GLWL-PWS Statistical Analysis Plan

A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome (Version 2 Final)

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GLWL-PWS

A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome

Version 2 Final

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ABBREVIATIONS/DEFINITIONS

Abbreviation	Definition
AG	acylated-ghrelin (AG)
AE	adverse event
AUC_{0-12}	Area under the concentration versus time curve from time zero to 12 hours
BMI	body mass index
CGIC	Caregiver Global Impression of Change
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	electronic case report form
GOAT	ghrelin-O-acyltransferase
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
IRT	Interactive response technology
MedDRA™	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model repeated measures
PK	pharmacokinetic
PWS	Prader-Willi Syndrome
QT	time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc_F	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	Statistical analysis plan
SOC	system organ class
TEAE	treatment emergent adverse event
UAG	unacylated-ghrelin
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION AND OBJECTIVES

1.1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the analysis variables and statistical procedures that will be used to analyze and report the results from a Phase 2 study evaluating the safety and efficacy of GLWL-01, an inhibitor of the ghrelin-O-acyltransferase (GOAT) enzyme that converts UAG into AG, in patients with Prader-Willi Syndrome (PWS). This SAP is based on the amended protocol, Protocol GLWL-PWS(d), which was approved on 27 June 2018.

Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require an amendment to the approved SAP. Similarly, changes to the planned analysis variables or statistical methods described in the approved SAP may also require an amendment to the SAP.

The formats for the tables, listings, and figures described in this SAP are provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the clinical study report (CSR).

Please see the study protocol for details about the study design, procedures, and schedule of assessments and see the electronic case report form (eCRF) for details about variables collected and their possible values.

1.2. Study Objectives

Table 1 shows the objectives and endpoints of the study.

Table 1. Objectives and Endpoints

Objectives	Endpoints
Primary • Evaluate the efficacy of GLWL-01 compared with placebo in reducing hyperphagia-related behaviors after 28 days of treatment in patients with PWS as measured using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT)	• Post-treatment HQ-CT total score
Secondary • Evaluate the safety and tolerability of GLWL-01 after 28 days of treatment in patients with PWS	• Treatment-emergent adverse events

Objectives	Endpoints
• Evaluate the efficacy of GLWL-01 compared with placebo in reducing hyperphagia-related behaviors after 28 days of treatment in patients with PWS as measured using the Caregiver Global Impression of Change (CGIC)	• CGIC score
• Evaluate the pharmacokinetics after single and multiple oral dosing of GLWL-01 in patients with PWS	• GLWL-01 – Area under the concentration versus time curve from time 0 to 12 hours (AUC0-12) – Maximum observed drug concentration (Cmax)
Exploratory	
• Evaluate the effect of GLWL-01 in the following measures in patients with PWS – Acylated-ghrelin (AG) – Unacylated-ghrelin (UAG) – AG/UAG ratio – Body weight – Percentage fat mass – Body mass index – Waist circumference – Low-density lipoproteins – Total cholesterol – Blood glucose	• Posttreatment: – AG – UAG – AG/UAG – Body weight – Percentage fat mass – Body mass index – Waist circumference – Low-density lipoproteins – Total cholesterol – Blood glucose

1.3. Determination of Sample Size

Approximately 34 patients were planned to be randomized to 1 of 2 treatment sequences (GLWL-01/placebo or placebo/GLWL-01) in a 1:1 ratio. Thirty-four patients would provide approximately 80% power to detect an effect size of 0.75 for the HQ-CT total score using a 2-sided exact paired t-test with an α=0.05, assuming 10% drop out.

2. GENERAL STATISTICAL METHODOLOGY AND CONVENTIONS

Chorus has designated EMB Statistical Solutions to generate the statistical analyses detailed in this SAP. All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data

manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

Before implementation of parametric methods of analysis, the distribution of analysis variables will be examined to determine if model assumptions are satisfied. Transformations or nonparametric methods of analysis may be used if warranted. However, in some cases, nonparametric analysis may be the initially proposed method due to the expected distribution of response. Whenever alternative methods of analysis are required, the description of the new method along with the rationale for its use will be documented in the CSR.

