STATISTICAL ANALYSIS PLAN

Study Code 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

Sponsor: Saniona, A/S
Baltorpvej 154
DK 2750 Ballerup
Denmark

Author: Leontina Levenzon
GCP-Service International Ltd. & Co. KG
Anne-Conway-Str. 2
28359 Bremen, Germany
Tel +49 (0)421 89 67 66 31

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Signatures

I confirm that this Statistical Analysis Plan (SAP) accurately describes the planned statistical analyses to the best of my knowledge and was finalized before breaking the blind.

Author: Leontina Levenzon, M.Sc.
Biostatistician
GCP-Service Int. Ldt & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

27-Dec-2017 _____
Date Signature

Review: Malte Braitmaier, M.Sc.
Biostatistician
GCP-Service Int. Ldt & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

27-DEC-2017 _____
Date Signature

Approved: Roman Dvorak MD, PhD
Chief Medical Officer
Saniona, A/S
Baltorpvej, 154
DK 2750 Ballerup
Denmark

1-JAN-2018 _____
Date Signature

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List of Abbreviations and Key Terms

AE	Adverse Event
ANCOVA	Analysis of co-variance
ATC	Anatomical Therapeutic Chemical (Classification)
BMC	Bone Mineral Conent
BMD	Bone Mineral Density
BMI	Body-Mass-Index
BP	Blood Pressure
bpm	Beats per minute
CI	Confidence interval
CRF	Case Report Form
CRO	Contract Research Organization
cm	Centimeter
CV	Coefficient of variation
CZ	Czech Republic
DBP	Diastolic Blood Pressure
D(E)XA	Dual (Energy) X-ray Absorptiometry
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HbA_{1C}	Hemoglobin A1C
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
HDL	High-density lipoprotein
HR	Heart Rate
HU	Hungary
ICH	International Conference on Harmonization
ID	Identification number
IMP	Investigation Medicinal Product
L	Liter
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LPLV	Last Patient Last Visit
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligram
mIU	Milli-international units per liter
mL	Milliliter
Min	Minimum
n	Number of subjects
N Miss	Number of missing values
OP	Out-patient
P	Phone call
PK	Pharmacokinetic
PPP	Per Protocol Population
PT	Preferred term
PWS	Prader-Willi Syndrom
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SES	Safety Evalution Set
SBP	Systolic Blood Pressure
SD	Standard deviation
SOP	Standard Operating Procedure
SUKL	State Institute for Drug Control (Czech Republic)
WHO-DDE	World Health Organization - Drug Dictionary Enhanced

1. Introduction

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the study protocol TM002 (dated: 25 July 2017 Protocol Amendment Version 1.2 for Hungary and 25 July 2017 Protocol Amendment Version 1.3 for Czech Republic) (CZ) and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. In addition, Section 8 of this SAP summarizes all changes from the planned analysis known before finalization of this document. The SAP is finalised and signed prior to breaking the blind.

Data management and transfer of data will be carried out in accordance with the data management plan (DMP), statistical analysis in accordance with the SAP.

If changes in the conduct of the statistical analysis are unavoidable the reasons and the effect of these changes will be documented in the statistical report/clinical study report in full details.

All statistical activities within the framework of this study will be based on the standard operating procedures (SOPs) for clinical studies of GCP-Service, as well as the ICH Guideline for Good Clinical Practice (ICH-GCP).

2. Study Design and Objectives

2.1 Study Design

This clinical study is 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 (PWS). 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 PWS.

The study will be conducted in two steps each with two arms where the second step will only start following recommendation after a Data Safety Monitoring Board (DSMB) review and in CZ only a State Institute for Drug Control (SUKL) review:

- Step 1: 10-15 adult subjects with PWS
  - Arm 1: tesofensine 0.50 mg + metoprolol 50 mg administered once a day
  - Arm 2: placebo tablets matching tesofensine + metoprolol administered once a day
- Step 2: 10-15 children with PWS
  - Arm 1: tesofensine + metoprolol administered once a day. Firstly, an initial titration dose of tesofensine 0.25 mg + metoprolol 50 mg will be given for the first 4 weeks.

Following a favorable review of all safety data for each subject by the site clinician, tesofensine 0.50 mg + metoprolol 50 mg will be given for the final 9 weeks.

- Arm 2: placebo tablets matching tesofensine + metoprolol administered once a day

2.2 Treatments

2.2.1 Investigational Medicinal Product

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

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 Step 1 (adult subjects with PWS), 0.5 mg of tesofensine and 50 mg of extended release metoprolol or matching placebo will be administered.

Following Step 1, an independent DSMB will review unblinded data from Step 1, including PK, and will attest that it is safe to proceed to Step 2 in children as described in the clinical study protocol.

In the Step 2 (children with PWS), tesofensine 0.50 mg + metoprolol 50 mg administered once a day, in the morning with a meal – first, initial titration dose of tesofensine 0.25 mg + metoprolol 50 mg will be given for the first 4 weeks, in the morning with a meal. Following a favorable review of all safety data for each subject by the investigator, tesofensine 0.50 mg + metoprolol 50 mg will be given for the final 9 weeks (the above proposed dosing plan can be adjusted by the DSMB, if needed).

The Investigational Medicinal Product (IMP) is a kit of one tablet of tesofensine and one tablet of metoprolol, both formulated for oral use once a day, or a matching placebo. For Step 2 Day 28-91 two blinded kits A and B will be prepared (kit A – per protocol dose of IMP, kit B – lower dose of IMP). Tesofensine 0.25 mg and 0.50 mg are identical in size, shape and weight.

2.2.2 Placebo

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

2.3 Trial Schedule

Study medication will be administered for ninety (91) days (+2 days after the final assessments with half-dose of metoprolol).

Following all baseline assessments, eligible subjects will be randomly assigned to one of the two arms (3:2, IMP: placebo).

Screening visit is combined with the baseline and randomization visit (Day 0, Visit 1). All requested screening assessments and baseline blood draws and tests will be performed before randomization.

After the Day 0, subjects will visit the site on Days 7, 28, 56 and 91 (Visits 2, 5, 9, 14) for efficacy and safety evaluations and medication supply (in total 5 personal visits at the site are requested). On Day 91 subjects will come for the final personal visit.

On Days 14, 21, 35, 42, 49, 63, 70, 77, 84 (Visits 3, 4, 6, 7, 8, 10, 11, 12, 13) phone call follow ups will be performed. These phone calls will be used to provide additional reassurance regarding the safety of the subjects and collection of AEs.

On Day 105 (Visit 15) a phone call will be performed to check subjects' status and potential AE(s). This will conclude their participation in the study.

The study schedule is displayed in Table 1

Table 1: Study schedule

Visit	1 Screening /Baseline/ Randomization OP	2 OP	3, 4 P	5 OP	6, 7, 8 P	9 P	10, 11, 12, P	14 OP	15 F-up P
Day	0	7	14 21	28	35 42 49	56	63 70 77 84	91	105
Obtaining written Informed Content, Inclusion/Exclusion	x								
Generating screening number	x								

Demographic information	x								
Medical/medication history	X								
Physical exam	x							x	
Vital signs	x	X		x		x		x	
Randomization	x								
Safety review for uptitration				*x					
Weight, waist circumference	x	X		x		x		x	
Height, calculation of BMI	x								
HQ-CT	x	X		x		x		x	
ECG	x							x	
Hematology	x			x				x	
Blood chemistry	x			x				x	
FPG, HbA1c	x			x		x		x	
Lipids, insulin	x			x		x		x	
DEXA	x							x	
PK sample	x			x		x		x	
Lifestyle consultation	x								
Drug dispensation	x	X		x		x		** x	
AEs	x	X	x	x	x	x	x	x	x
Drug accountability		X		x		x		x	
Concomitant medication	x	X	x	x	x	x	x	x	x
Urinary pregnancy test	x							x	
Subject card dispensation	x								

Diary dispensation	x								
Diary review		X		x		x		x	
Diary collection								x	
Dispense Follow-up diary list								x	
End of study form									x

OP: Out-patient

P: Phone Call

*** only step 2 –IMP dose increase**

**** two half doses of metoprolol should be dispensed**

2.4 Study Objectives

2.4.1 Primary Objective

The primary objective of this clinical trial is:

- To examine the effect of co-administration of tesofensine/metoprolol on body weight in subjects with PWS.

2.4.2 Secondary Objectives

In addition, further objectives are

- To establish pharmacokinetic profile of tesofensine and metoprolol in subjects with PWS,
- To examine the change in hyperphagia-related behaviour 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.

2.5 Study Hypothesis

As this is an explorative study no formal study hypothesis will be tested but the study results may be used to generate study hypotheses for possible subsequent studies.

2.6 Handling of Screening Failures and Withdrawals

Enrolment will continue until a total of 10-15 adult subjects and 10-15 pediatric subjects are randomized. Randomized subjects who withdraw or are withdrawn from the study for any reason before completion are called "withdrawals". Withdrawals may be replaced, so that there are as close as possible to the minimum of 10 completers in each step of the study.

A participant who fails during the screening phase, before randomisation, for any reason, e.g. because of violation against the eligibility criteria, is regarded as "screening failure". Subjects excluded during the screening period may be considered for another selection visit at a later date but will need to undergo complete rescreening.

2.7 Randomization and Stratification

A centre-stratified block randomization with fixed block size is used. For each step of the study, one randomization list with complete blocks is prepared. This is done to achieve a balanced distribution of subject characteristics between the two treatment groups within each study centre and step of the study as far as possible. Subjects will be randomly assigned to the two study groups in a 3:2 fashion (IMP:Placebo). A more detailed description of the randomization procedure is given in the Randomization Plan version 2.0, dated 24. August 2017.

2.8 Blinding

The study will be double blind. Neither the investigators nor the subjects will be informed about the type of subject´s medication. In general, emergency unblinding is to be done only when absolutely necessary for the clinical management of an individual subject and where stopping the blinded medication is not sufficient in the opinion of the investigator.

A more detailed description of the blinding and unblinding procedure is given in the Randomization Plan version 2.0, dated 24 August 2017 and the study protocol TM002.

2.9 Sample Size Calculation

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

Each site should randomize a minimum of five eligible adult and a minimum of five eligible pediatric patients. In total there should be randomized a minimum of 20 and a maximum of 30 patients, 10-15 male and female adult and 10-15 male and female pediatric subjects with confirmed diagnosis of PWS.

2.10 Planned Safety and PK Analysis

Deviations from the initially planned analysis described below, specifically the conduct of an early safety and PK analysis with 9 subjects without the involvement of a Data Safety Monitoring Board (DSMB) and the State Institute for Drug Control (SUKL), are described in section 8.

According to the study protocol TM002 (dated: 25 July 2017 Protocol Amendment Version 1.2 for Hungary and 25 July 2017 Protocol Amendment Version 1.3 for Czech Republic), a review of unblinded efficacy, safety and PK data as well as all data from the study in subjects with type 2 diabetes (TM001) will be performed by an independent Data Safety Monitoring Board (DSMB) and the State Institute for Drug Control (SUKL) after LPLV (Last Patient Last Visit) of Step 1 (adult subjects with PWS only). The independent DSMB will be created for this study and will be comprised of experts in the area of metabolic diseases, pediatric endocrinology, cardiovascular, clinical pharmacology, and statistics. A CRO statistician who will not be involved in the conduct of the study will prepare an unblinded data package with efficacy, safety and PK data from Step 1. In addition, the DSMB for HU and SUKL for CZ will have available unblinded data from the ongoing Phase 2 study in subjects with T2DM (TM001), and the DSMB will provide answers to the Sponsor to the following questions:

1) Based on the presented safety data, is it safe to proceed to Step 2, children (≥12 years of age) with PW syndrome "as is"? Any recommended modifications to the protocol?

2) Based on the provided PK data, do you recommend proceeding at the recommended dose of 0.5/50 mg (0.25/50 mg for the first 4 weeks, if considered safe by the investigator increased to 0.5/50 mg) or would you recommend a different dose? If a different dose is recommended, please specify the dose of tesofensine and/or metoprolol.

Safety criteria: There will be no set pre-defined criteria as to what constitutes a safety signal which would be considered serious enough not to recommend administration of the study drug to children. The DSMB will be asked to comprehensively evaluate the provided data and determine the resulting risk/benefit for the pediatric subjects and make their recommendation accordingly.

PK criteria: if the 90% confidence interval of a log-transformed exposure measure (mean trough concentrations from all follow-up samples (i.e. excluding the baseline sample collected prior to treatment with the study medication) collected from all adult participants for both metoprolol and tesofensine) falls completely within the range 80% of the 0.25 mg dose and 125% of the 1.0 mg dose previously measured trough concentrations in obese adult subjects in the study TIPO-1, the exposure achieved in the adult subjects will be considered in the expected safe range and no dose adjustment for the pediatric patients should be necessary. If the 90% confidence interval falls outside

the 80-125% range the exposures will be considered sufficiently "different" from the expected values and a dosing adjustment should be considered by the DSMB for HU and DSMB and SULK for CZ.

2.11 Handling of Changes to Study Protocol

Any deviations from planned analyses, the reasons for such deviations, and all alternative or additional statistical analyses that may be planned before breaking the blind, respectively, will be described in amendments to the study protocol and/or the SAP. All deviations and/or alterations from the statistical analyses described in the protocol, especially those after database lock will be summarized in the clinical project report.

All statistical analyses not pre-specified by the SAP and run after data lock will be considered as additional/exploratory analyses.

3. Technical Aspects and Coding Conventions

All programs will be written using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.4 or higher. Tables, listings and figures will be provided in separate PDF documents and will contain a separate table of contents. Courier New will be used as font for all tables and listings. In headings, titles and listings only the first word will be capitalised. A noncommittal list of all tables and listings can be found in the Appendix.

A minimum font size of 8 points will be used for the tables, corresponding to a linesize of 140 digits and a pagesize of 52 lines for an output in DIN A4 format. All tables should be self-explaining. Therefore, necessary information should be available in the footnotes. The footnote and title of each table will be left-adjusted while the table will be centered.

