in HbA1c
- Change from baseline to end of treatment in insulin
- Change from baseline to end of treatment in lipids
- Change from baseline to end of treatment in FPG
- Change from baseline to end of treatment in fasting insulin
- Change from baseline to end of treatment in waist circumference
- Change from baseline to end of treatment in fat- and fat-free mass

- PK levels collected for tesofensine and metoprolol

Other secondary endpoints may be added and will be described in the SAP.

8.7 SAFETY CRITERIA

- AEs
- Clinical labs (Hematology, Blood Chemistry)
- ECG
- Vital signs
- Physical examination

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

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

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

Permission for direct access to subject's data will be sought in writing by the investigator and from the subject or parents/guardians/caregivers 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 Regulatory Authorities, study monitor and auditors) with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subject's identities and sponsor's proprietary information. It is the monitor's responsibility to verify that each subject has consented, in writing, to direct access. It is to be ensured by the investigator that documents that are given to Saniona A/S or its representatives do not contain the name or address of the subject, or other information that would affect the anonymity of the subject.

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

9.1 SOURCE DATA

Source data is information included in the original records and/or certified copies of original records from clinical results, observations or other activities pertaining to the study, which are necessary in order to reconstruct and evaluate a clinical study. The investigator will ensure

direct access to these source data to the study monitor, sponsor's representative, auditor, ethical committee and regulatory authority.

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

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

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

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

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

9.2 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 Randomization List". For completeness the monitor will review this document. A "Screening Log" that reports all subjects that were seen to determine eligibility for inclusion in the clinical study also has to be completed by the investigator. The Subject Screening Log and Subject Randomization Log may be combined in one list.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 DEFINITIONS

Quality Assurance

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

Quality Control
The monitor will visit the 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.

10.2 AUDITS AND INSPECTIONS
An independent quality control unit may audit the study protocol, the documentation and, if applicable, the performance of the study and the clinical study report to ensure that the study will be performed in accordance with ICH-GCP guidelines, FDA requirements and other regulatory requirements. The investigator will make all study-related source data and records available to a medically qualified quality assurance auditor mandated by the sponsor, or to regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the investigational medicinal product have been reported to the sponsor.

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

11.2 APPROVALS
The sponsor will authorize a CRO for submitting the documents to the IEC and RA.

11.3 ETHICS COMMITTEE
This protocol, a sample subject information sheet and informed consent form, and any other materials provided to the subjects and/or parents/guardians/caregivers where applicable according to existing country legislation will be submitted to the appropriate IEC. The study approval letter must be available before any subject is exposed to a study-related procedure, including screening tests for eligibility. During the study, the following documents will be sent to the IEC for their review:

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

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

11.4 REGULATORY AUTHORITY

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

11.5 PROTOCOL MODIFICATIONS

If it turns out during the study that some procedures cannot be conducted according to the clinical study protocol, the principal investigator has to be informed immediately by the study personnel. The principal investigator will be responsible for informing the clinical monitor or the clinical project manager of the issue. It will then be decided if a protocol amendment has to be written and approved by the RA/IEC before the study can continue. Any amendment becomes part of the clinical study protocol.

The amended protocol will be approved and signed by the relevant personnel at Saniona A/S and by the principal investigator. 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/favorable opinion of the appropriate IEC and, if legally required, Regulatory Authority, except where necessary to eliminate an immediate hazard to the subjects, or when the change(s) that were approved by Saniona A/S involve only logistical or administrative aspects of the study.

11.6 SUBJECT INFORMATION AND INFORMED CONSENT

RA/IEC approval of the written Subject Information and Informed Consent (for subjects/ parents/guardians/caregivers where applicable according to existing country legislation) must be obtained prior to their use. This consent form contains a phrase by which consent is given for the access to the non-personalized data by the sponsor, national and regulatory authorities. In addition, it states that the subject is free to withdraw from the study at any time without any negative consequences. The Subject Information gives a complete and comprehensive explanation of the significance, nature, extent and possible risks of the study.
The informed consent form must be signed, with name and date noted by the subject and/or parents/guardians/caregivers where applicable according to valid country legislation. The investigator will complete the informed consent section of the eCRF for each subject enrolled.
If new information becomes available that potentially affects the subject's safety or willingness to continue in the study, or if a protocol amendment is issued that affects subject's safety, study procedures or any aspects of the study that may influence the subject's willingness to continue in the study, the subject information leaflet and informed consent form will be revised. After the new documents have received approval from the RA/IEC in accordance with applicable regulations, the subject/parents/guardians/caregivers where applicable according to existing country legislation will be asked to sign the new consent form to confirm his or her willingness to continue in the study.

