GLWL-PWS Protocol

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

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

GLWL-01

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Protocol Electronically Signed and Approved by GLWL Research Inc. on date provided below.

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1. Synopsis

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

Rationale:
The aim of this study is to evaluate efficacy, safety, and pharmacokinetics of GLWL-01 in the treatment of patients with Prader-Willi Syndrome (PWS).

Objectives/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)	• Posttreatment HQ-CT total score
Secondary • Evaluate the safety and tolerability of GLWL-01 after 28 days of treatment in patients with PWS • 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) • Evaluate the pharmacokinetics after single and multiple oral dosing of GLWL-01 in patients with PWS	• Treatment-emergent adverse events • CGIC score • GLWL-01 o Area under the concentration versus time curve from time zero to 12 hours (AUC_{0-12}) o Maximum observed drug concentration (C_{max})
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	Posttreatment: • AG • UAG • AG/UAG • Body weight • Percentage fat mass • Body mass index • Waist circumference • Low-density lipoproteins • Total cholesterol

Summary of Study Design:

Study GLWL-PWS is a multicenter, double-blind, randomized, placebo-controlled, crossover study of GLWL-01 in patients with PWS.

The study consists of 5 periods, including 2 active treatment periods, as depicted below:

Period	Phase	Duration
Screening	NA	28 days
Treatment Period 1	Single-blind placebo lead-in[a]	14 days
	Double-blind treatment phase[b]	28 days
Washout	NA	28 days
Treatment Period 2	Single-blind placebo lead-in[a]	14 days
	Double-blind treatment phase[b]	28 days
Follow-up	NA	14 days

Abbreviation: NA = not applicable

[a] Only patient/caregiver will be blinded.

[b] Both investigator and patient/caregiver will be blinded.

Patients and caregivers will be required to visit the site on 8 occasions at Visits 1, 3, 4, 5, 8, 9, 10, and 11. Patients and caregivers will be required to participate in phone calls with the site at Visits 2, 6, and 7.

Treatment Arms and Duration:

Patients will be randomized to 1 of 2 treatment sequences; GLWL-01/placebo or placebo/GLWL-01 (Treatment Period 1 double-blind treatment phase/Treatment Period 2 double-blind treatment phase). During single-blind placebo lead-in phases, patients will receive 3 capsules of 150-mg placebo twice daily (BID) for 14 days. During double-blind treatment phases, patients will receive 3 capsules of 150-mg GLWL-01 (450 mg total dose) BID or identical placebo BID for 28 days.

Number of Patients:

Approximately 34 patients with PWS will be randomized.

Statistical Analysis:

Efficacy: Efficacy analyses will be conducted on the randomized analysis set. The primary analysis will be conducted using a restricted maximum likelihood-based, mixed-effect model repeated measures analysis. The analysis will be the contrast between GLWL-01 and placebo at the end of the double-blind treatment phase on the primary endpoint of the posttreatment HQ-CT score.

The secondary analysis will be conducted similar to the primary analysis. The secondary efficacy endpoint is the CGIC.

Safety: Safety analyses will be conducted on the safety analysis set. Safety data will be summarized by treatment group. Safety parameters that will be assessed include adverse events,

clinical laboratory parameters, C-SSRS, vital signs, electrocardiogram parameters, and weight. The parameters will be listed and summarized using standard descriptive statistics.

Pharmacokinetics/Pharmacodynamics: Plasma GLWL-01 pharmacokinetic (PK) parameters will be calculated using noncompartmental methods after single and multiple dose administration. Additional PK parameters may be calculated if deemed appropriate. Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Mean and individual GLWL-01 plasma concentration-time curves will be represented graphically.

Pharmacodynamics of GLWL-01 will be based on plasma AG and potentially UAG measures. Raw and change from baseline values will be reported and summarized for AG and potentially UAG.

The PK/PD relationship of GLWL-01 with PD, efficacy, and/or safety measures may be explored.

2. Schedule of Activities

Table GLWL-PWS.1. Schedule of Activities

Period	Screening[a]	Treatment Period 1				Washout (28 days)	Treatment Period 2				Follow-up	ET[c]
Phase		Single-blind Placebo Lead-in Phase (14 days)	Double-blind Treatment Phase (28 days)[b]				Single-blind Placebo Lead-in (14 days)	Double-blind Treatment Phase (28 days)[b]				
Visit No/ Type Procedure	V1	V2[e] Phone	V3[d]	V4	V5	V6[e] Phone	V7[e] Phone	V8	V9	V10	V11	
Day	-28 to -3	0 (±3)	14 (±2)	21 (±2)	42 (±2)	56 (±2)	70 (±2)	84 (±2)	91 (±2)	112 (±2)	126 (±3)	
Informed consent	X											
Demographics	X											
Physical examination[f]	X		X	X	X			X	X	X	X	X
Height[g]	X											
Initial history/ preexisting conditions	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg, HCAB, HIV	X											
Urinalysis[h]	X											
Substance abuse screen[i]	X											
Inclusion/exclusion review	X		X[e]									
Study drug dispensing		X	X				X	X				
Study drug administration at site			X		X							
Study drug accountability			X		X			X		X		X
Efficacy and Outcome Measures												
HQ-CT		X	X	X	X	X	X	X	X	X	X	X
CGIC					X					X		X
Body weight[g]	X		X		X			X		X	X	X
Percentage fat mass (calipers)			X		X			X		X		X
BMI	X		X		X			X		X	X	X
Waist circumference			X		X			X		X		X
Vital signs[j]	X		X	X	X			X	X	X	X	X