For listings, a minimum font size of 8 points with the linesize and pagesize as defined above will be used to produce the output in DIN A4 format. Footnotes, titles and listings will be left-adjusted. Missing data will be represented on subject listings as blank field for text field or "." for numeric variables. Derived data will be marked by '#'. Listings will be sorted by site, treatment and screening number (equivalent to subject identification number) unless specified otherwise.

3.1 Date Coding and Day Numbering

The format for presentation of date variables will be DDMMMYYYY. The format for presentation of time variables will be hh:mm.

If dates are partially given, they will be completed, if necessary for the calculation of durations, according to a worst-case imputation. Dates with missing years will only be imputed if the correct year is obvious.

Deviations will be documented and explained.

3.2 Coding Systems and Conventions

3.2.1 Coding of Adverse Events and Medical History

Adverse event (AE), medical history and concomitant diseases terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed. Details are described in the DMP.

3.2.2 Separation of Medical History from Concomitant Diseases

Separation of medical history from concomitant diseases will be done by comparison of the stop date of the medical condition with the start of study treatment. Each medical condition will be allocated unambiguously either to medical history or concomitant diseases.

- **Medical history:** If the stop date is before start of treatment, the medical condition is allocated to medical history. If the stop date is partially given and unambiguously before start of treatment, the medical condition is also allocated to medical history. Furthermore, if the stop date is missing and the medical condition is not known to be ongoing, findings coded as "Surgical and medical procedures" are also allocated to medical history.

- **Concomitant diseases:** If the stop date is at or after start of treatment or the medical condition is ongoing, the medical condition is allocated to concomitant diseases. Furthermore, if the stop date is missing and the medical condition is not known to be active at start of study, the worst case is assumed for findings **not** coded as "Surgical and medical procedures". Consequently, the medical condition is allocated to concomitant diseases.

3.2.3 Coding of Medications

Previous and concomitant medications will be coded using WHO-DDE (World Health Organization - Drug Dictionary Enhanced) based on different Anatomical Therapeutic Chemical Classification (ATC) code levels. Details are described in the DMP.

3.2.4 Separation of Medications

Separation of previous medications and concomitant medications will be done by comparison of the stop date of the medication with the start of study treatment. Each medication will be allocated unambiguously either to previous or concomitant medications.

- **Previous medications:** If the stop date is before start of treatment, the medication is allocated to previous medications. If the stop date is partially given and unambiguously after start of treatment, the therapy is allocated to previous medications.

- **Concomitant medications:** If the stop date is at or after start of treatment or the medication is ongoing, the medication is allocated to concomitant medications. Furthermore, if the stop date is missing, the worst case is assumed. Consequently, the medication is allocated to concomitant medications. If the stop date is partially given and implies stop date after start of treatment, the medication is also allocated to concomitant medications.

4. Analysis Populations and Subgroups

4.1 Analysis Populations

Within the framework of this study, the following two main populations are analysed:

- The Per Protocol Population (PPP) includes all randomized subjects without any major protocol violations. Subjects in the PPP will contribute to the evaluation 'as treated'.
- The Safety Evaluation Set (SES) includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the SES will contribute to the evaluation 'as treated'.

4.2 Subgroups

The primary analysis for each endpoint will be using the combined data from steps 1 and 2 of this study. In addition, subgroup analyses are planned for step 1 and step 2 of this study to evaluate differences between treated adults and children.

4.3 Stratification

Not applicable.

5. Data Handling

5.1 Handling of Missing Data and Outliers

Since all analyses are explorative and with reference to the low sample size per step of this study, it is not planned to replace or impute missing data by complex imputation methods. Instead data will be used as available and analysis will be performed on observed cases only. The appropriateness of this procedure will be discussed during the blind data review and, if applicable, the handling of missing data will be adapted.

For outliers, i.e. impossible or implausible values, queries are raised to the investigator before hard lock of the database. The investigator will either confirm or correct the value. Subsequently, the corrected or confirmed value is used for the analysis. If applicable, analysis will be performed with and without outliers to show robustness of the results. Complete exclusion of values should be only done in exceptional cases and is only valid for impossible and very implausible values with obvious justification. The decision to exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the investigator and the CRO statistician.

5.2 Handling of Data from Screening Failures and Withdrawals

In case of screening failures, the data will be listed but not further analyzed. The number of screening failures will be provided in a figure and a table for the disposition of subjects.

Data from withdrawals will be used as available without imputation. The number of early withdrawals and the corresponding reasons will be provided in a figure and a table for the disposition of subjects.

5.3 Handling of Multiple Comparisons and Multiple Primary Variables

As all data analyses in this study are explorative and will be interpreted accordingly, no adjustment for multiple comparisons is necessary.

5.4 Data Review

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. This review will be performed without revealing which treatment the subjects are assigned to. The blinding of the treatment will be maintained for everyone involved in allocating subjects to the analysis sets until data are released for statistical analysis. Furthermore, outliers will be identified by data review according to ICH-E9 (5), and a fake randomization. In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis. Obviously erroneous data points may be excluded from the analyses. The decision to

exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the investigator and the CRO statistician.

For review of the pharmacokinetic data, additional care needs to be taken to avoid premature unblinding of the reviewers due to drug concentration levels being recorded for each subject. Therefore, subject IDs will be replaced by a randomly selected 5-digit fake ID (one per subject) by an independent person not involved in the conduct, data review or analysis of the study. The list used for assignment of fake IDs to subject IDs will be stored in a secure location without access for any person involved in the trial. The PK data will be sorted anew by fake ID, the visit number (VISITNUM) and the analyzed drug (PCTEST), to ensure that the order of subjects does not give an indication of the true subject ID. This modified list will then be provided for data review. After complete review all issues will be traced back to the subject ID using the list used for assignment of fake IDs to subject IDs and querries will be solved or subjects excluded from the analysis as determined during the data review process.

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.

6. Variables for Analysis

6.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be evaluated:

- Demographic information (race, gender, age, height, weight, BMI, waist circumference)
- Medical history, concomitant diseases, previous and concomitant medications
- Baseline characteristics (vital signs, ECG, physical examination)
- Laboratory tests and measurements (fat mass, fat free mass, bone mineral density (BMD), bone mineral content (BMC), HbA_{1c}, Cholesterol, HDL, LDL, Triglyceride, Insulin, FPG)

6.2 Efficacy Endpoints

6.2.1 Primary Endpoint

The following primary variable is evaluated:

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

6.2.2 Secondary Endpoints

The following secondary endpoints are planned:

- Change from baseline to end of treatment in body weight [kg]
- Change from baseline to end of treatment in fat- and fat-free mass [%] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment in fat- and fat-free mass [g] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment in bone mineral density (BMD) [g/cm²] and bone mineral content (BMC) [g] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment of HbA_{1c} [%]
- Change from baseline to end of treatment in fasting plasma glucose (FPG) [mmol/L]
- Change from baseline to end of treatment in waist circumference [cm]
- Change from baseline to end of treatment in insulin [mIU/L]
- Change from baseline to end of treatment in lipid profile (Cholesterol, HDL, LDL, Triglyceride) [mmol/L])
- Change from baseline to end of treatment in total HQ-CT score

6.3 Safety Endpoints

6.3.1 Safety Endpoints

Safety endpoints include:

- Incidence of AEs, SAEs (serious adverse events),
- Blood analysis:
    - Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets
    - Blood chemistry: creatinine, gamma glutamyl transferase, aspartate aminotransferase, alkaline phosphatase, glomerular filtration rate (GFR) and urea
- Electrocardiogram (ECG):
    - Interpretation (normal/abnormal)
    - Change from baseline to end of treatment in R-R, P-R, QRS and Q-T intervals
- Vital signs:
    - Change from baseline to end of treatment in mean HR [bpm]

- Change from baseline to end of treatment in mean SBP [mmHg]
- Change from baseline to end of treatment in mean DBP [mmHg]
- Change from baseline to end of treatment in body temperature [°C]
- Change from baseline to end of treatment in respiratory rate [breaths/min]

- Physical examination
  - Change from baseline to end of treatment in examination findings (normal/abnormal (NCS)/abnormal (CS)/not done) of different body systems (Head, ear, eye, nose and throat, respiratory system, cardiovascular system, abdomen, central and peripheral nervous system, lymph nodes, skin, skelet and other body system)

6.4 Pharmacokinetic Endpoints

- Steady state concentrations of tesofensine and metoprolol as measured by trough values

7. Statistical Analysis Methods

7.1 Descriptive Statistics

The default summary statistics for quantitative variables will be the number of non-missing observations (n), number of missing values (N missing), arithmetic mean, geometric mean (if applicable), standard deviation (SD), coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum (min), median, and maximum (max) for those subjects with data available.

For categorical variables, the number (n) and percentage (%) of subjects per category will be the default summary presentation, and, if applicable, the number of missing values is provided in a "Missing" category. Missing data will not be included in the calculation of percentages as only available data are used, except if a subject did only answer specific questions of a questionnaire.

Percentages will be calculated using a denominator of all subjects in a specified population or treatment group. The denominator will be specified in a footnote to the tables for clarification if necessary. If missing data occur within population specified as denominator, they will not be included in the calculation of percentages, except if a subject did only answer specific questions of a questionnaire.

7.2 Rounding Rules

7.2.1 Estimates of the Mean and Standard Deviation

When using actual data, the mean and standard deviation are both calculated to 2 extra places than the actual data and the result is rounded to one more decimal place than the original data, with a maximum of 2 decimal places.

When mean values of repeated measurements are used for calculation of summary statistics, the mean and standard deviation are both calculated to one more decimal place than the used mean values and the result is rounded to the same number of decimal places given for the mean values of repeated measurements used for calculation, with a maximum of 2 decimal places.

7.2.2 Other data

Quartiles, CV and median are always presented with the same number of decimal places as the mean. Minimum and maximum are always provided with the same number of decimal places as the data used. For estimates of proportions always 4 decimal places are used for the computation and the result is rounded to 3 decimal places. If proportions are displayed as percentage, 1 decimal place is displayed. For example, a proportion of 0.655 will be presented in percentage as 65.5%.

7.3 Calculation of Study Days and Durations

Study days and, if applicable and meaningful, durations will be determined by comparing the respective date to the date of the first administration of the study medication.

- If the respective date is on or after the date of the first administration of the study medication:

  Study day/Duration = Date (e.g. date of visit) - Date of first administration + 1

- If the respective date precedes the date of the first administration of the study medication:

  Study day/Duration = Date (e.g. date of medical history event) - Date of first administration

Time to onset and duration of adverse events will be calculated as follows:

- Time to onset = start date of AE - date of first treatment [+1 for AE starting after start of treatment]

- Duration of adverse event = stop date – onset/worsening date + 1

7.4 Evaluation of Demographics and Baseline Characteristics

7.4.1 Disposition of Patients

Subject disposition will be tabulated including the numbers of screened subjects, screening failures, subjects exposed to study product, subjects completing the study and subjects in the PPP and SES. Subjects withdrawn from the study will be listed along with the primary reason for withdrawal. In addition, the primary reason for withdrawal will be tabulated.
Furthermore, a summary of the time to study termination is provided per treatment group.

7.4.2 Demographics and other Baseline Characteristics

Demographic information (race, gender, age, height, weight, BMI, waist circumference), baseline characteristics (vital signs, ECG, physical examination) and laboratory tests and measurements will be summarized by treatment group and step of the study (including a total column) using the default descriptive statistics for subjects in the PPP and SES.

7.4.3 Medical History, and Concomitant Diseases

Absolute and relative frequencies (n, %) of medical history and concomitant diseases will be described by treatment group based on MedDRA system organ class and preferred term levels for the PPP and SES.

7.4.4 Previous and Concomitant Medication

Absolute and relative frequencies (n, %) of previous and concomitant medication will be provided by treatment group based on Anatomical Therapeutic Chemical (ATC) Classification code levels 2 and 3 for the PPP and SES.

7.5 Evaluation of Primary Endpoint

The primary endpoint is

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

and will be calculated by:

%-change = (Weight at end of treatment – Weight at baseline) / (Weight at baseline * 100

where, according to the protocol, end of treatment is defined as Visit 14 (Day 91).

The primary endpoint will be presented and analysed based on the PPP.
Percent change from baseline in body weight will be summarized per Step and in total, by treatment group and visit via mean, , median, standard deviation, coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum and maximum value). Moreover, complete listings of individual values for the primary endpoint will be provided. Figures displaying the values for individual subjects

(spaghetti plots) as well as figures displaying mean and standard deviation for percentage change from baseline in body weight at each visit per treatment group by Step and in total will also be provided.

The primary endpoint percent change from baseline to end of treatment will be compared between treatment arms by means of an ANCOVA model including Step, site and treatment as fixed factors and baseline value as covariate. Estimates and 95% confidence interval of treatment differences will be calculated. The procedure for this analysis might be adapted during the blinded data review meeting. The primary analysis will be using the combined data from Steps 1 and 2; secondary analyses will be carried out for each step separately. The critical value will be set on a two-sided significance level of 5%.

For the ANCOVA the following SAS®-Code is recommended:

```
proc glm data = <name of primary analysis data set>;
        class step site treatment_group;
        model chg_from_base =  step site treatment_group baseline;
        lsmeans treatment / cl e stderr pdiff;
        estimate 'Difference IMP versus Placebo'    treatment 1 -1;
run;
quit;
```

The ANCOVA will be repeated with the data of all subjects in the PPP with available weight measurement as sensitivity analysis. For withdrawals, change from baseline will be imputed according to the last observation carried forward (LOCF) method using the last weight measurement before study termination.

7.6 Evaluation of Secondary and Exploratory Variables

The analysis of secondary and exploratory variables will be based on the PPP. The secondary and exploratory variables will be summarized per Step and in total by treatment group and visit and, where applicable, changes from baseline will be provided using standard descriptive statistics (mean, geometric mean (if applicable), median, standard deviation, coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum and maximum value). Individual (spaghetti plots) and mean and standard deviation curves over treatment duration will be plotted by treatment per Step and in total.