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

11.7 PARTICIPANT CONFIDENTIALITY

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

12 DATA HANDLING AND RECORD KEEPING

12.1 DATA COLLECTION AND DOCUMENTATION

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

12.2 STUDY MONITORING, SOURCE DATA VERIFICATION AND DATA MANAGEMET

Clinical Data Management is the responsibility of the CRO. All Data Management procedures will be detailed in a separate document known as the Data Management Plan (DMP). The DMP will also describe the Clinical Data Management System (CDMS) that will be used to collect data with an electronic Case Report Form (eCRF) in detail. For each enrolled study participant an eCRF will be maintained. ECRFs must be kept current to reflect subject status at each phase during the course of study. Data on subjects collected on eCRFs during the study will be documented in an anonymous fashion and contains an electronic audit trail.

In compliance with 21 CRF part 11 each user of the CDMS will be assigned a unique user name and will be allocated to a special user role. This special user role controls the user's permissions in the electronic data capture system depending on the function within the study. All staff involved in the study in each site has to be instructed how to maintain the eCRF and therefore be able to edit eCRF entries. 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 eCRF 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. Once eCRFs are completed, they will be available for review by the study monitor and CRO Clinical Data Management. Completed eCRFs will be reviewed remotely for logical discrepancies. The study monitor will ensure that all data queries and subsequent amendments in the eCRF documentation are made according to GCP guidelines.

12.3 DATA MANAGEMENT PLAN

The complete Data Management process will be described in detail and agreed on in the Data Management Plan for this study.

12.4 CASE REPORT FORMS (CRFs)

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

Database Lock

After all data are entered, all queries are solved and quality control procedures have been completed respectively each subject's evaluability is determined, the database will be authorized for lock. Electronic case report form data per site will be provided to the responsible investigator at the end of the study and will need to be retained by the investigator. The complete data will be provided to the sponsor at the close of the study for archiving.

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.

12.5 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.

12.6 LOGS

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

12.7 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.

12.8 RECORD KEEPING

To enable evaluations and/or audits from regulatory authorities or Sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., case report forms and hospital records), all original signed informed consent forms, copies of all case report forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to Sponsor. The investigator must obtain Sponsor's written permission before disposing of any records.

13 FINANCE AND INSURANCE

13.1 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.

13.2 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 A/S together with help of the contracted CRO.

14 PUBLICATION POLICY

14.1 REPORTING AND PUBLICATION

CRO will prepare a study report after the completion of the study. The sponsor representative will sign the final study report intended to be submitted to Regulatory Authorities.

The results of this study may be published or presented at scientific meetings. The sponsor will be responsible for publication of all the data generated in this study. In accord with standard editorial and ethical practice, the sponsor will support publication of multicentre studies only in their entirety and not as individual site data. Sites or investigators must not publish any data from this study without obtaining prior written permission from the Sponsor.

15 REFERENCES

1. https://ghr.nlm.nih.gov/condition/prader-willi-syndrome

2. Astrup A, Madsbad S, Breum L, et al. Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1916-1913.

3. Bentzen BH, Grunnet, M, Hyveled-Nielsen, L. Anti-Hypertensive Treatment Preserves Appetite Suppression While Preventing Cardiovascular Adverse Effects of Tesofensine in Rats. Obesity 2013;21:985-992.

4. ICH Harmonised Tripartite Guideline. Good Clinical Practice [Internet]. 1996 [cited 2015 Oct 28]. Available from: https://firstclinical.com/regdocs/doc/?db=ICH_E6_Good_Clinical_Practice

16 Appendices

16.1 Appendix I: table of recommended concomitant medication use

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	Y	N	Prohibited for 2 weeks prior to randomisation, however, hypnotics and/or anxiolytics at a stable dose for at least 4 weeks prior to screening and up to the follow-up visit could be alowed, i.e.up to zolpidem (10 mg/day), choral hydrate (1 g/day), triazolam (0.5 mg/day), or lorazepam (1 mg/day)
Beta- blockers	N	N	Per protocol
Buproprion (non-SSRI antidepressant)	N	N	Strong inhibitor of CYP2D6
Calcium channel blockers	N	N	Per protocol
Carbonic anhydrase inhibitors (e.g., acetazolamide, dichlorphenamide, dorzolamide, methazolamide)	N	N	
Cinacalcet (calcimimetic)	N	N	Strong inhibitor of CYP2D6
Dopamine reuptake inhibitors (e.g. bupropion)	N	N	
Glucocorticoids	Y	N	
Hypnotic sedative (glutethimide)	N	N	Strong inducer of CYP2D6
H2-receptor antagonist (cimetidine)	N	N	Weak inhibitor of CYP2D6
Immunosuppressives	N	N	
Insulin and/or other injectable anti-diabetic medications, or TZDs	N	N	Per protocol
Lithium	N	N	
Monoamine oxidase (MAO) inhibitors	N	N	
Opioids, cannabinidiols	N	N	
Oral hypoglycemic	-	-	Per protocol
Orlistat	N	N	
Phenothiazines	N	N	
Selective serotonin reuptake inhibitors (SSRIs)	N	N	
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	N	N	