The eCRF data for all patients will be provided in Standard Data Tabulation Model (SDTM) datasets. Any additional data listings supplied as part of the CSR will be sorted by investigative site and patient identification number, and patients will be identified in the listings by the investigator number concatenated with the patient number.

2.1. Randomization Schedule and Unblinding Plan

This is a double-blind, 2-period, crossover study in which the patients, caregivers, investigators, and study site personnel will be blinded to treatment allocation. ClinPhone will be responsible for building the interactive response technology (IRT) system that randomly assigns treatment sequences (either Placebo/GLWL or GLWL/Placebo) to patients.

To preserve the blinding of the study, only a minimum number of Chorus personnel will see the randomization table and treatment assignments before the study is complete. This limited group will have access to unblinded treatment information to ensure the safety of patients in the study and to manage clinical trial supplies for the investigative sites. Site personnel and patients will remain blinded until the study is complete.

Emergency unblinding of site personnel may be performed through the IRT system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IRT system.

Unblinding will occur after the last patient completes the study and all data management activities have been completed (i.e. data entered, coding completed, and all queries resolved).

2.2. Analysis Populations

The **Entered Population** is defined as all patients who signed informed consent. The **Evaluable Population** is defined as all randomized patients who received at least one dose of double-blind study drug.

The Entered Population will be used to summarize enrollment at the study sites, for the summary of patient disposition, and in all listings. Otherwise, tables and figures will summarize the Evaluable Population according to the treatment the patient actually received. Any discrepancies between the randomized treatment and the treatment actually received will be noted in the listings.

2.3. Definition of Study Time Points

For the summarization of demographic and background characteristics, the value of an endpoint will be the last measurement taken prior to the first dose of double-blind study drug during Treatment Period 1 on Study Day 14.

Baseline values will be determined separately for each treatment phase. The baseline values for each double-blind treatment phase will include the last measurements taken prior to or on the date of the first dose of the double-blind study drug, on Study Day 14 and Study Day 84, unless the time of the assessment/event was after the time the dose was administered. Treatment phase day will be defined separately for each treatment phase as

Treatment phase day = Visit Date – Date of 1st dose of double-blind study drug.

Therefore, Study Day 14 and Study Day 84 will be considered Treatment Phase Day 0 (i.e. Baseline) for Treatment Phase 1 and Treatment Phase 2, respectively. Similarly, Study Day 42 and Study Day 112 will be considered Treatment Phase Day 28 for Treatment Phase 1 and Treatment Phase 2, respectively.

2.3.1. Reporting Periods for Concomitant Medications and Safety Endpoints

For adverse events and concomitant medications, and for unscheduled safety assessments (e.g. laboratory measurements), the reporting period for each treatment phase will include all data recorded after the first dose of double-blind study drug up to 14 days after the last dose of double-blind study drug.

2.4. Handling of Dropouts and Missing Data

For the analyses of endpoints that are collected longitudinally, a last observation analysis may be performed by carrying forward the last post-baseline assessment within a treatment phase. In addition, for many of the endpoints, mixed effect model repeated measures (MMRM) analyses will be performed to mitigate the impact of missing data, assumed to be missing at random.

If only a missing or partial date for AEs or concomitant medications is available and a complete date is required for calculations, the following algorithms will be applied:

- For the start date:
  - If year, month, and day are missing then use the minimum of the patient's first visit date or the consent date.
  - If either only month or month and day are missing then use January 1.
  - If only day is missing, impute the first day of the month.
- For the end date:
  - If year, month, and day are missing then use the patient's last visit date.
  - If either only month or month and day are missing then use December 31.
  - If only day is missing then use the last day of the month.
  - Do not expand the record past the patient's last visit.

The original missing or partial date, the imputed complete date, and the indicator variable that indicates which dates were imputed will be retained in the database.

For vital signs and electrocardiograms, for which the time of assessment is to be captured, assessments made on Study Day 14 or Study Day 84 will be assumed to have occurred prior to dosing (i.e. as planned) if the time of the assessment is missing. For adverse events, for which the time of onset is to be captured, adverse events that start on Study Day 14 or Study Day 84 will be assumed to have occurred after dosing if the time of the assessment is missing.