Change from baseline analysis to the end of treatment for the corresponding secondary and exploratory endpoints will be performed using ANCOVA, logistic regression models as applicable. For continuous variables, the ANCOVA model will be analogous to the model used for the primary endpoint. pvalues, 95% confidence intervals and, if applicable, odds ratios for the comparison

between treatments will be estimated. Also, the primary analysis of secondary endpoints will be using the combined data from Steps 1 and 2; secondary analyses will be carried out for each step separately. The critical values for each two-sided and one-sided statistical test will be based on a significance level of 5% and 2.5%, respectively. Figures displaying the mean and standard deviation of the raw data at each visit per treatment group will be also provided. Moreover, complete listings of individual values for all secondary and exploratory endpoints will be provided.

A 9-item score will be calculated for the HQ-CT. Change in HQ-CT answers (by question and in total) will be calculated as (answer at visit 2, 5, 9 or 14) minus (answer at screening visit (visit 1)) and presented using standard descriptive statistics (mean), median, standard deviation, coefficient of variation (CV), lower quartile (Q1), uppe quartile (Q3), minimum and maximum value). Scores for each question range from 0 to 4 (with a higher score indicating a worse outcome), resulting in a maximum 9-item sum of 436. A decrease in total score (compared to the baseline assessment) indicates an improvement in hyperphagia. If less than three questions have not been answered by a subject, the missing answers will be imputed by the mean score of all available answers. In case of more missing answers, the total scores will not be calculated. Results will be presented by treatment per Step and in total.

Subject compliance [%] will be calculated as 100 x (number of tablets dispended – number of tablets returned)/(number of days of treatment) and will be calculated for both study drugs separately. The compliance will be summarized using standard descriptive statistics (mean, standard deviation, coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum and maximum value and listed per subject as well.

7.7 Evaluation of Safety Variables

The analysis of the safety variables described in Section 6.3 will be based on the SES. Values will be summarized by treatment per Step and in total, using non-missing counts, mean, standard deviation, median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum for continuous data. Categorical data will be summarized using counts and percentages. Change from baseline to end of treatment analysis for vital signs will be done as described in Section 7.6.

All AEs occurring after the randomization of the subject will be reported as AE (any AEs that occurred between screening and randomization will be reported in medical history, but not as an AE).

Incidences (number and percentage of subjects experiencing adverse events) per treatment group will be calculated for AEs on the system organ class (SOC) level and on the preferred term (PT) level (i.e., total, by step, by intensity, by relationship and by outcome). Listings and tables displaying incidences for AEs leading to discontinuation, serious AEs, treatment-related serious AEs and deaths will also be provided.

Differences in the incidence of treatment-related AEs between treatment groups will be analyzed using a logistic regression model with Step and treatment as fixed factor. This model might be adapted during the blind data review depending on the amount and quality of data. Odds ratios, p-values, and 95% confidence intervals corresponding to the logistic regression model will be estimated for the comparisons between treatments.

The following basic SAS code is used for the analysis and expanded if needed:

```
proc logistic data=<name of safety analysis data set> plots(only)=effect;
   class Step treatment_group;
   model <binary variable for occurrence of treatment-related AE (1/0)> = Step
   treatment_group;
run;
```

In addition, the time to the first treatment-related adverse event and treatment-related serious adverse event will be calculated by Step and in total and displayed in Kaplan-Meier curves.

The findings of the physical examinations are summarized by number (n) and percentage (%) of subjects per category (Normal/Abnormal (NCS)/Abnormal (CS)/Not done) per Step and in total by treatment group and visit each body system (Head, ear, eye, nose and throat, respiratory system, cardiovascular system, abdomen, central and peripheral nervous system, lymph nodes, skin, skelet and other body system). In addition, shift tables will be provided to further evaluate the change before first administration of the medication and the end of treatment.

ECG data, vital signs as well as laboratory data (hematology and blood chemistry) will be summarized as continuous data by treatment group and visit per Step and in total. In addition, where available, the interpretation of the measured data (Normal/Abnormal (NCS)/Abnormal (CS)/Not done) will be analyzed as the findings of the physical examinations.

7.8 Evaluation of Pharmacokinetic Data

Drug concentrations will be summarized by descriptive statistics for both metoprolol and tesofensine using only the data from subjects exposed to the IMP. To take into account that pharmacokinetic parameters are often lognormally distributed, the geometric mean and the geometric coefficient of variation will be calculated additionally. The geometric mean is defined as the nth root of the product of n concentration measurements. The geometric coefficient of variation can be easily obtained by subtracting 1 from the geometric standard deviation and multiplication with 100.

In addition, the 90% confidence interval of a log-transformed exposure measure (mean trough concentrations from all follow-up samples (i.e. excluding the baseline sample collected prior to treatment with the study medication) collected from all adult participants for both metoprolol and tesofensine) will be provided. Furthermore, figures will be provided detailing the concentration of

metoprolol/tesofensine over time since first exposure to metoprolol/tesofensine and the log-transformed mean concentration over time since first exposure to metoprolol/tesofensine.

It should be noted that values below the lower limit of quantification will be excluded from the analysis, since the subjects are considered not to be exposed to the IMP in this case. The number of subjects in the IMP group with a value below the lower limit of quantification during the treatment phase will be listed in a footnote to the corresponding table.

8. Changes in the Planned Analysis

The analysis of this study is described in the study protocol TM002 (dated: 25 July 2017 Protocol Amendment Version 1.2 for Hungary and 25 July 2017 Protocol Amendment Version 1.3 for Czech Republic), Nevertheless, minor changes to the conduct of the analysis have to be performed and are described below in detail.

At the request of the Sponsor, an unblinded safety and PK analysis not planned in the study protocol TM002 (dated as described above) is conducted based on the data of nine adult patients included in the study at the time of finalization of this SAP. This deviation from the initial plan to have 10-20 randomized subjects with PWS results is deemed necessary since there are no subjects available at the participating sites anymore. Depending on the results of this unblinded analysis including efficacy, safety and PK data, next steps will be propsed, including potential pediatric plan by the Sponsor. Before any new patients are enrolled the updated plan will be submitted for approval to respective regulatory authorities and ECs as outlined in the study protocol. For this unblinded safety and PK analysis, all data will be used as available and no analysis of subgroups (SES, PPP) will be performed. This is deemed necessary due to the low number of subjects that will be analysed. As the safety and PK analysis is only performed with subjects of the first phase of the study, Step and subgroup will not be included as factors for the analysis.

The wording of the primary endpoint was changed from "Percent change from baseline to end of treatment in mean body weight" to "Percent change from baseline to end of treatment in body weight" to address that no replicated measurements were performed during the body weight assessment at a visit. That means that the relative change of body weight as assessed by single measurements performed at the screening visit and the end of treatment is calculated. The same applies to the secondary endpoint "Change from baseline to end of treatment in body weight (kg)".

If the study stops after Step 1 the statistical analysis will be based on the data available from Step 1 according to this SAP.

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The selection, naming and numeration of the tables is not mandatory but might be adapted in accordance with the described analyses in this SAP.

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The selection, naming and numeration of the listingsis not mandatory but might be adapted in accordance with the described analyses in this SAP.

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The selection, naming and numeration of the figures are not mandatory but might be adapted in accordance with the described analyses in this SAP.

STATISTICAL ANALYSIS PLAN

Study Code 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

Sponsor: Saniona, A/S
Baltorpvej 154
DK 2750 Ballerup
Denmark

Author: Andreas Beust
GCP-Service International Ltd. & Co. KG
Anne-Conway-Str. 2
28359 Bremen, Germany
Tel +49 (0)421 89 67 66 31

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Final 1.1	18-Jan-2019	Andreas Beust	Update according to new protocol version

Signatures

I confirm that this Statistical Analysis Plan (SAP) accurately describes the planned statistical analyses to the best of my knowledge and was finalized before breaking the blind.

Author: Andreas Beust, PhD.
Biostatistician
GCP-Service Int. Ldt & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

21JAN2019 — Date
Signature

Review: Shobhit Agrawal, M.Sc.
Biostatistician
GCP-Service Int. Ldt & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

21JAN2019 — Date
Signature

Approved: Roman Dvorak MD, PhD
Chief Medical Officer
Saniona, A/S
Baltorpvej, 154
DK 2750 Ballerup
Denmark

20 JAN 2019 — Date
Signature

Table of Contents

List of Abbreviations and Key Terms

AE	Adverse Event
ANCOVA	Analysis of co-variance
ATC	Anatomical Therapeutic Chemical (Classification)
BMC	Bone Mineral Conent
BMD	Bone Mineral Density
BMI	Body-Mass-Index
BP	Blood Pressure
bpm	Beats per minute
CI	Confidence interval
CRF	Case Report Form
CRO	Contract Research Organization
cm	Centimeter
cm^2	Square centimeter
CV	Coefficient of variation
CZ	Czech Republic
DBP	Diastolic Blood Pressure
D(E)XA	Dual (Energy) X-ray Absorptiometry
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HbA_{1C}	Hemoglobin A1C
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
HDL	High-density lipoprotein
HLGT	Highest Level Group Term
HLT	Highest Level Term
HR	Heart Rate
HU	Hungary
ICH	International Conference on Harmonization
ID	Identification number
IMP	Investigation Medicinal Product
Kg	Kilogramme
L	Liter
LDL	Low-density lipoprotein

LLT	Lowest Level Term
LOCF	Last observation carried forward
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mIU	Milli-international units per liter
mL	Milliliter
min	Minute
Min	Minimum
mmHg	Millimeter of mercury
mmol	Millimole
n	Number of subjects
N missing	Number of missing values
OP	Out-patient
P	Phone call
PK	Pharmacokinetic
PPP	Per Protocol Population
PT	Preferred term
PWS	Prader-Willi Syndrom
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SES	Safety Evalution Set
SBP	Systolic Blood Pressure
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUKL	State Institute for Drug Control (Czech Republic)
WHO-DDE	World Health Organization - Drug Dictionary Enhanced

1. Introduction

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the study protocol TM002 (dated: 13 March 2018 Protocol Amendment Version 1.4 for Hungary and 09 February 2018 Protocol Amendment Version 1.5 for Czech Republic) (CZ) and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. In addition, Section 8 of this SAP summarizes all changes from the planned analysis as described in the SAP version 1.0 as as known before finalization of this document. As the study is performed in two steps (Step 1 and Step 2), the SAP is updated and signed after Step 1 and prior to breaking the blind for Step 2.

Data management and transfer of data will be carried out in accordance with the data management plan (DMP), statistical analysis in accordance with the SAP.

If changes in the conduct of the statistical analysis are unavoidable, the reasons and the effect of these changes will be documented in the statistical report/clinical study report in full details.

All statistical activities within the framework of this study will be based on the standard operating procedures (SOPs) for clinical studies of GCP-Service, as well as the ICH Guideline for Good Clinical Practice (ICH-GCP).

2. Study Design and Objectives

2.1 Study Design

This clinical study is 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). 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 PWS.

The study will be conducted in two steps, each with two arms. The second step will only start following an unblinded interim analysis[a] by the Sponsor and in CZ following the review and approval of the State Institute for Drug Control (SUKL; the HU regulatory authority did not request this review):

[a] The unblinded interim analysis was conducted in January 2018 after nine of the envisioned ten to twenty patients of Step 1 were randomized and have finished treatment. The interim analysis results were reviewed by the Sponsor, but not the Data

- Step 1: 10-20 adult subjects with PWS planned, but finished after 9 adult subjects as no more subjects were available
    - Arm 1: tesofensine 0.50 mg + metoprolol 50 mg administered once a day, with the morning meal
    - Arm 2: placebo tablets matching tesofensine + metoprolol administered once a day, with the morning meal
- Step 2: 5-15 children with PWS planned
    - Arm 1: tesofensine 0.125 mg (0.25 mg every second day) + metroprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, with the morning meal
    - Arm 2: placebo tablets matching tesofensine every second day + metoprolol administered once a day, with the morning meal

2.2 Treatments

2.2.1 Investigational Medicinal Product

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

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 Step 1 (adult subjects with PWS), 0.5 mg of tesofensine and 50 mg of extended release metoprolol or matching placebo will be administered.

Following Step 1, an unblinded interim analysis was performed. The Sponsor reviewed the unblinded data and a summary of key results from Step 1, including PK data, and attested, following recommendations by the State Institute for Drug Control (SUKL) for CZ, that it was safe to proceed to Step 2 in children as described in the clinical study protocol.

Safety Monitoring Board (DSMB) as initially planned. This change was introduced for HU with protocol version 1.3, dated 31 October 2017, and for CZ with protocol version 1.4, dated 31 October 2017.

In the Step 2 (children with PWS), tesofensine 0.125 mg (0.25 mg every second day) + metoprolol 25 mg will be administered once a day, in the morning with a meal.

2.2.2 Placebo

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

2.3 Trial Schedule

Study medication will be administered for ninety-two (92) days (+2 days after the final assessments with half-dose of metoprolol/placebo). Study procedures in Step 1 and 2 will be the same, except for a comprehensive psychiatric evaluation, which will be included for Step 2 during screening and every site visit.

Following all baseline assessments, eligible subjects will be randomly assigned to one of the two arms (3:2, IMP: placebo).

Screening visit is combined with the baseline and randomization visit (Day 0, Visit 1). All requested screening assessments and baseline blood draws and tests will be performed before randomization.

After the Day 0, subjects will visit the site on Days 7, 28, 56 and 91 (Visits 2, 5, 9, 14) for efficacy and safety evaluations, pharmacokinetic (PK) sampling and medication supply.

On Days 14, 21, 35, 42, 49, 63, 70, 77, 84 (Visits 3, 4, 6, 7, 8, 10, 11, 12, 13) phone call follow ups will be performed. These phone calls will be used to provide additional reassurance regarding the safety of the subjects and collection of AEs.

In Step 1, on Day 105 (Visit 15) a phone call was performed to check subjects' status and potential AE(s). This concluded a subjects' participation in the study. In Step 2, the subjects will be invited for the final safety check and PK sampling on Day 121 (30 days after last dose), which will conclude their participation in the study.

The study schedule is displayed in Table 1.