Period	**Screening[a]**	**Treatment Period 1**			**Washout (28 days)**	**Treatment Period 2**				**Follow-up**	**ET[c]**
Phase		**Single-blind Placebo Lead-in Phase (14 days)**	**Double-blind Treatment Phase (28 days)[b]**			**Single-blind Placebo Lead-in (14 days)**	**Double-blind Treatment Phase (28 days)[b]**				
Visit No/ Type Procedure	**V1**	**V2[e] Phone**	**V3[d]**	**V4**	**V5**	**V6[e] Phone**	**V7[e] Phone**	**V8**	**V9**	**V10**	**V11**	
Day	**-28 to -3**	**0 (±3)**	**14 (±2)**	**21 (±2)**	**42 (±2)**	**56 (±2)**	**70 (±2)**	**84 (±2)**	**91 (±2)**	**112 (±2)**	**126 (±3)**	
12-lead ECG[k]	X		X	X	X			X	X	X	X	X
12-lead ECG 2 hours post-dose[k]			X					X				
Serum pregnancy test[l]	X									X		X
Urine pregnancy test[l]			X					X				
Clinical chemistry and hematology[h]	X		X	X	X			X	X	X		X
Troponin			X	X	X			X	X	X		
Lipid panel			X		X			X		X		X
AG and UAG[m]			X		X			X		X		X
Plasma sample collection for PK analysis[n]			X		X							X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AG = acylated-ghrelin; BMI = body mass index; CGIC = Caregiver Global Impression of Change; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; EDC = electronic data capture; ET = early termination; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; HBsAg = hepatitis B surface antigen; HCAB = hepatitis C antibody; HIV = human immunodeficiency virus; PK = pharmacokinetic; UAG = unacylated-ghrelin; V = Visit.

[a] Screening visit must occur between -28 days to -3 days of V2.

[b] Double-blind Treatment Phase must not exceed 28 days and patients must not take the study drug beyond 28 days. For example, if the V3 occurs on Day 14, then corresponding V5 would occur on Day 42. Similarly, if V3 occurs on Day 15 (Day 14 +1), then corresponding V5 would occur on Day 43 (Day 42 +1).

[c] The primary reason for early termination of the patient will be entered in EDC and recorded in the patient's source documents. The patient will attend an early termination visit as soon as possible after participation ceases.

[d] Confirm that the patient has met all inclusion/exclusion criteria. Patients will only be dosed after the investigator has completed the appropriate protocol assessments and determined that it is acceptable to dose the patient.

[e] Patients/caregivers will receive phone calls from the site; no visit required. Both patient and caregiver should be on the phone in order for the site to conduct AE assessments and the C-SSRS.

[f] A full physical examination with neurological assessments should be performed at Visit 1. Symptom-driven physical examinations should be performed at V3, V4, V5, and V8, V9, V10,V11, and at ET.

[g] Height will only be measured at Visit 1. Patients should be instructed to wear lightweight clothing and remove shoes during weighing.

[h] Refer to Appendix 2 for details on serum chemistry, hematology, and urinalysis clinical laboratory tests.

[i] Substance abuse screen test to be performed at Visit 1 and additionally at any visit per investigator's discretion.

[j] Vital sign assessments will include triplicate sitting blood pressure, and single pulse and body temperature. Additional vital sign assessments may be performed as clinically indicated. For visits in which both vital signs and blood samples are collected, vital signs should be obtained prior to blood collection. Any clinically significant result of vital sign assessment will be documented in the source documentation and EDC as an AE.

[k] Single 12-lead ECGs to be collected according to the schedule and may be collected at any time if deemed clinically necessary. Patients must be supine for at least 5 minutes prior to ECG collection. When ECG collections are scheduled at the same time point as any other tests, ECGs, followed by vital signs, should be recorded prior to any clinical laboratory or PK blood sampling.

[l] For all female patients, the investigator will document potential childbearing status. For women who are postmenopausal, a confirmatory test of serum follicule-stimulating hormone and estradiol levels will be done at Visit 1. For all women of childbearing potential, a pregnancy serum test will be done at Visit 1, which must be negative to enroll. Subsequently, urine pregnancy tests will be done for all women of childbearing potential as indicated in the schedule; the results must be confirmed negative. In case of a positive urine pregnancy test, the serum pregnancy test must be performed to confirm the pregnancy results.

[m] The blood samples for AG and UAG should be collected in the fasted state.

[n] On Day 14 and Day 42, a total of 7 PK samples each day will be taken at the following times: pre-dose, and 0.5, 1, 2, 4, 6, and between 8 and 12 hours postdose. Times of sampling are intended as a guide and can be modified to accommodate clinical procedures. Actual time of sample must be collected, as well as date and time of dosing on the day of PK sample collection. For patients who discontinue early, a sample should be obtained at the ET visit.

3. Introduction

3.1. Study Rationale

The aim of this study is to evaluate efficacy, safety, and pharmacokinetics (PK) of GLWL-01 in patients with Prader-Willi syndrome (PWS). The trial will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements. The patient population will be comprised of adolescent (aged 16 to 18 years) and adult (aged >18 to 65 years) male and female patients with PWS.