Drug Class	Episodic Use	Chronic Use	Comment
Tricyclic antidepressants	N	N	
Drug inducing ocular toxicity Chloroquine Hydrochloroquine	N	N	
Non-drugs			
Weight loss supplements	N	N	

Anti-depression, anxiety, epilepsy, psychotics OTC, supplements	N	N	

16.2 STUDY FLOW CHART: VISITS 17 - 21 (all visits are ±3 day)

Visit	17 Equal to last visit of first OLE Treatment	18 Treatment	19 Treatment	20 End of Treatment	21 End of study
Day	**180**	**210 (30 days ± 3 days)**	**240(30 days ± 3 days)**	**270(30 days ± 3 days)**	**300(30 days ± 3 days)**
Obtaining second Addendum to double blind ICF for the second open label part	X				
Subject screening number (keeping the same as in Step2 and the first OLE)	X				
Psychiatric examination	x	x	x	x	x
Physical examination	x			x	
Vital signs	x	x	x	x	x
Weight, waist circumference	x	x	x	x	x
Height, calculation of BMI	x				
HQCT	x	x	x	x	x
ECG	x			x	
Hematology	x			x	
Blood chemistry	x			x	
FPG, HbA1c	x	x	x	x	
Lipids, insulin	x	x	x	x	
DEXA	x			x	
PK sample	x**	x**	x**	x**	x
Drug dispensation and accountability	x	x	x	*x	
AEs	x	x	x	x	x

Concomitant medication	x	x	x	x	x
Urinary pregnancy test	x			x	
Diary dispensation, Subject card for OLE dispensation	x				
Diary review		x	x	x	x
Diary collection				x	x
Dispense Follow-up diary list				x	
End of study form					x

***two half doses of metoprolol should be dispensed**
**** Blood samples of metoprolol taken 2 and 4 hours after dose administration– to be done only once in each patient during the study. Time point for dosing and the two blood samples should be noted!**

Phone calls in-between the onsite visits will be used to provide additional reassurance regarding the safety of the subjects and collect adverse events.

Visit	**17.1 Phone call**	**18.1 Phone call**	**19.1 Phone call**	**20.1 Phone call**
Frequency	Once per month	Once per month	Once per month	Once per month
AEs	X	X	X	X
Hypoglycemic episodes (at DM subjects)	X	X	X	X
Concomitant medication	X	X	X	X

16.3 Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

Instructions:
The following items refer to the person in your care and assessment of his/her food-related behavior during the past 2 weeks.

(1) During the past 2 weeks, how upset did the person generally become when denied a desired food?

□ Not at all upset
□ A little upset
□ Moderately upset
□ Very upset
□ Extremely upset

(2) During the past 2 weeks, how often did the person try to bargain or manipulate to get more food at meals?

□ Never
□ Up to 2 times a week
□ 3 to 6 times a week
□ Every day
□ Several times a day

(3) During the past 2 weeks, how often did the person forage through trash for food?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(4) During the past 2 weeks, how often did the person get up at night to food seek?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(5) During the past 2 weeks, how persistent was the person in asking or looking for food after being told “no” or “no more”?

□ Not at all persistent
□ A little persistent
□ Moderately persistent
□ Very persistent
□ Extremely persistent

(6) During the past 2 weeks, outside of normal meal times, how much time did the person generally spend asking or talking about food?

□ Less than 5 minutes a day
□ 5 to 15 minutes a day
□ 15 to 30 minutes a day
□ 30 minutes to 1 hour a day
□ More than 1 hour a day

(7) During the past 2 weeks, how often did the person try to sneak or steal food (that you are aware of)?

□ Never
□ 1 time
□ 2 times
□ 3 times
□ 4 or more times

(8) During the past 2 weeks, when others tried to stop the person from asking about food, how distressed did he or she generally appear?

□ Not at all distressed
□ A little distressed
□ Moderately distressed
□ Very distressed
□ Extremely distressed

(9) During the past 2 weeks, how often did food-related behavior interfere with the person’s normal daily activities, such as self-care, recreation, school, or work?