Table 1: Study schedule

Visit	1 Screening /Baseline/ Randomization OP	2 OP	3, 4 P	5 OP	6, 7, 8 P	9 (O) P	10, 11, 12, 13 P	14 OP	15 F-up[1] (O)P
Day	0	7	14 21	28	35 42 49	56	63 70 77 84	91	105 / 121
Obtaining written Informed Content, Inclusion/Exclusion	x								
Generating screening number	x								
Demographic information	x								
Medical/medication history	x								
Psychiatric examination*	x	x		x		x		x	x
Physical examination	x							x	
Vital signs	x	x		x		x		x	
Randomization	x								
Weight, waist circumference	x	x		x		x		x	
Height, calculation of BMI	x								
HQ-CT	x	x		x		x		x	
ECG	x							x	
Hematology	x			x				x	
Blood chemistry	x			x				x	
FPG, HbA1c	x			x		x		x	

Lipids, insulin	x			x		x		x	
DEXA	x							x	
PK sample	x			x		x		x	x
Lifestyle consultation	x								
Drug dispensation	x	x		x		x		** x	
AEs	x	x	x	x	x	x	x	x	x
Drug accountability		x		x		x		x	
Concomitant medication	x	x	x	x	x	x	x	x	x
Urinary pregnancy test	x							x	
Subject card dispensation	x								
Diary dispensation	x								
Diary review		x		x		x		x	
Diary collection								x	
Dispense Follow-up diary list								x	
End of study form									x

OP: Out-patient

P: Phone Call

[1] **Step 1: Phone call after study day 105 / Step 2: Personal visit postponed to study day 121**

*** Only applicable for Step 2**

**** two half doses of metoprolol should be dispensed**

2.4 Study Objectives

2.4.1 Primary Objective

The primary objective of this clinical trial is:

- To examine the effect of co-administration of tesofensine/metoprolol on body weight in subjects with PWS.

2.4.2 Secondary Objectives

In addition, further objectives are

- To establish pharmacokinetic profile of tesofensine and metoprolol in subjects with PWS,
- To examine the change in hyperphagia-related behaviour 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.

2.5 Study Hypothesis

As this is an explorative study no formal study hypothesis will be tested but the study results may be used to generate study hypotheses for possible subsequent studies.

2.6 Handling of Screening Failures and Withdrawals

Nine subjects were randomized in Step 1. In Step 2, enrolment will continue until a total of 5-15 pediatric subjects are randomized. Randomized subjects who withdraw or are withdrawn from the study for any reason before completion are called "withdrawals". Withdrawals may be replaced, so that there are as close as possible to the minimum of 5 (Step 2) or 10 (Step 1) completers in each step of the study.

A participant who fails during the screening phase, before randomisation, for any reason, e.g. because of violation against the eligibility criteria, is regarded as "screening failure". Subjects excluded during the screening period may be considered for another selection visit at a later date but will need to undergo complete rescreening.

2.7 Randomization and Stratification

A centre-stratified block randomization with fixed block size is used. For each step of the study, one randomization list with complete blocks is prepared. This is done to achieve a balanced distribution of subject characteristics between the two treatment groups within each study centre and step of the study as far as possible. Subjects will be randomly assigned to the two study groups in a 3:2 fashion (IMP:Placebo). A more detailed description of the randomization procedure is given in the Randomization Plan version 2.0, dated 24. August 2017.

2.8 Blinding

The study will be double blind. Neither the investigators nor the subjects will be informed about the type of subject´s medication. In general, emergency unblinding is to be done only when absolutely necessary for the clinical management of an individual subject and where stopping the blinded medication is not sufficient in the opinion of the investigator.

A more detailed description of the blinding and unblinding procedure is given in the Randomization Plan version 2.0, dated 24 August 2017 and the study protocol TM002.

2.9 Sample Size Calculation

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

Each site should randomize a minimum of five (5) eligible adult and a minimum of three (3) eligible pediatric patients. In total there should be randomized a minimum of 14 and a maximum of 29 patients, 9 male and female adult subjects with confirmed diagnosis of PWS from Step 1 and 5-15 male and female pediatric subjects with confirmed diagnosis of PWS.

2.10 Planned Safety and PK Analysis

With protocol version 1.3 (HU) and 1.4 (CZ) coming into effect, no DSMB review of study data after Step 1 was performed and instead, an unblinded interim analysis was conducted in January 2018 after nine instead of the ten patients planned were ultimately randomized. The interim analysis results were reviewed by the Sponsor and in CZ by the SUKL (the HU regulatory authority did not request such a review).
A CRO statistician prepared an unblinded data package with efficacy, safety and PK data from Step 1. The interim analysis provided answers to the Sponsor regarding the following questions:

1) Based on the presented safety data, is it safe to proceed to Step 2, children (≥12 years of age) with PW syndrome “as is”? Any recommended modifications to the protocol?

2) Based on the provided PK data, do you recommend proceeding at the recommended dose of 0.25 mg every second day (which is equal to 0.125 mg Tesofensine daily) and metoprolol ER 25 mg (Metoprolol Orion 25 mg) every day or would you recommend a different dose? If a different dose is recommended, please specify the dose of tesofensine and/or metoprolol.

Safety criteria: There were no set pre-defined criteria as to what constitutes a safety signal which would be considered serious enough not to recommend administration of the study drug to children. For CZ, the SUKL was asked to comprehensively evaluate the provided data and determine the resulting risk/benefit for the pediatric subjects and make their recommendation accordingly.

PK criteria: If the 90% confidence interval (CI) of a log-transformed exposure measure (mean trough concentrations from all follow-up samples,i.e., excluding the baseline sample collected prior to treatment with the study medication, collected from all adult participants for both metoprolol and tesofensine) after back-transformation falls completely within the range 80% of the 0.25 mg dose and 125% of the 1.0 mg dose previously measured trough concentrations in obese adult subjects in the study TIPO-1, the exposure achieved in the adult subjects will be considered in the expected safe range and no dose adjustment for the pediatric patients should be necessary. If the 90% confidence interval falls outside the 80-125% range the exposures will be considered sufficiently "different" from the expected values and a dosing adjustment should be considered by the SULK.

2.11 Handling of Changes to Study Protocol

Any deviations from planned analyses, the reasons for such deviations, and all alternative or additional statistical analyses that may be planned before breaking the blind, respectively, will be described in amendments to the study protocol and/or the SAP. All deviations and/or alterations from the statistical analyses described in the protocol, especially those after database lock will be summarized in the clinical project report.

All statistical analyses not pre-specified by the SAP and run after data lock will be considered as additional/exploratory analyses.

3. Technical Aspects and Coding Conventions

All programs will be written using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.4 or higher. Tables, listings and figures will be provided in separate PDF documents and will contain a separate table of contents. Courier New will be used as font for all tables and listings. In headings, titles and listings only the first word will be capitalised. A noncommittal list of all tables and listings can be found in the Appendix.

A minimum font size of 8 points will be used for the tables, corresponding to a linesize of 140 digits and a pagesize of 52 lines for an output in DIN A4 format. All tables should be self-explaining. Therefore, necessary information should be available in the footnotes. The footnote and title of each table will be left-adjusted while the table will be centered.

For listings, a minimum font size of 8 points with the linesize and pagesize as defined above will be used to produce the output in DIN A4 format. Footnotes, titles and listings will be left-adjusted. Missing data will be represented on subject listings as blank field for text field or "." for numeric variables. Derived data will be marked by '#'. Listings will be sorted by site, treatment and screening number (equivalent to subject identification number) unless specified otherwise.

3.1 Date Coding and Day Numbering

The format for presentation of date variables will be DDMMMYYYY. The format for presentation of time variables will be hh:mm.

If dates are partially given, they will be completed, if necessary for the calculation of durations, according to a worst-case imputation. Dates with missing years will only be imputed if the correct year is obvious.

Deviations will be documented and explained.

3.2 Coding Systems and Conventions

3.2.1 Coding of Adverse Events and Medical History

Adverse event (AE), medical history and concomitant diseases terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed. Details are described in the DMP.

3.2.2 Separation of Medical History from Concomitant Diseases

Separation of medical history from concomitant diseases will be done by comparison of the stop date of the medical condition with the start of study treatment. Each medical condition will be allocated unambiguously either to medical history or concomitant diseases.

- **Medical history:** If the stop date is before start of treatment, the medical condition is allocated to medical history. If the stop date is partially given and unambiguously before start of treatment, the medical condition is also allocated to medical history. Furthermore, if the stop date is missing and the medical condition is not known to be ongoing, findings coded as "Surgical and medical procedures" are also allocated to medical history.

- **Concomitant diseases:** If the stop date is at or after start of treatment or the medical condition is ongoing, the medical condition is allocated to concomitant diseases. Furthermore, if the stop date is missing and the medical condition is not known to be active

at start of study, the worst case is assumed for findings **not** coded as "Surgical and medical procedures". Consequently, the medical condition is allocated to concomitant diseases.

3.2.3 Coding of Medications

Previous and concomitant medications will be coded using WHO-DDE (World Health Organization - Drug Dictionary Enhanced) based on different Anatomical Therapeutic Chemical Classification (ATC) code levels. Details are described in the DMP.

3.2.4 Separation of Medications

Separation of previous medications and concomitant medications will be done by comparison of the stop date of the medication with the start of study treatment. Each medication will be allocated unambiguously either to previous or concomitant medications.

- **Previous medications:** If the stop date is before start of treatment, the medication is allocated to previous medications. If the stop date is partially given and unambiguously after start of treatment, the therapy is allocated to previous medications.

- **Concomitant medications:** If the stop date is at or after start of treatment or the medication is ongoing, the medication is allocated to concomitant medications. Furthermore, if the stop date is missing, the worst case is assumed. Consequently, the medication is allocated to concomitant medications. If the stop date is partially given and implies stop date after start of treatment, the medication is also allocated to concomitant medications.

4. Analysis Populations and Subgroups

4.1 Analysis Populations

Within the framework of this study, the following two main populations are analysed:

- The Per Protocol Population (PPP) includes all randomized subjects without any major protocol violations. Subjects in the PPP will contribute to the evaluation 'as treated'.
- The Safety Evaluation Set (SES) includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the SES will contribute to the evaluation 'as treated'.
- The intention to treat (ITT) includes all subjects which receive at least one dose of the investigational product or its comparator and have a subsequent assessment of weight. Subjects in the ITT will contribute to the evaluation 'as treated'.

4.2 Subgroups

The primary analysis for each endpoint will be using the combined data from steps 1 and 2 of this study. In addition, subgroup analyses are planned for step 1 and step 2 of this study to evaluate differences between treated adults and children.

4.3 Stratification

Subjects will be stratified according to study centre.

5. Data Handling

5.1 Handling of Missing Data and Outliers

Since all analyses are explorative and with reference to the low sample size per step of this study, it is not planned to replace or impute missing data by complex imputation methods. Instead data will be used as available and analysis will be performed on observed cases only. The appropriateness of this procedure will be discussed during the blind data review and, if applicable, the handling of missing data will be adapted.

For outliers, i.e. impossible or implausible values, queries are raised to the investigator before hard lock of the database. The investigator will either confirm or correct the value. Subsequently, the corrected or confirmed value is used for the analysis. If applicable, analysis will be performed with and without outliers to show robustness of the results. Complete exclusion of values should be only done in exceptional cases and is only valid for impossible and very implausible values with obvious justification. The decision to exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the investigator and the CRO statistician.

5.2 Handling of Data from Screening Failures and Withdrawals

In case of screening failures, the data will be listed but not further analyzed. The number of screening failures will be provided in a figure and a table for the disposition of subjects.

Data from withdrawals will be used as available without imputation except for the analysis of the primary endpoint, which will be repeated using Last Observation Carried Forward (LOCF) imputations as sensitivity analysis. The number of early withdrawals and the corresponding reasons will be provided in a figure and a table for the disposition of subjects.

For those subjects with early termination visits, the data is recorded either in the eCRF for the actual visit or into the Visit 14 (day 91) eCRF. In the latter case, these visit assignments will be replaced by the scheduled next visit assignment of the subject.

5.3 Handling of Multiple Comparisons and Multiple Primary Variables

As all data analyses in this study are explorative and will be interpreted accordingly, no adjustment for multiple comparisons is necessary.

5.4 Data Review

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. This review will be performed without revealing which treatment the subjects are assigned to. The blinding of the treatment will be maintained for everyone involved in allocating subjects to the analysis sets until data are released for statistical analysis. Furthermore, outliers will be identified by data review according to ICH-E9 (5), and a pseudo randomization (randomization simulation / simulated randomization). In addition, protocol deviations, which may potentially affect the results, will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis. Obviously erroneous data points may be excluded from the analyses. The decision to exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the investigator and the CRO statistician.

For review of the pharmacokinetic data, additional care needs to be taken to avoid premature unblinding of the reviewers due to drug concentration levels being recorded for each subject. Therefore, subject IDs will be replaced by a randomly selected 5-digit pseudo - ID (one per subject) by an independent person not involved in the conduct, data review or analysis of the study. The list used for assignment of fake IDs to subject IDs will be stored in a secure location and will not be accessible to any person involved in the trial. The PK data will be sorted anew by pseudo- ID, the visit number (VISITNUM) and the analyzed drug (PCTEST), to ensure that the order of subjects does not give an indication of the true subject ID. This modified list will then be provided for data review. After acomplete review, all issues will be traced back to the subject ID using the list used for assignment of pseudo - IDs to subject IDs and queries will be resolved or subjects excluded from the analysis as determined during the data review process.

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.