2.5. Adjustment for Multiple Centers

The randomization is not stratified by investigative site, and the variable "site" will not be included in the statistical models by default.

2.6. Interim Analysis and Adjustment for Multiplicity

There are no planned interim analyses for this study, and there is only a single primary efficacy endpoint. Because this is a Phase 2 study, no adjustments for multiplicity will be made for statistical tests of secondary or exploratory endpoints.

2.7. Coding of Concomitant Medications and Adverse Events

Adverse events (AEs) and conditions/procedures from the patients' medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). The versions of these dictionaries used for reporting will be provided in the CSR.

2.8. Reporting Conventions

This section details the general conventions to be used for the statistical analyses. Departures from these general conventions will be provided in the specific detailed sections of this analysis plan. The following conventions will be applied to all data presentations and analyses:

- Data will be summarized by treatment sequence (i.e. Placebo/GLWL, GLWL/Placebo, and Overall) and/or treatment (i.e. Placebo and GLWL) as appropriate :
- Continuous variables will generally be summarized by the number of patients, mean, standard deviation, median, minimum, and maximum. Exceptions to these conventions will be specifically noted. Categorical variables will be summarized by the number and percent of patients within each category.
- All mean and median values will be formatted to one more decimal place than the measured value.
- Standard deviation values will be formatted to two more decimal places than the measured value.
- Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- The number and percent of responses will be presented in the form XX (XX), where the percentage is in parentheses. Percentages will be rounded to the nearest percent. In the case

of a frequency of zero, the frequency and percentage will be presented as 0 rather than 0 (0%).

- All summary tables will include the analysis population sample size (i.e. number of patients) in each treatment group or sequence.
- Date variables will be formatted as ddMMMYYYY for presentation.

2.9. Changes to the Planned Analyses

Note that what is now called the **Evaluable Population** was called the **Randomized Population** in the protocol.

Blood glucose was added to the list of exploratory endpoints.

The determination of a treatment-emergent adverse event has been changed from that in the protocol, because the way adverse events are actually being captured is not as was anticipated. Specifically, an ongoing adverse event that worsens during the study will be captured as a new adverse event, so that adverse events that start during one period of the trial and get worse during a different period of the trial (which defines treatment-emergent) will have separate records that will be summarized separately.

The statistical analyses will be performed as 1-sided tests rather than 2-sided tests as originally planned, because enrollment was stopped prior to obtaining the intended 34 patients. With the anticipated 19 patients, there is at least 70% power for the primary treatment comparison, which is still considered acceptable for a proof of concept trial.

3. PATIENT ACCOUNTING AND DISPOSITION

3.1. Patient Accounting

For each study site, the number of patients entered and randomized (overall and by treatment sequence) will be presented. The date of the first patient visit and the last patient visit for each study site will also be provided. These dates and patient totals will also be summarized for the whole study and by country.

A list of protocol deviations that could potentially impact the analysis of the study will be determined during the conduct of the study by study team members who are blinded to assigned study treatment. The number and percentage of patients with each deviation will be tabulated overall and by treatment using the Evaluable Population.

3.2. Patient Disposition

The disposition of patients in the Evaluable Population will be presented separately. The summaries will include the number of patients randomized and randomized but not treated, as well as the number of patients treated in each treatment phase. The number of patients completing the study will be presented. For patients who do not complete the study, the reasons for study discontinuation as well as the study stage of discontinuation (i.e. Placebo Lead-in Phase 1, Treatment Phase 1, Washout, Placebo Lead-in Phase 2, Treatment Phase 2, and Follow-up) will be tabulated.

4. BASELINE CHARACTERISTICS

Demographic data, baseline body measurements, and medical history will be summarized using descriptive statistics. Patients who are missing measurements of the baseline variable being analyzed will not be included in the summary for that variable.

4.1. Demographics

Year of birth, gender, race, and ethnicity are collected during screening. As only the year of birth was collected, the patient's birthday will be approximated assuming the date as 1 July. Age at study entry will be based on the age of the patient on the date the informed consent is signed. Age at study entry will be analyzed as a continuous variable. Sex will be analyzed as a categorical variable. Patient race will be captured using multiple racial categories (i.e. American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, and Unwilling to provide). Patients selecting more than one race category will tabulated using the category Multiple. The response for ethnicity could be Hispanic or Latino, Non-Hispanic or Non-Latino, or Unwilling to provide. Ethnicity will be analyzed as a categorical variable.