Prader-Willi syndrome is a complex, rare genetic disorder that affects appetite, growth, metabolism, cognitive function, and behavior. It is caused by a spontaneous genetic error that leads to a lack of expression of paternal genes on chromosome 15. In a majority of the cases (about 75%), there is a deletion of paternal genes (15q11-q13). In most of the remaining cases, the 2 copies of chromosome 15 originate from the mother (maternal uniparental disomy; PWSA USA Resource Page; The University of Chicago Resource Page). Paternally expressed genes are crucial for hypothalamic development and their lack of expression causes hypothalamic dysfunction; this ultimately results in problems with hunger, growth, sexual development, body temperature, mood, and sleep (Goldstone 2004).

Patients with PWS exhibit gross hyperphagia behaviors that are triggered by a constant feeling of hunger. As a result, these patients have difficulty keeping their weight under control and suffer from complications of obesity (such as type 2 diabetes, high blood pressure (BP), high levels of cholesterol, heart disease, and sleep apnea) and from inadequate hormone production (sterility, osteoporosis).

To our knowledge, there are no approved therapies that would obviate the need for a strict externally controlled diet and limited access to food for these patients (PWSA USA Resource Page). Treatments use a multifaceted approach including diet management, hormones (human growth hormone, sex hormones), sleep apnea treatment, mental healthcare, and behavioral therapies.

Ghrelin is secreted primarily by the stomach and circulates as both acylated (AG) and unacylated-ghrelin (UAG). Acylated-ghrelin stimulates appetite, and AG concentrations are elevated in PWS (Kuppens et al. 2015), suggesting that AG may contribute to hyperphagia and obesity in these patients.

GLWL-01 is an inhibitor of the ghrelin-O-acyltransferase (GOAT) enzyme that converts UAG into AG. In a previous clinical study (GLWL-SMP; Clinicaltrials.gov identifier NCT02377362) in obese patients with type 2 diabetes, GLWL-01 doses ≥150 mg twice a day (BID) given over 28 days have shown a numerical decrease in plasma AG concentrations. In the same study, doses of GLWL-01 up to 600 mg BID for 28 days were generally well tolerated. Therefore, it is of interest to assess the efficacy of GLWL-01 compared with placebo in reducing hyperphagia-related behaviors through 28 days in patients with PWS.

3.2. Background

Acylated ghrelin plays a pivotal role in metabolism and energy balance and is the only known orexigenic peptide hormone in human and mammals (Chen et al. 2009; Callaghan and Furness 2014). Acylated-ghrelin regulates short-term energy homeostasis by increasing hunger and food intake and long-term energy balance by promoting weight gain and adiposity (Tschop et al. 2000; Wren et al. 2001a; Wren et al. 2001b; Cummings et al. 2004). All these actions are believed to be mediated in part through its binding to growth hormone secretagogue receptor (GHSR-1a). Unacylated ghrelin is the only known physiological substrate of the GOAT enzyme. It has been shown that UAG counters the hyperglycemic effect of AG in healthy human volunteers when it is co-administered with AG. Infusion of UAG lowers average blood glucose levels, enhances insulin secretion, and reduces free fatty acids in plasma in healthy human volunteers (Benso et al. 2012). The mechanisms responsible for these actions are unclear as UAG binds to the GHSR-1a receptor with 1000-fold lower affinity than AG.

Prader-Willi syndrome is a neurogenetic disorder that is characterized by severe morbid obesity related to hyperphagia (Kuppens et al. 2015). Due to AG's well-known association with hunger, food intake, and weight gain, it is suggested that hyperphagia in PWS might be subsequent to increased ghrelin levels (Purtell et al. 2011; Kweh et al. 2015). Since UAG acts as a functional inhibitor of AG and that it suppresses ghrelin levels in humans, ratio of AG and UAG levels (AG/UAG ratio) could play a crucial role in maintaining the weight balance.

A clinical study conducted in 3 PWS expert centers in the Netherlands and France compared AG and UAG levels, and the AG/UAG ratio, in patients with PWS (n=138, 0.2 to 29.4 years), obese subjects (n=50; 4.3 to 16.9 years), and healthy control subjects (n=39, 0.8 to 28.6 years). Concentrations of AG were higher in PWS compared to healthy control subjects, while UAG was similar to that of control subjects. Both AG and UAG were significantly lower in the obese group than for PWS and control subjects. These differences in AG and UAG concentrations were reflected in elevated AG/UAG ratios in patients with PWS who exhibited weight gain and/or hyperphagia; while those without weight gain or hyperphagia had ratios comparable to those of age-matched control subjects. The authors proposed that the switch to excessive weight gain in PWS appears to coincide with an increase in the AG/UAG ratio, even preceding hyperphagia (Kuppens et al. 2015).

These AG and UAG data are overall consistent with a multiple ascending dose study of GLWL-01 in overweight and obese adult patients with type 2 diabetes (n=38), which showed a decrease in AG without weight loss, and low UAG concentrations. Since hyperphagia behaviors may be linked to elevated AG concentrations in patients with PWS, GLWL-01 may lower elevated AG concentrations and thus reduce hyperphagia behaviors.

GLWL-01 is a small molecule inhibitor of GOAT, which is superficially expressed primarily in the stomach and pancreas of humans and rats. GLWL-01 is the first GOAT inhibitor being clinically evaluated for the treatment of PWS. Inhibition of GOAT is expected to lower AG and raise UAG plasma levels.

GLWL-01 is a potent inhibitor of human GOAT with an IC_{50} of 192 nM in a primary enzyme assay and of 8.20 nM in a cell-based assay. In the nonclinical pharmacology studies, GLWL-01 demonstrated dose-dependent reduction in AG concentrations and increases in UAG concentrations (GLWL-01 2017).