□ Never
□ Up to 2 times a week
□ 3 to 6 times a week
□ Every day
□ Several times a day

CLINICAL STUDY PROTOCOL

VERSIONS OVERVIEW

TM002: A double-blind, randomized, placebo-controlled, multiple-dose, multi-centre safety and efficacy study of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome (PWS)
Saniona, A/S

HUNGARY				
Version	**Date**	**Approved by RA**	**Approved by EC**	**List of changes**
1.0	25 September 2016	22 December 2016	13 December 2016	N/A
1.1	16 February 2017	28 April 2017	20 April 2017	HQCT questionnaire added, Update of timelines of the clinical trial
1.2	25 July 2017	26 September 2017	18 September 2017	Decrease of dose of tesofensin to 0,25mg Maximum number of randomized patients was increased to 20 Wording of inclusion criteria No.7 was changed to „Growth hormone is allowed; but subject must be on a stable dose of growth hormone >2 months“ Update of timelines of the clinical trial Address of central laboratories (PK analysis) was changed
1.3	31 October 2017	03 January 2018	21 December 2017	An unblinded interim analysis after Step 1 will be performed by Sponsor and interim analysis will be done Information about PK samples unblinding was added Step 2 will start only after RA/EC positive opinion regarding to interim analysis and unblinded data Chapter „Data safety monitoring board“ changed to „Interim analysis“ Update of timelines of the clinical trial

CLINICAL STUDY PROTOCOL

VERSIONS OVERVIEW

1.4	13 March 2018	24 May 2018	02 May 2018	Dose reduction of tesofersin and metoprolol in pediatric patients. Psychiatric examinations are added to each patient visit. Change in Follow up, V15. Data on the duration of the clinical trial were updated. Exclusion criterium No. 7 was extended. The minimum number of patients was adjusted to 5.
1.5	26 September 2018	12 November 2018	30 October 2018	An Open label extension was added to the trial. OLE will be directly linked to Step II. The last study visit of Step II will be the first visit of OLE.
1.6	31 January 2019	26 February 2019	13 February 2019	A prolongation of the OLE phase was added to the trial. It will be directly linked to the OLE. The last study visit of OLE will be the first visit of the OLE II, thus there will be no discontinuation of medication of patients. The dosing schedule has been changed. Expected end is on Jun 2019.

Updated: 26.08.2019

CLINICAL STUDY PROTOCOL

VERSIONS OVERVIEW

TM002: A double-blind, randomized, placebo-controlled, multiple-dose, multi-centre safety and efficacy study of co-administration of tesofensine/metoprolol in subjects with Prader-Willi syndrome (PWS)
Saniona, A/S

CZECH REPUBLIC				
Version	**Date**	**Approved by RA**	**Approved by EC**	**List of changes**
1.0	25 September 2016	**Not approved, changes in protocol requested by SUKL during initial review**	12 October 2016	N/A
1.1	12 November 2016	18 January 2017	4 January 2017	SUKL as a Czech RA was added to paragraphs where information about SUKL oversight/approval is needed Dietary instructions for patient suffered from diabetes were added Wording of paragraph „UNBLINDING“ was updated
1.2	16 February 2017	22 March 2017	29 March 2017	HQCT questionnaire added, Update of timelines of the clinical trial
1.3	25 July 2017	10 August 2017	16 August 2017	Decrease of dose of tesofensin to 0,25mg Maximum number of randomized patients was increased to 20 Wording of inclusion criteria No.7 was changed to „Growth hormone is allowed; but subject must be on a stable dose of growth hormone “>2 months“ Update of timelines of the clinical trial Address of central laboratories was added
1.4	31 October 2017	4 December 2017	6 December 2017	An unblinded interim analysis after Step 1 will be performed by Sponsor and interim analysis will be done, SUKL will be given all the unblided data for review Step 2 will start only after SUKL positive opinion regarding to

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				interim analysis and unblinded data
1.5	09 Feb 2018	10 April 2018	28 March 2018	Dose reduction of tesofensine and metoprolol in pediatric patients. Psychiatric examinations are added to each patient visit. Change in Follow up, V15. Data on the duration of the clinical trial were updated. Exclusion criterium No. 7 was extended. The minimum number of patients was adjusted to 5.
1.6	09 September 2018	05 November 2018	10 October 2018	For CZ only. Open Label Phase was added. Visit V14 (last visit of step II) will be simultaneously first visit of OLE Phase for participated patient. To the Protocol Name was added „A 12 Weeks Open Label Extension. New exclusion and inclusion criteria were created. Overall study description was extended. Study procedure for V14-V18 are described in this Protocol. End of OLE was predicted to be in April/May 2019. Manufacture of IMP was changed. Unblinding is not applicable in OLE. For patient in OLE remain the same screening number as in step 2.
1.7	30 January 2019	06 February 2019	27 February 2019	Second Open Label Phase was added. Last visit V17 of OLE will be first visit of OLE II. To the Protocol Name was added „Second 12 Weeks Open Label Extension. Inclusion and exclusion criteria were updated. Estimated end of study is on Jun 2019.

Updated: 04.03.2019