4.2. Baseline Anthropometrics

The body measurements height, weight, body mass index (BMI), waist circumference, and percent fat mass will be recorded at baseline. Each will be reported as a continuous variable.

4.3. Medical History

The number and percent of patients reporting relevant medical history will be presented at the system organ class (SOC) and preferred term (PT) levels.

5. CONCOMITANT MEDICATIONS

Concomitant medications will be defined as medications taken during either treatment phase reporting period. This includes medications for which the start date is during a treatment phase reporting period, or for which the start date is before the date of the first dose of double-blind study drug but the end date is either during the treatment phase reporting period, after the end of the treatment phase reporting period, or for which the medication is on-going. Those medications where the stop date is documented as prior to the date of the first dose of double-blind study drug during the first treatment phase will be classified as prior medications.

6. EFFICACY ANALYSES

Efficacy analyses for this study will be based on the findings from two instruments. First, the HQ-CT is a validated tool developed specifically for PWS to capture observations of problematic behaviors related to food. It consists of 9 items, with a 2-week recall period. The scale provides a composite value from 9 questions, each rated on a scale of 0 to 4 units (total range of score of 0 to 36; Fehnel et al. 2015).

Second, the CGIC is a single-item question rated on a 0 to 7 scale directed at the caregiver asking for an assessment of the overall improvement of patients with PWS.

Both of these assessments will be collected longitudinally during the study.

All efficacy analyses will be performed using the Evaluable Population. The method of analysis or statistical technique employed to address missing data will be described separately for each variable. Presentations of efficacy will include the number of patients with data at each time point plus related statistics derived from the analysis.

All statistical tests will be 1-sided.

6.1. Primary Efficacy Analysis

The primary efficacy analysis will examine the contrast between GLWL-01 and placebo for the post-treatment HQ-CT total score at the end of the double-blind treatment phase.

The primary analysis will be conducted using a restricted maximum likelihood-based, mixed-effect model repeated measures analysis. The model for the primary analysis will include the fixed, categorical effects of sequence, period, and treatment, as well as the continuous, fixed covariate of the baseline Treatment Phase 1 HQ-CT score minus the baseline Treatment Phase 2 HQ-CT score (diff) and the interaction of period-by-diff (Mehrotra, 2014).

An unstructured covariance matrix will be used to model the within-patient errors. Satterthwaite's approximation will be used to estimate the denominator degrees of freedom. The significance of differences in least-square means will be based on Type III tests using the observed population margins. The analyses will be performed using the SAS procedure PROC MIXED.

The tabular output for these MMRM analyses will present the least squares means, standard errors, and 95% confidence intervals for each marginal main effect. Pairwise contrasts of the least squares means between GLWL-01 and Placebo will also be provided at each time point using LSMESTIMATE statements.

Descriptive statistics for the HQ-CT score and the within-treatment phase changes from baseline will be provided by treatment and time point.

6.1.1. Sensitivity Analyses for the Primary Efficacy Variable

Sensitivity analyses of the primary endpoint may be performed if the primary efficacy analysis demonstrates a difference between GLWL-01 and placebo. These contingent analyses will be detailed in an addendum to this SAP.

6.2. Secondary Efficacy Analyses

6.2.1. Additional analyses from the HQ-CT

The last observation of the HQ-CT in the treatment phase will be separately analyzed using the same methods used for the primary efficacy endpoint. Similarly, the sixth and ninth items of the HQ-CT comprise a measure of the severity of hyperphagia, which will be analyzed using the same methods.

6.2.2. Analyses of the Caregiver Global Impression of Change

The CGIC will be analyzed using similar methods used for the primary efficacy endpoint. The analysis of the CGIC will also be conducted using MMRM. The model for the analysis will include the fixed, categorical effects of sequence, period, and treatment.