Based on PK data in healthy subjects, both renal clearance and hepatic metabolism are involved in the clearance of GLWL-01 (GLWL-01 2017). In a multiple-dose study in obese patients with type 2 diabetes (GLWL-SMP), GLWL-01 exposure (based upon maximum observed drug concentration [C_{max}] and area under the concentration versus time curve (AUC) generally increased in a higher than dose-proportional manner with increasing doses of GLWL-01 (dose range: 50 to 600 mg BID and 300 to 450 mg once daily [QD]). Median time of maximum observed drug concentration values ranged from approximately 1 to 2 hours on Day 1, and on Day 28, ranged from approximately 1 to 4.5 hours, with an apparent trend of increasing with dose on Day 28. Mean values of half-life associated with the terminal rate constant in noncompartmental analysis were relatively short (approximately 3 to 6 hours).

3.3. Benefit/Risk Assessment

Based on GLWL-01 nonclinical and preliminary clinical data, there are no anticipated risks requiring monitoring beyond those included in this protocol. No clinically significant safety or tolerability concerns have been identified in patients or subjects to date for GLWL-01 up to the highest single dose given 600 mg in healthy subjects and multiple dose given 600 mg BID for up to 28 days in obese patients with type 2 diabetes.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of GLWL-01 can be found in the Investigator's Brochure (IB; GLWL-01 2017).

4. Objectives and Endpoints

Table GLWL-PWS.2 shows the objectives and endpoints of the study.

Table GLWL-PWS.2. Objectives and Endpoints

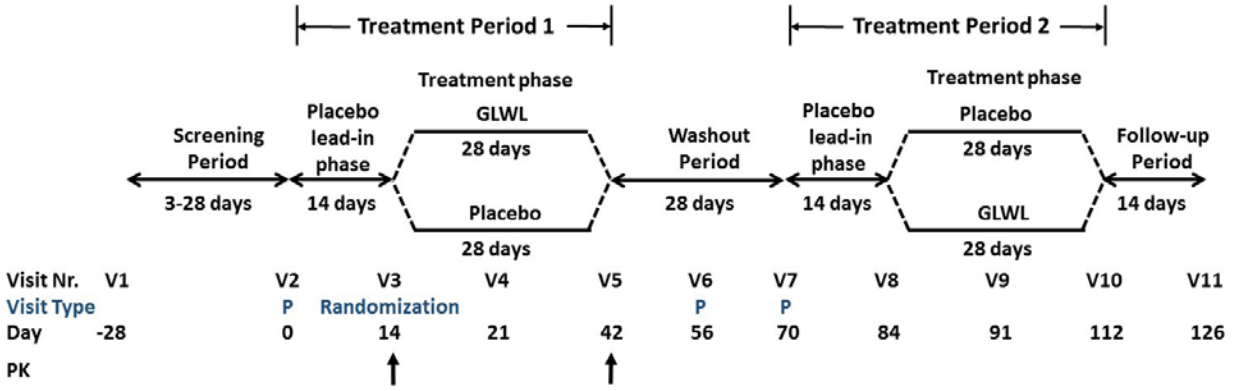
Objectives	Endpoints
Primary • Evaluate the efficacy of GLWL-01 compared with placebo in reducing hyperphagia-related behaviors after 28 days of treatment in patients with PWS as measured using the HQ-CT	• Posttreatment HQ-CT total score
Secondary • Evaluate the safety and tolerability of GLWL-01 after 28 days of treatment in patients with PWS • 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 CGIC • Evaluate the pharmacokinetics after single and multiple oral dosing of GLWL-01 in patients with PWS	• Treatment-emergent adverse events • CGIC score • GLWL-01 ○ AUC_{0-12} ○ C_{max}
Exploratory Evaluate the effect of GLWL-01 in the following measures in patients with PWS: • AG • UAG • AG/UAG ratio • Body weight • Percentage fat mass • Body mass index • Waist circumference • Low-density lipoproteins • Total cholesterol	Posttreatment: • AG • UAG • AG/UAG ratio • Body weight • Percentage fat mass • Body mass index • Waist circumference • Low-density lipoproteins Total cholesterol

Abbreviations: AG = acylated-ghrelin; AUC_{0-12} = area under the concentration versus time curve from time zero to 12 hours; CGIC = Caregiver Global Impression of Change; C_{max} = maximum observed drug concentration; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; PWS = Prader-Willi syndrome; UAG = unacylated-ghrelin.

5. Study Design

5.1. Overall Design

This is a multicenter, double-blind, randomized, placebo-controlled, crossover study to evaluate the efficacy of GLWL-01 in patients with PWS. The study consists of 5 periods, including 2 active treatment periods, as depicted below:



Abbreviations: P = phone visit; PK = pharmacokinetic sample

Note: Placebo lead-in phases will be single-blinded (patient/caregiver) and treatment phases will be double-blinded (investigator and patient/caregiver)

Figure GLWL-PWS.1. Illustration of study design for Clinical Protocol GLWL-PWS.

The Screening Period allows for evaluation of inclusion/exclusion criteria. Treatment Period 1 consists of 2 phases: a 14-day single-blind (patient/caregiver) placebo lead-in phase followed by a 28-day double-blind treatment phase. At the conclusion of the single-blind placebo lead-in phase, eligible patients will be randomly assigned (in 1:1 ratio) to 1 of 2 treatment sequences: GWLW-01/placebo or placebo/GLWL-01 (Treatment Period 1 double-blind treatment phase/Treatment Period 2 double-blind treatment phase). Following Treatment Period 1, there will be a 28-day Washout Period. Treatment Period 2 also consists of 2 phases: a 14-day single-blind (patient/caregiver) placebo lead-in followed by a 28-day double-blind treatment phase. Following Treatment Period 2, there will be a 14-day Follow-up Period (see Figure GLWL-PWS.1).