6. Variables for Analysis

6.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be evaluated:

- Demographic information (race, gender, age, height, weight, BMI, waist circumference)

- Medical history, concomitant diseases, previous and concomitant medications
- Baseline characteristics (vital signs, ECG, physical examination, psychiatric examination (Step 2 only))
- Laboratory tests and measurements (fat mass, fat free mass, bone mineral density (BMD), bone mineral content (BMC), HbA_{1c}, Cholesterol, HDL, LDL, Triglyceride, Insulin, FPG)

6.2 Efficacy Endpoints

6.2.1 Primary Endpoint

The following primary variable is evaluated:

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

6.2.2 Secondary Endpoints

The following secondary endpoints are planned:

- Change from baseline to end of treatment in body weight [kg]
- Change from baseline to end of treatment in fat- and fat-free mass [%] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment in fat- and fat-free mass [g] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment in bone mineral density (BMD) [g/cm²] and bone mineral content (BMC) [g] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment of HbA_{1c} [%]
- Change from baseline to end of treatment in fasting plasma glucose (FPG) [mmol/L]
- Change from baseline to end of treatment in waist circumference [cm]
- Change from baseline to end of treatment in insulin [mIU/L]
- Change from baseline to end of treatment in lipid profile (Cholesterol, HDL, LDL, Triglyceride) [mmol/L])
- Change from baseline to end of treatment in total HQ-CT score

6.3 Safety Endpoints

Safety endpoints include:

- Incidence of AEs, SAEs (serious adverse events),
- Blood analysis:

  - Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets
  - Blood chemistry: creatinine, gamma glutamyl transferase, aspartate aminotransferase, alkaline phosphatase, glomerular filtration rate (GFR) and urea
- Electrocardiogram (ECG):
  - Interpretation (normal/abnormal)
  - Change from baseline to end of treatment in R-R, P-R, QRS and Q-T intervals
- Vital signs:
  - Change from baseline to end of treatment in mean HR [bpm]
  - Change from baseline to end of treatment in mean SBP [mmHg]
  - Change from baseline to end of treatment in mean DBP [mmHg]
  - Change from baseline to end of treatment in body temperature [°C]
  - Change from baseline to end of treatment in respiratory rate [breaths/min]
- Physical examination
  - Change from baseline to end of treatment in examination findings (normal/abnormal (NCS)/abnormal (CS)/not done) of different body systems (Head, ear, eye, nose and throat, respiratory system, cardiovascular system, abdomen, central and peripheral nervous system, lymph nodes, skin, skelet and other body system)
- Psychiatric examination
  - Change from baseline to end of treatment in examination findings (normal/ abnormal (NCS)/abnormal (CS)/not done)

6.4 Pharmacokinetic Endpoints

- Steady state concentrations of tesofensine and metoprolol as measured by trough values

7. Statistical Analysis Methods

7.1 Descriptive Statistics

The default summary statistics for quantitative variables will be the number of non-missing observations (n), number of missing values (N missing). For non-missing observations, arithmetic mean, geometric mean (if applicable), standard deviation (SD), coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum (min), median, and maximum (max) will be calculated and reported.

For categorical variables, the number (n) and percentage (%) of subjects per category will be the default summary presentation, and, if applicable, the number of missing values is provided in a "Missing" category. Missing data will not be included in the calculation of percentages as only available data are used, except if a subject did only answer specific questions of a questionnaire.

Percentages will be calculated using a denominator of all subjects in a specified population or treatment group. The denominator will be specified in a footnote to the tables for clarification if necessary. If missing data occur within population specified as denominator, they will not be included in the calculation of percentages, except if a subject did only answer specific questions of a questionnaire.

7.2 Rounding Rules

7.2.1 Estimates of the Mean and Standard Deviation

When using actual data, the mean and standard deviation are both rounded to one more decimal place than the original data, with a maximum of 2 decimal places.

When mean values of repeated measurements are used for calculation of summary statistics, the mean and standard deviation are rounded to the same number of decimal places given for the mean values of repeated measurements used for calculation, with a maximum of 2 decimal places.

7.2.2 Other data

Quartiles and median are always presented with the same number of decimal places as the mean. Minimum and maximum are always provided with the same number of decimal places as the data used. For estimates of proportions, the result is rounded to 3 decimal places. If proportions are displayed as percentage, 1 decimal place is displayed. For example, a proportion of 0.655 will be presented in percentage as 65.5%. The coefficient of variation is rounded to two decimals.

7.3 Calculation of Study Days and Durations

Study days and, if applicable and meaningful, durations will be determined by comparing the respective date to the date of the first administration of the study medication.

- If the respective date is on or after the date of the first administration of the study medication:

  Study day/Duration = Date (e.g. date of visit) - Date of first administration + 1

- If the respective date precedes the date of the first administration of the study medication:

  Study day/Duration = Date (e.g. date of medical history event) - Date of first administration

Time to onset and duration of adverse events will be calculated as follows:

- Time to onset = start date of AE - date of first treatment [+1 for AE starting after start of treatment]

Duration of adverse event = stop date – onset/worsening date + 1

7.4 Evaluation of Demographics and Baseline Characteristics

7.4.1 Disposition of Patients

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 all three analysis populations (SES, PPP and ITT). Subjects withdrawn from the study will be listed along with the primary reason for withdrawal. In addition, the primary reason for withdrawal will be tabulated. Furthermore, a summary of the time to study termination is provided per treatment group.

7.4.2 Demographics and other Baseline Characteristics

Demographic information (race, gender, age, height, weight, BMI, waist circumference), baseline characteristics (vital signs, ECG, physical examination) and laboratory tests and measurements will be summarized by treatment group and step of the study (including a total column) using the default descriptive statistics for subjects in the PPP,SES and ITT.

7.4.3 Medical History, and Concomitant Diseases

Absolute and relative frequencies (n, %) of medical history and concomitant diseases will be described by treatment group based on MedDRA system organ class and preferred term levels for all three analysis populations SES. Results will be presented overall and by step.

7.4.4 Previous and Concomitant Medication

Absolute and relative frequencies (n, %) of previous and concomitant medication will be provided by treatment group based on Anatomical Therapeutic Chemical (ATC) Classification code levels 2 and 3 for all three analysis populations SES. Results will be presented overall and by step.

7.5 Evaluation of Primary Endpoint

The primary endpoint is

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

and will be calculated by:

%-change = (Weight at end of treatment – Weight at baseline) / (Weight at baseline) * 100

Where, according to the protocol, end of treatment is defined as Visit 14 (Day 91).

The primary endpoint will be presented and analysed based on the PPP and ITT.
Percent change from baseline in body weight will be summarized per Step and in total, by treatment group and visit via mean, median, standard deviation, coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum and maximum value). Moreover, complete listings of individual values for the primary endpoint will be provided. Figures displaying the values for individual subjects (spaghetti plots) as well as figures displaying mean and standard deviation for percentage change from baseline in body weight at each visit per treatment group by Step and in total will also be provided.

The primary endpoint percent change from baseline to end of treatment will be compared between treatment arms by means of an ANCOVA model including Step, site and treatment as fixed factors and baseline value as covariate. Estimates and 95% confidence interval of treatment differences will be calculated. The procedure for this analysis might be adapted during the blinded data review meeting. The primary analysis will be using the data from Steps 1 and 2 separately; secondary analyses will be carried out for both steps combined. The critical value will be set on a two-sided significance level of 5%.

For the ANCOVA a variation of the following SAS®-Code is recommended:

```
proc glm data = <name of primary analysis data set>;
        class step site treatment_group;
        model chg_from_base = step site treatment_group baseline;
        lsmeans treatment / cl e stderr pdiff;
        estimate 'Difference IMP versus Placebo'    treatment 1 -1;
run;
quit;
```

The ANCOVA will be repeated with the data of all subjects in the PPP with available weight measurement as sensitivity analysis. For withdrawals, change from baseline will be imputed according to the last observation carried forward (LOCF) method using the last weight measurement before study termination.

7.6 Evaluation of Secondary and Exploratory Variables

The analysis of secondary and exploratory variables will be based on the PPP and ITT . The secondary and exploratory variables will be summarized per Step and in total by treatment group and visit and, where applicable, changes from baseline will be provided using standard descriptive statistics (mean, geometric mean (if applicable), median, standard deviation, coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum and maximum value). Individual (spaghetti plots)

and mean and standard deviation curves over treatment duration will be plotted by treatment per Step and in total.

Change from baseline analysis to the end of treatment for the corresponding secondary and exploratory endpoints will be performed using ANCOVA, logistic regression models as applicable. For continuous variables, the ANCOVA model will be analogous to the model used for the primary endpoint. P-values, 95% confidence intervals and, if applicable, odds ratios for the comparison between treatments will be estimated. Also, the primary analysis of secondary endpoints will be using the data from Steps 1 and 2 separately and additional analyses will be carried out for the combined data. The critical values for each two-sided and one-sided statistical test will be based on a significance level of 5% and 2.5%, respectively. Figures displaying the mean and standard deviation of the raw data at each visit per treatment group will be also provided. Moreover, complete listings of individual values for all secondary and exploratory endpoints will be provided.

A 9-item score will be calculated for the HQ-CT. Change in HQ-CT answers (by question and in total) will be calculated as (answer at visit 2, 5, 9 or 14) minus (answer at screening visit (visit 1)) and presented using standard descriptive statistics (mean), median, standard deviation, coefficient of variation (CV), lower quartile (Q1), uppe quartile (Q3), minimum and maximum value). Scores for each question range from 0 to 4 (with a higher score indicating a worse outcome), resulting in a maximum 9-item sum of 36. A decrease in total score (compared to the baseline assessment) indicates an improvement in hyperphagia. If less than three questions have not been answered by a subject, the missing answers will be imputed by the mean score of all available answers. In case of more missing answers, the total scores will not be calculated. Results will be presented by treatment per Step and in total.

Subject compliance [%] will be calculated as 100 x (number of tablets dispended – number of tablets returned)/(number of days of treatment) and will be calculated for both study drugs separately. The compliance will be summarized using standard descriptive statistics (mean, standard deviation, coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum and maximum value and listed per subject as well.

7.7 Evaluation of Safety Variables

The analysis of the safety variables described in Section 6.3 will be based on the SES. Values will be summarized by treatment per Step and in total, using non-missing counts, mean, standard deviation, median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum for continuous data. Categorical data will be summarized using counts and percentages. Change from baseline to end of treatment analysis for vital signs will be done as described in Section 7.6.

All AEs occurring after the randomization of the subject will be reported as AE (any AEs that occurred between screening and randomization will be reported in medical history, but not as an AE).

Incidences (number and percentage of subjects experiencing adverse events) per treatment group will be calculated for AEs on the system organ class (SOC) level and on the preferred term (PT) level, in total and by step, and by by intensity, by relationship and by outcome. Listings and tables displaying incidences for AEs leading to discontinuation, serious AEs, treatment-related serious AEs and deaths will also be provided.

Differences in the incidence of treatment-related AEs between treatment groups will be analyzed using a logistic regression model with Step and treatment as fixed factor. This model might be adapted during the blind data review depending on the amount and quality of data. Odds ratios, p-values, and 95% confidence intervals corresponding to the logistic regression model will be estimated for the comparisons between treatments.

A variation of following basic SAS code is recommended for the analysis and expanded if needed:

```
proc logistic data=<name of safety analysis data set>;
   class Step treatment_group (ref='0') / param = ref;
   model <binary variable for occurrence of treatment-related AE (1/0)> = Step
   treatment_group;
   oddsratio Step treatment_group;
run;
```

In addition, the time to the first treatment-related adverse event and treatment-related serious adverse event will be calculated by Step and in total and displayed in Kaplan-Meier curves.

The findings of the physical examinations are summarized by number (n) and percentage (%) of subjects per category (Normal/Abnormal (NCS)/Abnormal (CS)/Not done) per Step and in total by treatment group and visit each body system (Head, ear, eye, nose and throat, respiratory system, cardiovascular system, abdomen, central and peripheral nervous system, lymph nodes, skin, skelet and other body system). In addition, shift tables will be provided to further evaluate the change before first administration of the medication and the end of treatment.

ECG data, vital signs as well as laboratory data (hematology and blood chemistry) will be summarized as continuous data by treatment group and visit per Step and in total. In addition, where available, the interpretation of the measured data (Normal/Abnormal (NCS)/Abnormal (CS)/Not done) will be analyzed as the findings of the physical examinations.

Laboratory values will be evaluated in the provided units. Conversions of units will be done as necessary for a common analysis. For HbA1c measurements, values recorded in % will be converted to mmol/mol using the following formula:

HbA1c [mmol/mol] = (HbA1c [%] - 2.15) * 10.929

For ALP, ALT, AST and GGT measurements, values recorded in U/L will be converted to ukat/L using the following conversion:

Measurement [U/L] = 0.0167 * Measurement [µkat/L]

7.8 Evaluation of Pharmacokinetic Data

Drug concentrations will be summarized by descriptive statistics for both metoprolol and tesofensine using only the data from subjects exposed to the IMP. To take into account that pharmacokinetic parameters are often lognormally distributed, the geometric mean and the geometric coefficient of variation will be calculated additionally. The geometric mean is defined as the nth root of the product of n concentration measurements. The geometric coefficient of variation can be easily obtained by subtracting 1 from the geometric standard deviation and multiplication with 100.

In addition, the 90% confidence interval of a log-transformed exposure measure (mean trough concentrations from all follow-up samples (i.e. excluding the baseline sample collected prior to treatment with the study medication) collected from all adult participants for both metoprolol and tesofensine) will be provided after back-transformation. Furthermore, figures will be provided detailing the concentration of metoprolol/tesofensine over time since first exposure to metoprolol/tesofensine and the log-transformed mean concentration over time since first exposure to metoprolol/tesofensine.

It should be noted that values below the lower limit of quantification will be excluded from the analysis, since the subjects are considered not to be exposed to the IMP in this case. The number of subjects in the IMP group with a value below the lower limit of quantification during the treatment phase will be listed in a footnote to the corresponding table.

8. Changes in the Planned Analysis

The analysis of this study is described in the study protocol TM002 (dated: 13 March 2018 Protocol Amendment Version 1.4 for Hungary and 09 February 2018 Protocol Amendment Version 1.5 for Czech Republic). Nevertheless, minor changes to the conduct of the analysis have to be performed and are described below in detail.

The wording of the primary endpoint was changed from “Percent change from baseline to end of treatment in mean body weight” to “Percent change from baseline to end of treatment in body weight” to address that no replicated measurements were performed during the body weight assessment at a visit. That means that the relative change of body weight as assessed by single measurements performed at the screening visit and the end of treatment is calculated. The same applies to the secondary endpoint “Change from baseline to end of treatment in body weight (kg)”.

This does not change the intended analysis but rather more accurately reflects the envisaged analysis as described in the protocol.