7. SAFETY ANALYSES

All summaries of safety, including the extent of exposure to study medication, will be performed using the Evaluable Population. No statistical analyses are planned on safety endpoints.

7.1. Study Medication Exposure and Treatment Compliance

7.1.1. Extent of Exposure

Time on study will be derived for each patient as:

Time on study = Date of last dose of study drug – Date of 1st dose from lead-in phase 1 + 1.

The extent of exposure to double-blind study drug will be derived for each treatment phase as:

Extent of exposure = Date of last dose of double-blind study drug - Date of 1st dose of double-blind study drug + 1.

Time on study and extent of exposure will be descriptively summarized for each treatment sequence and treatment arm.

7.1.2. Treatment Compliance

Treatment compliance will be calculated for each treatment phase using the formula:

$$\text{Treatment Compliance} = 100 \left(\frac{\text{number of capsules received}}{\text{number of capsules intended}} \right).$$

The total number of tablets intended is equal to 6 times the number of days the patient spent in each treatment phase.

Treatment compliance will be descriptively summarized for each treatment arm. In addition, the number and percent of patients with compliance < 80% or > 120% will also be presented for each treatment arm.

7.2. Adverse Events

Adverse events (AEs) will be collected from the day the patient gives informed consent until the patient leaves the study. However, if the investigator learns of any serious adverse event (SAE) that occurs within 30 days after the final dose of study drug, that SAE will be collected even if the event occurred after the patient left the study.

TEAEs for each treatment phase reporting period are defined as reported AEs that first occurred or worsened after the first dose of double-blind study drug. Adverse events with an onset date on or after the first dose of double-blind study drug for Period 1 and before the first dose of double-blind study drug for Period 2 will be assigned to the study drug taken during Period 1; adverse

events with an onset date on or after the first dose of double-blind study drug for Period 2 will be assigned to the study drug taken during Period 2.

Treatment-emergent adverse events will be summarized by the number and percent of patients with the event.

Summaries of TEAEs will include the number of patients with at least one TEAE for each treatment arm. When reporting by system organ class (SOC) and preferred term (PT), the reports will present the SOC in alphabetical order; while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence in the GLWL-01 arm. A patient with multiple TEAEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for different PTs within that SOC. A patient with separate events of the same PT (different start/stop dates within a treatment phase) will be counted only once in the frequency tables for that PT.

An overview of all TEAEs will also be provided by treatment group using the types of AEs defined in the following subsections.

7.2.1. Treatment-Emergent Adverse Events

TEAEs will be summarized by SOC and PT for each treatment. In addition, a presentation of TEAE preferred terms in decreasing frequency in the GLWL-01 treatment arm will be provided.

7.2.2. Treatment-Related Treatment-Emergent Adverse Events

Every AE will be assessed by the investigator for its relationship to the randomly assigned study medication. The subset of TEAEs considered by the investigator as possibly or probably related to study treatment will be called treatment-related TEAEs. In addition, TEAEs that are missing the investigator assessment for relatedness will be considered treatment-related TEAEs. Treatment-related TEAEs will be summarized by SOC and PT for each treatment.

7.2.3. Serious Treatment-Emergent Adverse Events

Serious TEAEs and treatment-related SAEs will be summarized by SOC and PT. A separate listing of all SAEs will also be provided.

7.2.4. Treatment-Emergent Adverse Events Resulting in Death

If there are any TEAEs that result in death, a listing of all deaths will be provided.

7.2.5. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

For every AE in the eCRF, the investigator indicates whether the action taken with respect to the study drug was dose not changed, dose interrupted, or drug withdrawn.

The TEAEs leading to study drug discontinuation will be summarized for each treatment arm by SOC and PT and by decreasing frequency in the GLWL-01 arm. A separate listing of all TEAEs leading to study drug discontinuation will also be provided.

7.2.6. Treatment-Emergent Adverse Events by Maximal Severity

Every AE will be graded by the investigator as mild, moderate, or severe, so for each patient the greatest severity observed can be obtained by comparing the severity of all of a patient's TEAEs that share the same SOC or PT. A table of TEAEs by maximal severity will be prepared for each treatment arm by SOC and PT.