Patients and caregivers will be required to visit the site on 8 occasions at Visits 1, 3, 4, 5, 8, 9, 10, and 11; Patients and caregivers will be required to participate in phone calls with the site at Visits 2, 6, and 7.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Approximately 34 patients will be randomized 1:1 to 1 of 2 treatment sequences (GLWL-01/placebo or placebo/GLWL-01).

5.3. End of Study Definition

End of the study is the date of the last Follow-up Visit or End-of-Treatment/Discontinuation Visit shown in the Schedule of Activities (Section 2) for the last patient to complete or discontinue the study.

5.4. Scientific Rationale for Study Design

The use of a crossover design allows each patient to serve as his or her own control, thereby reducing variability. The single-blind placebo lead-in phase for Treatment Period 1 is included to minimize potential bias in completing the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) by the caregiver. The single-blind placebo lead-in phase for Treatment Period 2 is included to minimize potential bias in completing the HQ-CT by the caregiver and control for period effect. The washout period will allow for GLWL-01 to be eliminated from the body, based on the known GLWL-01 half-life, and to account for any potential behavioral changes from Treatment Period 1. The study is patient-/caregiver- and investigator-blind to minimize potential bias during the double-blind treatment phases.

5.5. Justification for Dose

Administration of single GLWL-01 doses of up to 600 mg QD in healthy subjects, and of multiple (up to 28 days) GLWL-01 doses of up to 600 mg BID in obese patients with type 2 diabetes was safe and generally well tolerated (GLWL-SMP study). Doses of GLWL-01 equal to or higher than 150 mg BID resulted in numerical decreases of plasma AG levels in obese patients with type 2 diabetes over 28 days, with the maximum decreases observed for the 450-mg BID dose group. Therefore, a 450-mg BID dosing regimen was chosen for this study as it has been demonstrated to be safe and to achieve target engagement.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

1. Male and female outpatients between 16 and 65 years of age inclusive, prior to signing informed consent.
2. Confirmed diagnosis of PWS based on genetic confirmation using DNA methylation test.
3. Body mass index (BMI) of 27 to 60 kg/m^2, inclusive, at Visit 1.
4. No evidence of weight excursion beyond 10% of baseline weight within 3 months prior to Visit 1 (self- or caregiver-reported).
5. Patients must provide assent and have a reliable caregiver (must have been caring for the patient for at least 6 months) who provides a separate written informed consent to participate. The caregiver is expected to be the primary caregiver throughout the study and must be in frequent contact with the patient (defined as at least 4 awake hours per day). The caregiver must be able to communicate with site personnel and in the investigator's opinion must have adequate literacy to complete the protocol-specified questionnaires. If a caregiver cannot continue, 1 caregiver replacement is allowed.
6. Male patients:

    a. agree to use a reliable method of birth control during the study and 3 months following the last dose of the study drug. Acceptable methods of birth control may include: 1) condom with spermicide; 2) diaphragm with spermicide; or 3) female condom with spermicide.

7. Female patients:

    a. Women of child-bearing potential may participate in the study if they test negative for pregnancy (based on a serum pregnancy test) prior to initiation of treatment. They must also agree to use either 1 highly effective method of contraception or a combination of 2 effective methods of contraception during the study.

        Highly effective method may include hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device or intrauterine system; vasectomy and tubal ligation.

        Effective methods may include barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge).

    Women may choose to use a double-barrier method of contraception. Barrier methods without concomitant use of a spermicide are not reliable or an acceptable

method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

- Women not of child-bearing potential may participate in the study and include those who have
    a. spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications that induced amenorrhea (e.g., oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy; or
    b. spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone (FSH) level greater than 40 mIU/mL; or
    c. women with a history of hysterectomy or bilateral oophorectomy must be at least 40 years of age and FSH >40 mIU/mL.

8. Are on a stable diet and exercise regimen for >2 months prior to Visit 1.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

9. Are Eli Lilly and Company, GLWL Research Inc. (sponsor hereafter), contract research organization employees, investigator or site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
10. Are currently enrolled in any other clinical trial involving a study drug or off-label use of a drug or device, or any other type of medical research judged not to be scientifically or medically compatible with this study.
11. Participated in a clinical trial within 30 days (defined as last dose of study drug), prior to the GLWL-PWS first dose.
12. Are currently living in a group home for more than 50% of the time.
13. Have a HQ-CT total score at Visit 3 <13.
14. Have clinical laboratory test results outside normal reference range, or any clinically significant laboratory abnormality, that in the judgment of the investigator, indicates a medical problem that would preclude study participation. Values for aspartate aminotransferase (AST)/alanine aminotransferase (ALT)/gamma-glutamyl transferase (GGT)/alkaline phosphatase (ALP) >3X upper limit of normal (ULN).
15. Have an estimated glomerular filtration rate <60 mL/minute/1.73 m^2. Have macroalbuminuria (defined as spot urine albumin to creatinine ratio of >300 µg/mg) or hematuria.
16. Are hypertensive (defined as sitting systolic BP ≥140 mmHg and diastolic BP ≥90 mmHg) on or off medications for the treatment of hypertension. Blood pressure may be re-tested up to 2 additional times, under well-rested conditions.