Furthermore, the expected minimum enrolment per site was changed from 2 to 3 to ensure a greater likelihood of both treamtents being present at each of the sites and the minimum total number of subjects was adjusted to reflect the number of subjects randomized during Step 1 and the minimum recruitment for Step 2 as defined in the protocol. Finally, changes were made to the provided 90% confidence interval of the mean trough drug concentration. The description now accurately states that the confidence interval will not be provided as log-transformed values but will instead be transformed back.

In addition, the following changes were made to the final SAP (version 1.0) after unblinded interim analysis and in response to changes in the protocol version of HU (CZ) from 1.2 (1.3) to 1.4 (1.5):

Major changes include the addition of an ITT population, which which will be used for all efficacy analyses in addition to the PPS. Further, the analysis of primary and secondary endpoints was updated to display separate results per step and in total, as differences between adults and children (step 1 and step 2) are expected based on current knowledge. This is expected to have an influence on the outcome of the trial in case strong differences between adults and children are observed. However, this will allow for a differentiation in efficacy of the treatment on the two distinct analysis populations (adults and children) rather than having a masking effect of combing them. The results of this change and the reasons for this decision will be discussed in detail in the Clinical Study Report.

Further major changes include that for those subjects with metroprolol/tesofensine concentrations below the lower limit of quantification (LLOQ), instead of not using the values it was conservatively assumed that these subjects had a concentration of LLOQ/2. These subjects were now included in the analysis.

Minor cosmetic and wording changes were added for additional clarification. The study design and visit schedule were updated to reflect protocol changes. Furthermore, a description of the evaluation of the psychiatric examination was that introduced with the protocol amendment was added. The description of the Interim Analysis was updated to match the description in the protocol. Also, a section was added to describe conversion of laboratory values of different sites required for an analysis of all values combined and the rounding rules were updated for additional clarity. The stratification section was changed to reflect the centre-stratified randomization that was in place already during Step 1.

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The selection, naming and numeration of the tables is not mandatory but might be adapted in accordance with the described analyses in this SAP.

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The selection, naming and numeration of the figures are not mandatory but might be adapted in accordance with the described analyses in this SAP.

STATISTICAL ANALYSIS PLAN

Study Code 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"

Sponsor: Saniona, A/S
Baltorpvej 154
DK 2750 Ballerup
Denmark

Author: Andreas Beust
GCP-Service International Ltd. & Co. KG
Anne-Conway-Str. 2
28359 Bremen, Germany
Tel +49 (0)421 20 80 98 51

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Signatures

I confirm that this Statistical Analysis Plan (SAP) accurately describes the planned statistical analyses to the best of my knowledge and was finalized before breaking the blind.

Author: Andreas Beust, PhD.
Biostatistician
GCP-Service Int. Ldt & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

Date Signature

Review: Dennis Neuschwander, M.Sc.
Biostatistician
GCP-Service Int. Ldt & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

Date Signature

Approved: Roman Dvorak MD, PhD
Chief Medical Officer
Saniona, A/S
Baltorpvej, 154
DK 2750 Ballerup
Denmark

Date Signature

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List of Abbreviations and Key Terms

AE	Adverse Event
ANCOVA	Analysis of co-variance
ATC	Anatomical Therapeutic Chemical (Classification)
BMC	Bone Mineral Conent
BMD	Bone Mineral Density
BMI	Body-Mass-Index
BP	Blood Pressure
bpm	Beats per minute
CI	Confidence interval
CRF	Case Report Form
CRO	Contract Research Organization
cm	Centimeter
cm²	Square centimeter
CV	Coefficient of variation
CZ	Czech Republic
DBP	Diastolic Blood Pressure
D(E)XA	Dual (Energy) X-ray Absorptiometry
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HbA_{1C}	Hemoglobin A1C
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
HDL	High-density lipoprotein
HLGT	Highest Level Group Term
HLT	Highest Level Term
HR	Heart Rate
HU	Hungary
ICH	International Conference on Harmonization
ID	Identification number
IMP	Investigation Medicinal Product
Kg	Kilogramme
L	Liter
LDL	Low-density lipoprotein

LLT	Lowest Level Term
LOCF	Last observation carried forward
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mIU	Milli-international units per liter
mL	Milliliter
min	Minute
Min	Minimum
mmHg	Millimeter of mercury
mmol	Millimole
n	Number of subjects
N missing	Number of missing values
OLE	Open Label Extension
OP	Out-patient
P	Phone call
PK	Pharmacokinetic
PPP	Per Protocol Population
PT	Preferred term
PWS	Prader-Willi Syndrom
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SES	Safety Evalution Set
SBP	Systolic Blood Pressure
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUKL	State Institute for Drug Control (Czech Republic)
WHO-DDE	World Health Organization - Drug Dictionary Enhanced

1. Introduction

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the study protocol TM002 (latest versions dated: 31 January 2019 Protocol Amendment Version 1.6 for Hungary and 30 January 2019 Protocol Amendment Version 1.7 for Czech Republic) (CZ) and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. In addition, Section 8 of this SAP summarizes all changes from the planned analysis as described in the SAP version 1.1 as known before finalization of this document. As the study has been extended beyond the originally envisaged steps 1 and 2 to encompass two open label extensions (OLE), this SAP is updated and signed prior to the evaluation of both open label extensions.

Data management and transfer of data will be carried out in accordance with the data management plan (DMP), statistical analysis in accordance with this SAP.

If changes in the conduct of the statistical analysis are unavoidable, the reasons and the effect of these changes will be documented in the statistical report/clinical study report in full details.

All statistical activities within the framework of this study will be based on the standard operating procedures (SOPs) for clinical studies of GCP-Service, as well as the ICH Guideline for Good Clinical Practice (ICH-GCP).

2. Study Design and Objectives

2.1 Study Design

This clinical study is 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). 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 PWS.

The study was conducted in two steps, each with two arms. The second step was started following an unblinded interim analysis[a] by the Sponsor, and in CZ following the review and approval of the State Institute for Drug Control (SUKL; the HU regulatory authority did not request this review):

- Step 1: 10-20 adult subjects with PWS planned, but finished after 9 adult subjects as no more subjects were available
    - Arm 1: tesofensine 0.50 mg + metoprolol 50 mg administered once a day, with the morning meal
    - Arm 2: placebo tablets matching tesofensine + metoprolol administered once a day, with the morning meal
- Step 2: 5-15 children with PWS planned, but finished after 9 pediatric subjects as no more subjects were available
    - Arm 1: tesofensine 0.125 mg (0.25 mg every second day) + metroprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, with the morning meal
    - Arm 2: placebo tablets matching tesofensine every second day + metoprolol administered once a day, with the morning meal

All eligible participants of Step 2 were offered to continue the trial in an open label extension for an initial 12 weeks (OLE1; according to protocol amendments 1.5 (HU) and 1.6 (CZ)), in which all participants received the following doses:

- Tesofensine 0.125 mg (0.25 mg every second day) and Metoprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, with the morning meal

All eligible participants of the first open label extension were offered a second extension of 12 weeks (according to protocol amendments 1.6 (HU) and 1.7 (CZ)), in which all particpants received the following doses:

- Tesofensine 0.125 mg (0.25 mg every second day) and Metoprolol ER 25 mg (Metoprolol Orion 25 mg) administered once a day, with the morning meal
- For all patients tolerating the OLE1 doses well, the dose was increased to 0.25 mg Tesofensine and 25 mg Metoprolol ER administered once a day, with the morning meal

[a] The unblinded interim analysis was conducted in January 2018 after nine of the envisioned ten to twenty patients of Step 1 were randomized and have finished treatment. The interim analysis results were reviewed by the Sponsor, but not the Data Safety Monitoring Board (DSMB) as initially planned. This change was introduced for HU with protocol version 1.3, dated 31 October 2017, and for CZ with protocol version 1.4, dated 31 October 2017.

In case a patient, in the opinion of the PI, experienced an adverse event that, by the PI, was suspected to be potentially related to an undesirable drug concentration of the investigational medication, the investigators at each site, based on their discretion, was allowed to modify the treatment schedule of the patients in order to optimally manage the wellbeing and safety of the patient.

2.2 Treatments

2.2.1 Investigational Medicinal Product

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

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 Step 1 (adult subjects with PWS), 0.5 mg of tesofensine and 50 mg of extended release metoprolol or matching placebo was administered.

Following Step 1, an unblinded interim analysis was performed. The Sponsor reviewed the unblinded data and a summary of key results from Step 1, including PK data, and attested, following recommendations by the State Institute for Drug Control (SUKL) for CZ, that it was safe to proceed to Step 2 in children as described in the clinical study protocol.

In the Step 2 (children with PWS), tesofensine 0.125 mg (0.25 mg every second day) + metoprolol 25 mg were administered once a day, in the morning with a meal. For OLE1 (initial 12 weeks extensions), participants of the Step 2 trial that continued were treated with tesofensine 0.125 mg (0.25 mg every second day) + metoprolol 25 mg (once a day). For OLE2 (second 12 weeks extension), participants that tolerated the OLE1 dose well were allowed to be treated at 0.25 mg tesofensine and 25 mg metoprolol per day. Patients that experienced, in the opinion of the PI, an adverse event potentially related to the investigational medication, could be treated with a reduced dose or alternative dosing schedule to optimally manage the wellbeing and safety of the patient.

2.2.2 Placebo

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

2.3 Trial Schedule

Study medication was administered for ninety-two (92) days (+2 days after the final assessments with half-dose of metoprolol/placebo) during Step 1 and Step 2 of the trial. Study medication was administered for ninety (90) days (+2 days after the final assessments with half-dose of metoprolol) during OLE1 and OLE2. Study procedures in Step 1 and 2 were the same, except for a comprehensive psychiatric evaluation, which was included for Step 2 during screening and every site visit. Study procedures in the OLE1 and OLE2 part of the trial followed the the described assessments of Step 2, with differences in the scheduling (see Table 2, 3 and 4, 5, respectively).

Following all baseline assessments, eligible subjects were randomly assigned to one of the two arms (3:2, IMP: placebo).

For Step 1 and 2, screening visit was combined with the baseline and randomization visit (Day 0, Visit 1). All requested screening assessments and baseline blood draws and tests were performed before randomization.

After the Day 0, subjects visited the site on Days 7, 28, 56 and 91 (Visits 2, 5, 9, 14) for efficacy and safety evaluations, pharmacokinetic (PK) sampling and medication supply.

On Days 14, 21, 35, 42, 49, 63, 70, 77, 84 (Visits 3, 4, 6, 7, 8, 10, 11, 12, 13) phone call follow ups were performed. During the OLE parts of the study, phone calls were performed once per month between visits (see Table 3, 5). These phone calls were used to provide additional reassurance regarding the safety of the subjects and collection of AEs.

In Step 1, on Day 105 (Visit 15) a phone call was performed to check subjects' status and potential AE(s). This concluded a subjects' participation in the study. In Step 2, the subjects were invited for the final safety check and PK sampling on Day 121 (30 days after last dose), which concluded their participation in the study. An exception to this was the participation in the OLE1 part of the study, for which the day 91 visit during Step 2 was used as Baseline visit. For those patients participating in the OLE1, the day 210 visit (30 days after last dose) concluded their participation in the study. An exception to this was the participation in the OLE2 part of the study, for which the day 180 visit during OLE1 was used as Baseline visit. For those patients participating in the OLE2, the day 300 visit (30 days after last dose) concluded their participation.

The study schedules for Part 2, OLE1 and OLE2 are displayed in Table 1, 2 and 3, and 4 and 5, respectively.

Table 1: Study schedule Step 1/2

Visit	1 Screening /Baseline/ Randomization OP	2 OP	3, 4 P	5 OP	6, 7, 8 P	9 (O) P	10, 11, 12, 13 P	14 OP	15 F-up[1] (O)P
Day	**0**	**7**	**14** **21**	**28**	**35** **42** **49**	**56**	**63** **70** **77** **84**	**91**	**105 / 121**
Obtaining written Informed Content, Inclusion/Exclusion	x								
Generating screening number	x								
Demographic information	x								
Medical/medication history	x								
Psychiatric examination*	x	x		x		x		x	x
Physical examination	x							x	
Vital signs	x	x		x		x		x	
Randomization	x								
Weight, waist circumference	x	x		x		x		x	
Height, calculation of BMI	x								
HQ-CT	x	x		x		x		x	
ECG	x							x	
Hematology	x			x				x	
Blood chemistry	x			x				x	
FPG, HbA1c	x			x		x		x	

Lipids, insulin	x			x		x		x	
DEXA	x							x	
PK sample	x			x		x		x	x
Lifestyle consultation	x								
Drug dispensation	x	x		x		x		** x	
AEs	x	x	x	x	x	x	x	x	x
Drug accountability		x		x		x		x	
Concomitant medication	x	x	x	x	x	x	x	x	x
Urinary pregnancy test	x							x	
Subject card dispensation	x								
Diary dispensation	x								
Diary review		x		x		x		x	
Diary collection								x	
Dispense Follow-up diary list								x	
End of study form									x

OP: Out-patient

P: Phone Call

[1] **Step 1: Phone call after study day 105 / Step 2: Personal visit postponed to study day 121**

*** Only applicable for Step 2**

**** two half doses of metoprolol should be dispensed**

Table 2: Study schedule OLE1

Visit	14 Equal to last visit of part 2 Treatment	15 Treatment	16 Treatment	17 End of Treatment	18 End of study
Day	**91**	**120 (28 days ± 3 days)**	**150(28 days ± 3 days)**	**180(28 days ± 3 days)**	**210(28 days ± 3 days)**
Obtaining the Addendum to double blind ICF for the open label part	x				
Subject screening number (keeping the same as in Step2)	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
Lifestyle consultation	x				
Drug dispensation	x			x	
AEs	x	x	x	x	x
Drug accountability		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. Time point for dosing and the two blood samples should be noted!**

Table 3: Phone call schedule OLE1

Visit	14.1 Phone call	15.1 Phone call	16.1 Phone call	17.1 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

Table 4: Study schedule OLE2

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
Lifestyle consultation	x				
Drug dispensation	x			x	
AEs	x	x	x	x	x
Drug accountability		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!**

Table 5: Phone call schedule OLE2

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

2.4 Study Objectives

2.4.1 Primary Objective

The primary objective of this clinical trial is:

- To examine the effect of co-administration of tesofensine/metoprolol on body weight in subjects with PWS.