7.3. Clinical Laboratory Summaries

Blood samples for hematology and serum chemistry will be collected during screening; on Treatment Phase Day 0 (i.e. Baseline) and Treatment Phase Day 28 of each treatment phase; and at a patient's early termination visit, if applicable.

Each laboratory parameter will be classified as low, normal or high relative to the central laboratory's normal range. For each treatment group, shift tables will be generated from the pre-dose category to the category post-dose for each laboratory parameter. The shift tables will present the number (percent) of patients who started in a category (low, normal, high) at baseline and ended in a category at each post-baseline scheduled visit and for the last assessment (including unscheduled and early termination assessments) for each treatment.

Shift tables comparing baseline to the other time points in the study may be generated if warranted after data review.

7.4. Vital Signs

The vital signs pulse, temperature, and the mean (from triplicate measurements) sitting blood pressure will be assessed during screening; on Treatment Phase Day 0 (i.e. Baseline), Treatment Phase Day 7, and Treatment Phase Day 28 of each treatment phase; and at a patient's early termination visit, if applicable.

The number and percent of patients with any post-baseline pulse rate or mean blood pressure of potential clinical interest (including unscheduled and early termination assessments) will be summarized. Readings of potential clinical interest will be determined using the following criteria:

- Pulse rate either < 50 bpm, or > 100 bpm, or a change of ≥ 15 bpm;
- Systolic blood pressure either ≤ 90 mmHg, or ≥ 160 mmHg, or a change of ≥ 20 mmHg;
- Diastolic blood pressure either ≤ 50 mmHg, or ≥ 100 mmHg, or a change of ≥ 10 mmHg.

7.5. Electrocardiogram Summaries

Single 12-lead electrocardiograms (ECGs) will be assessed during screening; on Treatment Phase Day 0 (i.e. Baseline), Treatment Phase Day 7, and Treatment Phase Day 28 of each treatment phase; and at a patient's early termination visit, if applicable. Two-hour post-dose ECG assessments will also be made at Baseline of each treatment phase.

The number and percent of patients with any post-baseline Fridericia-corrected QT values of potential clinical interest (including unscheduled and early termination assessments) will be summarized. QTcF values of potential clinical interest will be determined using the following criteria:

- QTcF ≥ 480 msec, or ≥ 500 msec, or ≥ 550 msec
- Change from baseline in QTcF ≥ 30 msec, or ≥ 60 msec.

7.6. Columbia Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be listed by patient and visit.

Only patients that show suicidal ideation and/or behavior will be displayed (i.e. if a patient's answers are all 'no' for the CSSRS, that patient will not be listed). However, if a patient reported any suicidal ideation and/or behavior, all of their ideation and behavior will be displayed, even if not positive.

8. EXPLORATORY ANALYSES

Exploratory endpoints will be summarized separately as pharmacodynamic (i.e. AG, UAG, AG/UAG ratio), anthropometric (i.e. body weight, percentage fat mass, BMI, waist circumference), and exploratory blood chemistry (i.e. low-density lipoproteins, total cholesterol, and blood glucose) endpoints.

All exploratory endpoint analyses will be performed using the Evaluable Population, using the same methods used for the primary efficacy endpoint. Descriptive statistics for the value and change from baseline will be tabulated for each time point.

In addition, plots of the individual AG and UAG levels as well as their mean levels by treatment will be plotted over time.

9. PHARMACOKINETIC ANALYSES

Analyses of the pharmacokinetic (PK) parameters will be addressed in a separate PK-specific analysis plan.

To investigate the potential effect of GLWL-01 on QT interval prolongation, the changes from baseline in QTcF values versus the plasma GLWL-01 concentration will be plotted.

References

1. Fehnel S, Brown TM, Nelson L, Chen A, Roof E, Kim DD, Dykens EM. Development of the hyperphagia questionnaire for use in Prader-Willi syndrome clinical trials [poster]. In: ISPOR 20th Annual International Meeting; May 16-20, 2015; Philadelphia. Poster nr pp. A25–A25.
2. Mehrotra D. A recommended analysis for 2 × 2 crossover trials with baseline measurements. Pharm Stat. 2014; 13(6):376-387.