17. In addition to conditions described below, have a history or presence of any other medical illness including but not limited to any autoimmune disorder, cardiovascular, hepatic, respiratory, hematological, or uncontrolled neurological disease.

    a. Have a history of clinically overt uncontrolled or untreated endocrine illness such as growth hormone insufficiency, adrenal gland, or thyroid illness.
    b. Have evidence of other chronic liver disease, including but not limited to chronic alcoholic disease, cirrhosis of any cause, recent history (within 3 months of screening) of acute viral hepatitis or chronic autoimmune hepatitis. Patients with a history of biliary disease, including primary sclerosing cholangitis, must be excluded. Patients with a history of cholecystectomy longer than 6 months prior to screening could be enrolled.
    c. Have evidence of significant active or unstable/uncontrolled psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders. Note: Patients whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

18. Have an abnormality in the 12-lead electrocardiogram (ECG), including corrected QT interval with Frederica's correction (QTcF) >450 msec for men and >470 msec for women or an abnormality that, in the opinion of the investigator, increases the risks associated with participating in the study. If QTcF does not meet criteria, ECGs may be repeated once after 5 minutes of rest.
19. Have a family history of Long QT Syndrome.
20. Have evidence of human immunodeficiency virus (HIV) infection, hepatitis B, hepatitis C and/or positive results at screening for the respective antibodies for HIV, hepatitis B surface antigen, or hepatitis C antibodies.
21. Patients who, in the clinician's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or those who have answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the Columbia–Suicide Severity Rating Scale (C-SSRS), or answer "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C–SSRS; and the ideation or behavior occurred within a month of Visit 1.
22. Patients on weight loss medications within 30 days of dosing. Patients with a history of bariatric surgery should also be excluded.
23. Unable to refrain from or anticipates the use of

    a. Any drugs known to be significant inhibitors of cytochrome P450 (CYP)3A enzymes and/or P-glycoprotein (P-gp) including regular consumption of grapefruit or grapefruit juice for 14 days prior to the first dose of study medication and throughout the study. Appropriate sources will be consulted

by the principal investigator (PI) or designee to confirm lack of PK or pharmacodynamic (PD) interaction with study medication. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study.

b. Any drugs known to be significant inducers of CYP3A enzymes and/or P-gp, including St. John's Wort, for 28 days prior to the first dose of study medication and throughout the study. Appropriate sources will be consulted by the PI or designee to confirm lack of PK/PD interaction with study medication.
c. Any medications that prolong the QT/QTc interval, unless the patient has been on a stable dose of said medication for at least 3 months and has a QTc <450 msec at Visit 1 and Visit 3.

24. Currently taking simvastatin >10 mg per day, atorvastatin >20 mg per day, or lovastatin >20 mg per day. The doses of these statins in combination products should not exceed these defined dose levels. Patients with a history of statin-induced myopathy/rhabdomyolysis should also be excluded.
25. Current smokers, or any use of tobacco and nicotine products within 3 months of dosing.
26. Regular user of known drugs of abuse and/or shows positive findings on urinary drug screening.
27. An average weekly alcohol intake that exceeds 21 units per week (males ≤65 years of age) and 14 units per week (females and males >65 years of age), or is unwilling to stop alcohol consumption for the duration of the study (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
28. Venous access insufficient to allow for blood sampling as per the protocol.
29. Any major surgery within 60 days prior to the first dose or has planned elective surgeries to occur during the study.
30. Unsuitable for inclusion in the study in the opinion of the investigator.

6.3. Lifestyle Restrictions

Consumption of foods and beverages containing the following substances will be limited or prohibited as indicated:

- xanthine/caffeine: throughout the study, patients are required to maintain their regular intake of caffeinated beverages for the duration of the study
- Alcohol: an average weekly alcohol intake should not exceed 21 units per week (males ≤65 years of age) and 14 units per week (females and males >65 years of age).
- Grapefruit/Seville orange: 14 days before first dosing and throughout the study.

Following the morning dose on Day 14 and Day 42, and on Day 84 and Day 112, patients will remain ambulatory or seated upright for the first 4 hours, except when they are supine or semi-reclined for study procedures.

Patients will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from Visit 1 until completion of the study

participation. Patients should otherwise minimize changes in their activity levels during study participation.

6.4. Screen Failures

Patients who do not meet the criteria for participation in this study (screen failure) at Visit 1 may be rescreened. Individuals may be rescreened up to 1 time. The rescreen should be at the discretion of the PI after discussion with sponsor medical representative. If a rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatments

7.1. Treatments Administered

GLWL-01 drug product is supplied for clinical trial use as size 0 dark blue opaque capsules for oral administration. Capsules will contain 150 mg of GLWL-01. No additional excipients are used, with the exception of the capsule itself.

The GLWL-01 drug product placebo will consist of microcrystalline cellulose and magnesium stearate filled directly into size 0 dark blue opaque capsules, identical in appearance to GLWL-01 150-mg capsules.

Capsules must be taken whole.

In Treatment Period 1, all eligible patients will undergo a single-blind (patients/caregiver) placebo lead-in phase, wherein they will receive 3 capsules of placebo BID for 14 days. Following this, patients will be randomly assigned to either GLWL-01 450 mg BID/placebo or placebo/GLWL-01 450 mg BID treatment sequence. During Treatment Period 1, patients will receive 3 capsules of 150-mg GLWL-01 (450-mg total dose) or identical matching placebo BID for 28 days.