2.4.2 Secondary Objectives

In addition, further objectives are

- To establish pharmacokinetic profile of tesofensine and metoprolol in subjects with PWS,
- To examine the change in hyperphagia-related behaviour 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.

2.5 Study Hypothesis

As this is an explorative study no formal study hypothesis will be tested but the study results may be used to generate study hypotheses for possible subsequent studies.

2.6 Handling of Screening Failures and Withdrawals

Nine subjects were randomized in Step 1 and Step 2, each. Of the nine patients participating in Step 2, eight continued into the OLE1 phase of the trial, of which five continued to the OLE2 phase of the trial.

A participant who failed during the screening phase, before randomisation, for any reason, e.g. because of violation against the eligibility criteria, was regarded as "screening failure". Subjects excluded during the screening period could have been considered for another selection visit at a later date but needed to undergo complete rescreening.

2.7 Randomization and Stratification

A centre-stratified block randomization with fixed block size was used. For each step of the study, one randomization list with complete blocks was prepared. This was done to achieve a balanced distribution of subject characteristics between the two treatment groups within each study centre and step of the study as far as possible. Subjects were randomly assigned to the two study groups in a 3:2 fashion (IMP:Placebo). A more detailed description of the randomization procedure is given in the Randomization Plan version 2.0, dated 24. August 2017.

For the OLE part of the study, all included subjects received the IMP, irrespective of their previous allocation.

2.8 Blinding

Step 1 and 2 of the study were conducted double blind. Neither the investigators nor the subjects were informed about the type of subject´s medication. In general, emergency unblinding had to be done only when absolutely necessary for the clinical management of an individual subject and where stopping the blinded medication was not sufficient in the opinion of the investigator.

A more detailed description of the blinding and unblinding procedure is given in the Randomization Plan version 2.0, dated 24 August 2017 and the study protocol TM002.

2.9 Sample Size Calculation

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

2.10 Planned Safety and PK Analysis

With protocol version 1.3 (HU) and 1.4 (CZ) coming into effect, no DSMB review of study data after Step 1 was performed and instead, an unblinded interim analysis was conducted in January 2018 after nine instead of the ten patients planned were ultimately randomized. The interim analysis results were reviewed by the Sponsor and in CZ by the SUKL (the HU regulatory authority did not request such a review).
A CRO statistician prepared an unblinded data package with efficacy, safety and PK data from Step 1. The interim analysis provided answers to the Sponsor regarding the following questions:

1) Based on the presented safety data, is it safe to proceed to Step 2, children (≥12 years of age) with PW syndrome "as is"? Any recommended modifications to the protocol?

2) Based on the provided PK data, do you recommend proceeding at the recommended dose of 0.25 mg every second day (which is equal to 0.125 mg Tesofensine daily) and metoprolol ER 25 mg (Metoprolol Orion 25 mg) every day or would you recommend a different dose? If a different dose is recommended, please specify the dose of tesofensine and/or metoprolol.

Safety criteria: There were no set pre-defined criteria as to what constitutes a safety signal which would be considered serious enough not to recommend administration of the study drug to children. For CZ, the SUKL was asked to comprehensively evaluate the provided data and determine the resulting risk/benefit for the pediatric subjects and make their recommendation accordingly.

PK criteria: If the 90% confidence interval (CI) of a log-transformed exposure measure (mean trough concentrations from all follow-up samples,i.e., excluding the baseline sample collected prior to treatment with the study medication, collected from all adult participants for both metoprolol and tesofensine) after back-transformation falls completely within the range 80% of the 0.25 mg dose and 125% of the 1.0 mg dose previously measured trough concentrations in obese adult subjects in the study TIPO-1, the exposure achieved in the adult subjects will be considered in the expected safe range and no dose adjustment for the pediatric patients should be necessary. If the 90% confidence interval falls outside the 80-125% range the exposures will be considered sufficiently "different" from the expected values and a dosing adjustment should be considered by the SULK.

2.11 Handling of Changes to Study Protocol

Any deviations from planned analyses, the reasons for such deviations, and all alternative or additional statistical analyses that may be planned before breaking the blind, respectively, will be described in amendments to the study protocol and/or the SAP. All deviations and/or alterations from the statistical analyses described in the protocol, especially those after database lock will be summarized in the clinical project report.

All statistical analyses not pre-specified by the SAP and run after data lock will be considered as additional/exploratory analyses.

3. Technical Aspects and Coding Conventions

All programs will be written using SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.4 or higher. Tables, listings and figures will be provided in separate PDF documents and will contain a separate table of contents. For each analysis (Step 2, Step 2 and OLE1, Step 2, OLE1 and OLE2, OLE1 alone, OLE2 alone), separate documents will be prepared. Tables for each analysis will additionally be split into different documents based on their content as follows:

- Baseline/Demographics/Disposition
- Efficacy data
- Safety data
- Other

Courier New will be used as font for all tables and listings. In headings, titles and listings only the first word will be capitalised. A noncommittal list of all tables and listings can be found in the Appendix.

A minimum font size of 8 points will be used for the tables, corresponding to a linesize of 140 digits and a pagesize of 52 lines for an output in DIN A4 format. All tables should be self-explaining. Therefore, necessary information should be available in the footnotes. The footnote and title of each table will be left-adjusted while the table will be centered.

For listings, a minimum font size of 8 points with the linesize and pagesize as defined above will be used to produce the output in DIN A4 format. Footnotes, titles and listings will be left-adjusted. Missing data will be represented on subject listings as blank field for text field or "." for numeric variables. Derived data will be marked by '#'. Listings will be sorted by site, treatment and screening number (equivalent to subject identification number) unless specified otherwise.

3.1 Date Coding and Day Numbering

The format for presentation of date variables will be DDMMMYYYY. The format for presentation of time variables will be hh:mm.

If dates are partially given, they will be completed, if necessary for the calculation of durations, according to a worst-case imputation. Dates with missing years will only be imputed if the correct year is obvious.

Deviations will be documented and explained.

3.2 Coding Systems and Conventions

3.2.1 Coding of Adverse Events and Medical History

Adverse event (AE), medical history and concomitant diseases terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed. Details are described in the DMP.

3.2.2 Separation of Medical History from Concomitant Diseases

Separation of medical history from concomitant diseases will be done by comparison of the stop date of the medical condition with the start of study treatment, referring to the start of treatment during Step 2 of the trial. Each medical condition will be allocated unambiguously either to medical history or concomitant diseases.

- **Medical history:** If the stop date is before start of treatment, the medical condition is allocated to medical history. If the stop date is partially given and unambiguously before start of treatment, the medical condition is also allocated to medical history. Furthermore, if the stop date is missing and the medical condition is not known to be ongoing, findings coded as "Surgical and medical procedures" are also allocated to medical history.

- **Concomitant diseases:** If the stop date is at or after start of treatment or the medical condition is ongoing, the medical condition is allocated to concomitant diseases. Furthermore, if the stop date is missing and the medical condition is not known to be active at start of study, the worst case is assumed for findings **not** coded as "Surgical and medical procedures". Consequently, the medical condition is allocated to concomitant diseases.

3.2.3 Coding of Medications

Previous and concomitant medications will be coded using WHO-DDE (World Health Organization - Drug Dictionary Enhanced) based on different Anatomical Therapeutic Chemical Classification (ATC) code levels. Details are described in the DMP.

3.2.4 Separation of Medications

Separation of previous medications and concomitant medications will be done by comparison of the stop date of the medication with the start of study treatment, referring to the start of treatment during Step 2 of the trial. Each medication will be allocated unambiguously either to previous or concomitant medications.

- **Previous medications:** If the stop date is before start of treatment, the medication is allocated to previous medications. If the stop date is partially given and unambiguously after start of treatment, the therapy is allocated to previous medications.

- **Concomitant medications:** If the stop date is at or after start of treatment or the medication is ongoing, the medication is allocated to concomitant medications. Furthermore, if the stop date is missing, the worst case is assumed. Consequently, the medication is allocated to concomitant medications. If the stop date is partially given and implies stop date after start of treatment, the medication is also allocated to concomitant medications.

4. Analysis Populations and Subgroups

4.1 Analysis Populations

Within the framework of this study, the following two main populations are analysed:

- The Per Protocol Population (PPP) includes all randomized subjects without any major protocol violations. Subjects in the PPP will contribute to the evaluation 'as treated'.
- The Safety Evaluation Set (SES) includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the SES will contribute to the evaluation 'as treated'.
- The intention to treat (ITT) includes all subjects which receive at least one dose of the investigational product or its comparator and have a subsequent assessment of weight. Subjects in the ITT will contribute to the evaluation 'as treated'.

For the evaluation of the OLE1 and OLE2 parts of the study (analyses 2-5 as described in section 4.2), the analysis will only be performed for the SES and ITT populations.

4.2 Subgroups

The analysis for the Step 2 and OLE1 and OLE2 will be performed sequentially as follows:

1. Based on Step 2 data, for all patients that were enrolled in the Step 2 part of the trial
2. Based on Step 2 and OLE1 data, for all patients that were enrolled in the OLE1 part of the trial
3. Based on Step 2, OLE1 and OLE2 data, for all patients that were enrolled in the OLE2 part of the trial
4. Based on OLE1 data, for all patients that were enrolled in the OLE1 part of the trial
5. Based on OLE2 data, for all patients that were enrolled in the OLE2 part of the trial

The definition for baseline and end of treatment vary for the five subgroups as follows:

1. Baseline is defined as baseline of Step 2 (Visit 1) and End of Treatment (EoT) is defined as Visit 14 of Step 2
2. Baseline is defined as baseline of Step 2 (Visit 1) and EoT is defined as Visit 17 of OLE1
3. Baseline is defined as baseline of Step 2 (Visit 1) and EoT is defined as Visit 20 of OLE2
4. Baseline is defind as Visit 14 of Step 2/OLE1 and EoT is defined as Visit 17 of OLE1
5. Baseline is defined as Visit 17 of OLE1/OLE2 and EoT is defined as Visit 20 of OLE2

For subgroups 4 and 5, only the following parameters will be analyzed:

- Body weight
- Waist circumference
- Hyperphagia score
- Heart rate
- Blood pressure

4.3 Stratification

Subjects will be stratified according to study centre.

5. Data Handling

5.1 Handling of Missing Data and Outliers

Since all analyses are explorative and with reference to the low sample size per step of this study, it is not planned to replace or impute missing data by complex imputation methods. Instead data will be used as available and analysis will be performed on observed cases only.

For outliers, i.e. impossible or implausible values, queries are raised to the investigator before hard lock of the database. The investigator will either confirm or correct the value. Subsequently, the corrected or confirmed value is used for the analysis. If applicable, analysis will be performed with and without outliers to show robustness of the results. Complete exclusion of values should be only done in exceptional cases and is only valid for impossible and very implausible values with obvious justification. The decision to exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the investigator and the CRO statistician.

5.2 Handling of Data from Screening Failures and Withdrawals

In case of screening failures, the data will be listed but not further analyzed. The number of screening failures will be provided in a figure and a table for the disposition of subjects.

Data from withdrawals will be used as available without imputation except for the analysis of the primary endpoint, which will be repeated using Last Observation Carried Forward (LOCF) imputations

as sensitivity analysis if meaningful. The number of early withdrawals and the corresponding reasons will be provided in a figure and a table for the disposition of subjects.

For those subjects with early termination visits, the data is recorded either in the eCRF for the actual visit or into the End of Treatment (EoT) eCRF. In the latter case, these visit assignments will be replaced by the scheduled next visit assignment of the subject.

5.3 Handling of Multiple Comparisons and Multiple Primary Variables

As all data analyses in this study are explorative and will be interpreted accordingly, no adjustment for multiple comparisons is necessary.

5.4 Data Review

Before data are released for statistical analysis, a review of all data of OLE1 and OLE2 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.

6. Variables for Analysis

6.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be evaluated:

- Demographic information (race, gender, age, height, weight, BMI, waist circumference)
- Medical history, concomitant diseases, previous and concomitant medications
- Baseline characteristics (vital signs, ECG, physical examination, psychiatric examination (Step 2 only))
- Laboratory tests and measurements (fat mass, fat free mass, bone mineral density (BMD), bone mineral content (BMC), HbA_{1c}, Cholesterol, HDL, LDL, Triglyceride, Insulin, FPG)

6.2 Efficacy Endpoints

6.2.1 Primary Endpoint

The following primary variable is evaluated:

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

6.2.2 Secondary Endpoints

The following secondary endpoints are planned:

- Change from baseline to end of treatment in total HQ-CT score
- Change from baseline to end of treatment in body weight [kg]
- Change from baseline to end of treatment in fat- and fat-free mass [%] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment in fat- and fat-free mass [g] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment in bone mineral density (BMD) [g/cm²] and bone mineral content (BMC) [g] by dual X-ray absorptiometry (DEXA)
- Change from baseline to end of treatment of HbA_{1c} [%]
- Change from baseline to end of treatment in fasting plasma glucose (FPG) [mmol/L]
- Change from baseline to end of treatment in waist circumference [cm]
- Change from baseline to end of treatment in insulin [mIU/L]
- Change from baseline to end of treatment in lipid profile (Cholesterol, HDL, LDL, Triglyceride) [mmol/L])

6.3 Safety Endpoints

Safety endpoints include:

- Incidence of AEs, SAEs (serious adverse events),
- Blood analysis:
    - Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets
    - Blood chemistry: creatinine, gamma glutamyl transferase, aspartate aminotransferase, alkaline phosphatase, glomerular filtration rate (GFR) and urea
- Electrocardiogram (ECG):

  - Interpretation (normal/abnormal)
  - Change from baseline to end of treatment in R-R, P-R, QRS and Q-T intervals
- Vital signs:
  - Change from baseline to end of treatment in mean HR [bpm]
  - Change from baseline to end of treatment in mean SBP [mmHg]
  - Change from baseline to end of treatment in mean DBP [mmHg]
  - Change from baseline to end of treatment in body temperature [°C]
  - Change from baseline to end of treatment in respiratory rate [breaths/min]
- Physical examination
  - Change from baseline to end of treatment in examination findings (normal/abnormal (NCS)/abnormal (CS)/not done) of different body systems (Head, ear, eye, nose and throat, respiratory system, cardiovascular system, abdomen, central and peripheral nervous system, lymph nodes, skin, skelet and other body system)
- Psychiatric examination
  - Change from baseline to end of treatment in examination findings (normal/ abnormal (NCS)/abnormal (CS)/not done)

6.4 Pharmacokinetic Endpoints

- Steady state concentrations of tesofensine and metoprolol as measured by trough values

7. Statistical Analysis Methods

7.1 Descriptive Statistics

The default summary statistics for quantitative variables will be the number of non-missing observations (n), number of missing values (N missing). For non-missing observations, arithmetic mean, geometric mean (if applicable), standard deviation (SD), coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum (min), median, and maximum (max) will be calculated and reported.