Before Treatment Period 2, patients will undergo a 28-day Washout Period following which all patients will receive 3 capsules of placebo BID during the 14-day single-blind placebo lead-in phase.

During Treatment Period 2 double-blind treatment phase, patients will receive 3 capsules of 150-mg GLWL-01 (450-mg total dose) or identical matching placebo BID for 28 days. The double-blind treatment phases in both treatment periods must not exceed 28 days and patients must not administer the double-blind study drug beyond 28 days. The study drugs can be administered in fed or fasted conditions.

The investigator or designee is responsible for

- explaining the correct use of the study drug to patients and caregivers;
- verifying that instructions are followed properly;
- maintaining accurate records of study drug dispensation and collection;
- and returning all unused medications to sponsor or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

7.1.1. Packaging and Labeling

The sponsor or its designee will provide sufficient quantities of GLWL-01 drug products to allow completion of this study. GLWL-01 drug products are manufactured, tested, packaged, and labeled in accordance with all applicable good manufacturing practice requirements, guidelines, and regulations and will be labeled according to the country's regulatory

requirements. A certificate of release confirming that study drugs are released for human use in clinical trials will be supplied. GLWL-01 drug products are for investigational use only and are to be used only within the context of this study.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized 1:1 to 1 of 2 treatment sequences: GLWL-01/placebo or placebo/GLWL-01 (Treatment Period 1 double-blind treatment phase/Treatment Period 2 double-blind treatment phase). Assignment to treatment sequence will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign bottles containing study drug to each patient. During the patient's/caregiver's visit, site personnel will access the IWRS for the correct bottle numbers to dispense.

7.2.1. Timing of Dose Administration

The doses should be administered at approximately the same times on each day.

The study drug will be administered at the site on Days 14 and 42 (Treatment Period 1) only.

7.3. Blinding

This study has both single-blind (patient and caregiver) and double-blind (patient, caregiver, and investigator) phases.

To preserve the blinding of the study, a minimum number of sponsor personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling 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 using the IWRS.

If an investigator, site personnel performing assessments, caregiver, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to retain the patient in the study, the investigator must obtain specific approval from the sponsor medical representative for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient's safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

The GLWL-01 capsules are supplied in high-density polyethylene bottles. All GLWL-01 drug products will be stored in a secure and locked area with strictly limited access and monitored for temperature, and allocated and dispensed by appropriately trained personnel. Study drugs will be stored between 15°C and 30°C.

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drug.
- ensuring that only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

Patient compliance with study drug will be assessed at the end of each treatment period. Compliance will be assessed by counting returned capsules. The patient will be considered significantly noncompliant if he or she takes <80% or >120% of dispensed capsules. Deviations from the prescribed dosage regimen should be recorded in the electronic data capture (EDC).

7.7. Concomitant Therapy

Patients may not take any medication (including over-the-counter products), herbal products, or vitamin supplements, which are CYP3A and/or P-gp inhibitors for 14 days prior to dosing and throughout the study. In cases that require the use of such medication for the treatment of an AE or comorbidity, GLWL-01 dosing must be terminated before the CYP3A inhibitor can be started.

Medications that prolong the QT/QTc interval are allowed provided the patient has been on a stable dose of said medication for at least 3 months and has a QTc < 450 msec at Visit 1 and Visit 3. A list of medications with a potential for QTc prolongation will be provided separately to the investigators.

If the need for the initiation of other medication arises during the study, the investigator must consult with sponsor medical representative and such medication change must be reported in the EDC.

All medications taken by patients during the course of the study will be recorded. Concomitant medications will be listed by treatment and coded using the most current World Health Organization drug dictionary.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Patient participation in the study may be discontinued for any of the following reasons:

- Enrollment in any other clinical study involving any study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- **Investigator's decision**: the investigator decides that the patient should be discontinued from the study.
- **Patient's/caregiver's decision**: the patient or caregiver requests to be discontinued from the study.
- **Sponsor's decision**: GLWL stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
- **Adverse event**: any SAE or a significant change in a laboratory value occurs that merits the study drug being discontinued and necessitates appropriate measures being taken. In this case, the sponsor is to be notified immediately.
- **Hepatic event or liver test abnormality**: Patients who are discontinued from using study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via electronic data entry.
  Discontinuation of the study drug for abnormal liver test results **should be** considered by the investigator when a patient meets 1 of the following conditions after consultation with the sponsor medical representative:

  - ALT or AST >5X ULN
  - ALT or AST >3X ULN along with 1 of the following criteria:
    - sustained for more than 2 weeks or
    - total bilirubin level (TBL) >2X ULN or
    - prothrombin time >1.5X ULN or
    - the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - ALP >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Marked prolongation of the QT/QTc interval >500 ms or >60 ms over baseline, judged medically significant following repeat ECG after 5 minutes of rest from the initial ECG.
- A clinically significant systemic hypersensitive reaction occurs following administration of the study drug (e.g., study drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension), that requires parenteral medication, does not respond to symptomatic medication, or result in clinical sequelae or an anaphylactic reaction.
- An elevated troponin I level (greater than 0.04 ng/mL); the patient must be referred for further evaluation.

- Patient has stopped eating or drinking for more than 24 hours.
- Requirement of prohibited concomitant medication.
- Patient failure to comply with protocol requirements or study-related procedures.
- Termination of the study by the sponsor or regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal.