For categorical variables, the number (n) and percentage (%) of subjects per category will be the default summary presentation, and, if applicable, the number of missing values is provided in a "Missing" category. Missing data will not be included in the calculation of percentages as only available data are used, except if a subject did only answer specific questions of a questionnaire.

Percentages will be calculated using a denominator of all subjects in a specified population or treatment group. The denominator will be specified in a footnote to the tables for clarification if necessary. If missing data occur within population specified as denominator, they will not be included in the calculation of percentages, except if a subject did only answer specific questions of a questionnaire.

7.2 Rounding Rules

7.2.1 Estimates of the Mean and Standard Deviation

When using actual data, the mean and standard deviation are both rounded to one more decimal place than the original data, with a maximum of 2 decimal places.

When mean values of repeated measurements are used for calculation of summary statistics, the mean and standard deviation are rounded to the same number of decimal places given for the mean values of repeated measurements used for calculation, with a maximum of 2 decimal places.

7.2.2 Other data

Quartiles and median are always presented with the same number of decimal places as the mean. Minimum and maximum are always provided with the same number of decimal places as the data used. For estimates of proportions, the result is rounded to 3 decimal places. If proportions are displayed as percentage, 1 decimal place is displayed. For example, a proportion of 0.655 will be presented in percentage as 65.5%. The coefficient of variation is rounded to two decimals.

7.3 Calculation of Study Days and Durations

Study days and, if applicable and meaningful, durations will be determined by comparing the respective date to the date of the first administration of the study medication (referring to the start of administration during Step 2 of the trial with exception of the analysis done on data of OLE1 or OLE2 only).

- If the respective date is on or after the date of the first administration of the study medication:

  Study day/Duration = Date (e.g. date of visit) - Date of first administration + 1

- If the respective date precedes the date of the first administration of the study medication:

  Study day/Duration = Date (e.g. date of medical history event) - Date of first administration

Time to onset and duration of adverse events will be calculated as follows:

- Time to onset = start date of AE - date of first treatment [+1 for AE starting after start of treatment]

Duration of adverse event = stop date – onset/worsening date + 1

7.4 Evaluation of Demographics and Baseline Characteristics

7.4.1 Disposition of Patients

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 all analysis populations (SES, PPP and ITT). Subjects withdrawn from the study will be listed along with the primary reason for withdrawal. In addition, the primary reason for withdrawal will be tabulated. Furthermore, a summary of the time to study termination is provided per treatment group.

7.4.2 Demographics and other Baseline Characteristics

Demographic information (race, gender, age, height, weight, BMI, waist circumference), baseline characteristics (vital signs, ECG, physical examination) and laboratory tests and measurements will be summarized by treatment group and step of the study (including a total column) using the default descriptive statistics for subjects in the PPP, SES and ITT.

7.4.3 Medical History, and Concomitant Diseases

Absolute and relative frequencies (n, %) of medical history and concomitant diseases will be described by treatment group based on MedDRA system organ class and preferred term levels for all three analysis populations SES. Results will be presented overall and by step.

7.4.4 Previous and Concomitant Medication

Absolute and relative frequencies (n, %) of previous and concomitant medication will be provided by treatment group based on Anatomical Therapeutic Chemical (ATC) Classification code levels 2 and 3 for all three analysis populations SES. Results will be presented overall and by step.

7.5 Evaluation of Primary Endpoint

The primary endpoint is

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

and will be calculated by:

%-change = (Weight at end of treatment – Weight at baseline) / (Weight at baseline) * 100

Where end of treatment and baseline are defined as described in section 4.2.

The primary endpoint will be presented and analysed based on the PPP and ITT for each subgroup.

Percent change from baseline in body weight will be summarized per subgroup and visit, by treatment group during Step 2 and in total, via mean, median, standard deviation, coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum and maximum value). Moreover, complete listings of individual values for the primary endpoint will be provided. Figures displaying the values for individual subjects (spaghetti plots) as well as figures displaying mean and standard deviation for percentage change from baseline in body weight at each visit per treatment group by Step and in total will also be provided.

The primary endpoint percent change from baseline to end of treatment will be compared between treatment groups during Step 2 and in total by means of an ANCOVA model including site and treatment (the latter not for the total analysis) as fixed factors and baseline value as covariate. Estimates and 95% confidence interval of treatment differences will be calculated. The critical value will be set on a two-sided significance level of 5%.

For the ANCOVA a variation of the following SAS®-Code is recommended:

```
proc glm data = <name of primary analysis data set>;
        class site treatment_group;
        model chg_from_base = site treatment_group baseline;
        lsmeans treatment / cl e stderr pdiff;
        estimate 'Difference IMP versus Placebo'    treatment 1 -1;
run;
quit;
```

The ANCOVA will be repeated with the data of all subjects in the PPP with available weight measurement as sensitivity analysis. For withdrawals, change from baseline will be imputed according to the last observation carried forward (LOCF) method using the last weight measurement before study termination, if meaningful.

7.6 Evaluation of Secondary and Exploratory Variables

The analysis of secondary and exploratory variables will be based on the ITT for each subgroup. The secondary and exploratory variables will be summarized by treatment during Step 2 and in total, and by visit. Where applicable, changes from baseline will be provided using standard descriptive statistics (mean, geometric mean (if applicable), median, standard deviation, coefficient of variation (CV), lower quartile (Q1), upper quartile (Q3), minimum and maximum value). Individual (spaghetti plots) and mean and standard deviation curves over treatment duration will be plotted by treatment during Step 2 and in total.

Change from baseline analysis to the end of treatment for the corresponding secondary and exploratory endpoints will be performed using ANCOVA models,. For continuous variables, the

ANCOVA model will be analogous to the model used for the primary endpoint. Treatment differenceswith 95% confidence intervals and p-values for the comparison between treatments will be estimated. The critical values for each two-sided statistical test will be based on a significance level of 5. Figures displaying the mean and standard deviation of the raw data at each visit by treatment during Step 2 and in total will be also provided. Moreover, complete listings of individual values for all secondary and exploratory endpoints will be provided.

A 9-item score will be calculated for the HQ-CT. Change in HQ-CT answers (by question and in total) will be calculated as (answer at respective visit) minus (answer at baseline (see section 4.2 for definitions)) and presented using standard descriptive statistics (mean), median, standard deviation, coefficient of variation (CV), lower quartile (Q1), uppe quartile (Q3), minimum and maximum value). Scores for each question range from 0 to 4 (with a higher score indicating a worse outcome), resulting in a maximum 9-item sum of 36. A decrease in total score (compared to the baseline assessment) indicates an improvement in hyperphagia. If less than three questions have not been answered by a subject, the missing answers will be imputed by the mean score of all available answers. In case of more missing answers, the total scores will not be calculated. Results will be presented by treatment during Step 2 and in total.

Subject compliance [%] will be calculated as 100 x (number of tablets dispended – number of tablets returned)/(number of days of treatment) and will be calculated for both study drugs separately. The compliance will be summarized using standard descriptive statistics (mean, standard deviation, lower quartile (Q1), upper quartile (Q3), minimum and maximum value and listed per subject as well.

7.7 Evaluation of Safety Variables

The analysis of the safety variables described in Section 6.3 will be based on the SES. Values will be summarized by treatment during Step 2 and in total, using non-missing counts, mean, standard deviation, median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum for continuous data. Categorical data will be summarized using counts and percentages. Change from baseline to end of treatment analysis for vital signs will be done with an ANCOVA model as described in Section 7.6.

All AEs occurring after the randomization of the subject will be reported as AE (any AEs that occurred between screening and randomization will be reported in medical history, but not as an AE).

Incidences (number and percentage of subjects experiencing adverse events) per treatment during Step 2 and in total will be calculated for AEs on the system organ class (SOC) level and on the preferred term (PT) level, by intensity, by relationship and by outcome. Listings and tables displaying incidences for AEs leading to discontinuation, serious AEs, treatment-related serious AEs and deaths will also be provided.

Differences in the incidence of treatment-related AEs between treatment groups will be analyzed for the Step 2 data only using a logistic regression model with treatment as fixed factor. Odds ratios, p-values, and 95% confidence intervals corresponding to the logistic regression model will be estimated for the comparisons between treatments.

A variation of following basic SAS code is recommended for the analysis and expanded if needed:

```
proc logistic data=<name of safety analysis data set>;
   class treatment_group (ref='0') / param = ref;
   model <binary variable for occurrence of treatment-related AE (1/0) within patient> =
   treatment_group;
   oddsratio treatment_group;
run;
```

In addition, the time to the first treatment-related adverse event and treatment-related serious adverse event will be calculated by treatment during Step 2 and in total and displayed in Kaplan-Meier curves considering all data from Step 2 to end of OLE2 (subgroup 3 only). For those patients that received placebo during Step 2 and continued to OLE1 of the trial, an additional analysis will be performed using the start date of treatment with IMP (Visit 14) for the time to event analysis.

The findings of the physical examinations are summarized by number (n) and percentage (%) of subjects per category (Normal/Abnormal (NCS)/Abnormal (CS)/Not done) per treatment during Step 2 and in total, for each body system (Head, ear, eye, nose and throat, respiratory system, cardiovascular system, abdomen, central and peripheral nervous system, lymph nodes, skin, skelet and other body system). In addition, shift tables will be provided to further evaluate the change before first administration of the medication and the end of treatment (definitions of section 4.2 apply).

ECG data, vital signs as well as laboratory data (hematology and blood chemistry) will be summarized as continuous data by treatment during Step 2 and in total as well as by visit. In addition, where available, the interpretation of the measured data (Normal/Abnormal (NCS)/Abnormal (CS)/Not done) will be analyzed as the findings of the physical examinations.

Laboratory values will be evaluated in the provided units. Conversions of units will be done as necessary for a common analysis. For HbA1c measurements, values recorded in % will be converted to mmol/mol using the following formula:

HbA1c [mmol/mol] = (HbA1c [%] - 2.15) * 10.929

For ALP, ALT, AST and GGT measurements, values recorded in U/L will be converted to ukat/L using the following conversion:

Measurement [U/L] = 0.0167 * Measurement [µkat/L]

7.8 Evaluation of Pharmacokinetic Data

Drug concentrations will be summarized by descriptive statistics for both metoprolol and tesofensine using only the data from subjects exposed to the IMP. To take into account that pharmacokinetic parameters are often lognormally distributed, the geometric mean and the geometric coefficient of variation will be calculated additionally. The geometric mean is defined as the nth root of the product of n concentration measurements. The geometric coefficient of variation can be easily obtained by subtracting 1 from the geometric standard deviation and multiplication with 100. Results will be displayed by visit, and additionally by time point (h0/h2/h4) for the OLE1 and OLE2 part of the trial.

8. Changes in the Planned Analysis

The analysis of this study is described in the study protocol TM002 (for Step 2: dated: 13 March 2018 Protocol Amendment Version 1.4 for Hungary and 09 February 2018 Protocol Amendment Version 1.5 for Czech Republic; for OLE1: dated: 26 September 2018 Protocol Amendment Version 1.5 for Hugnary and 09 September 2018 Protocol Amendment Version 1.6 for Czech Republic; for OLE2: dated: 31 January 2019 Protocol Amendment Version 1.6 for Hungary and 30. January 2019 Protocol Amendment Version 1.7 for Czech Republic). Nevertheless, minor changes to the conduct of the analysis have to be performed and are described below in detail.

The wording of the primary endpoint was changed from “Percent change from baseline to end of treatment in mean body weight” to “Percent change from baseline to end of treatment in body weight” to address that no replicated measurements were performed during the body weight assessment at a visit. That means that the relative change of body weight as assessed by single measurements performed at the screening visit and the end of treatment is calculated. The same applies to the secondary endpoint “Change from baseline to end of treatment in body weight (kg)”. This does not change the intended analysis but rather more accurately reflects the envisaged analysis as described in the protocol.

In addition, the following changes were made to the final SAP (version 1.1) after unblinded interim analysis:

The analysis was updated to display separate results for the defind subgroups and to allow for the display of results in total and based on the treatment each subject received during Step 2, as differences in the outcome are expected based on the different lengths of treatment.

Minor cosmetic and wording changes were added for additional clarification. The study design and visit schedule were updated to reflect protocol changes.

9. APPENDIX 1

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The selection, naming and numeration of the tables is not mandatory but might be adapted in accordance with the described analyses in this SAP.

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The selection, naming and numeration of the listingsis not mandatory but might be adapted in accordance with the described analyses in this SAP.

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The selection, naming and numeration of the figures are not mandatory but might be adapted in accordance with the described analyses in this SAP.

Signatures

I confirm that this Statistical Analysis Plan (SAP) accurately describes the planned statistical analyses to the best of my knowledge and was finalized before breaking the blind.

Author: Andreas Beust, PhD.
Biostatistician
GCP-Service Int. Ldt & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

10AUG2019 _____
Date Signature

Review: Dennis Neuschwander, M.Sc.
Biostatistician
GCP-Service Int. Ldt & Co. KG
Anne-Conway-Straße 2
28359 Bremen, Germany

10 AUG 2019 _____
Date Signature

Approved: Roman Dvorak MD, PhD
Chief Medical Officer
Saniona, A/S
Baltorpvej, 154
DK 2750 Ballerup
Denmark

8 AUG 2019 _____
Date Signature