Patient discontinuing from the study prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessment – Hyperphagia Questionnaire for Clinical Trials

The HQ-CT is a validated tool developed specifically for PWS, to capture observations of problematic behaviors related to food. It was adapted in a rigorous and systematic manner for use in clinical trials (HQ for Clinical Trials or HQ-CT) by Zafgen, Inc. for the ZAF-312 clinical trial, and donated to the Foundation for Prader-Willi Research in 2016 to facilitate its use across clinical trials for PWS. 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 zero to 4 units (total range of score of zero to 36; Fehnel et al. 2015).

9.1.2. Secondary Efficacy Assessment – Caregiver Global Impression of Change

Caregiver Global Impression of Change (CGIC) is a single-item question rated on a 0 to 7 scale directed at the caregiver asking them to assess overall improvement in patients with PWS. This tool was adapted by Zafgen, Inc. for the ZAF-312 clinical trials.

9.2. Adverse Events

A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

The sponsor has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate healthcare option, AEs that are serious or otherwise medically important, considered related to the study drug or the study, or that caused them to discontinue the study drug before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via EDC the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or study treatment via EDC.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the study drug, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Ratings of AEs will be based on the following 3-point severity scale:

Mild	Awareness of sign or symptom, but it is easily tolerated; does not interfere with daily activities
Moderate	Discomfort enough to slightly disrupt daily activities. Medical intervention and/or close follow-up may be considered
Severe	Incapacitating with complete disruption of daily activities. Medical intervention and/or close follow-up likely.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's study drug is discontinued as a result of an AE, study site personnel must report this to sponsor or its designee via EDC, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

Study site personnel must alert the sponsor or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. Serious adverse event reporting to the sponsor begins after the patient has signed the ICF.

If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the EDC (Section 9.4.5.1).

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Previously planned (prior to the signing of ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

The following terms will be utilized to assess the relationship of the SAE to administration of study treatment:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unlikely**: likely to be due to another etiology.
- **Not related**: without question, the AE is definitely not associated with the study treatment.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study. Serious adverse events occurring after a patient has taken the last dose of study drug will be collected for 30 days after the last dose of the study drug. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify the sponsor.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

The medical representative of the sponsor will monitor safety data throughout the course of the study. The sponsor and/or its designee will review SAEs within appropriate timeframes to meet reporting obligations imposed by regulatory authorities. All serious and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives, and regulations.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB (GLWL-01 2017) and that the investigator identifies as related to the study drug or procedure. The sponsor has procedures that will be followed for identifying, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.2. Complaint Handling

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the IB (GLWL-01 2017).

9.4. Safety

9.4.1. Electrocardiograms

For each patient, 12-lead ECG recordings and ECG extractions should be performed according to the Schedule of Activities (Section 2).

Patients must be in a quiet environment without significant external stimulation (e.g., television or internet), must be in supine position for at least 5 to 10 minutes before the specified ECG collection time, and must remain supine but awake during ECG collection and for at least 5 minutes afterward. Patients are to be encouraged to remain still if possible during this time.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the study drug should be reported to the sponsor or its designee as an AE via EDC.

9.4.2. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2). Triplicate measurements (collected approximately 1 minute apart) of sitting BP, and single pulse and temperature, will be measured.

Any clinically significant findings from vital sign measurements that result in a diagnosis and that occur after the patient receives the first dose of study drug should be reported to the sponsor or its designee as an AE via electronic data entry.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2). The blood samples should be collected in a fasted state.

With the exception of laboratory test results that may unblind the study, sponsor or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of study drug should be reported to the sponsor or its designee as an AE via electronic data entry.

9.4.4. Columbia Suicide-Severity Rating Scale

Columbia Suicide-Severity Rating Scale: A scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience or some or all of the patients may have these data solicited through interactive web-response system or electronic patient reported outcome technology. This tool was developed by the National Institute of Mental Health trial group (Treatment of Adolescent Suicide Attempters) for the purpose of being a counterpart to the C-CASA categorization of suicidal events.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

Terms captured by the use of the C-SSRS can be mapped to Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007) to facilitate future pooling of data.

The first time the scale is administered in this study, the C-SSRS “Lifetime/Recent-Clinical” version will be used, and the findings will constitute the baseline assessment. The “Since Last Visit-Clinical” version will be used for all subsequent assessments. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided. If, based on administration of

the C-SSRS, it is determined that suicide-related behaviors have occurred, then the additional information will be collected to allow for a more complete assessment of these behaviors.

9.4.5. Safety Monitoring

The sponsor and designee will periodically review evolving aggregate safety data within the study using appropriate methods.

9.4.5.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the electronic data entry if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE

9.5. Pharmacokinetics

9.5.1. Blood Sampling and Processing

For all patients, serial blood samples will be collected on Day 1 and Day 28 of Treatment Period 1 for the determination of plasma concentrations of GLWL-01. Sample collection time points are specified in the Schedule of Activities (Section 2). Times of sampling are intended as a guide and may be modified to accommodate clinical procedures. The actual date and time (24-hour clock time) of each sample collection will be recorded. The date and time of dosing on the days of PK sample collection will also be recorded. Instructions for the collection and handling of blood samples will be provided by the sponsor in a separate document.

A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. For patients who discontinue early, a PK sample should be taken at the early termination visit.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Placebo samples are not planned to be assayed.

9.5.2. Bioanalytical Method

Plasma sample bioassays of GLWL-01 will be performed using validated procedures and methods at a laboratory approved by the sponsor. Placebo samples will be shipped to the laboratory in order to maintain the blind, and are not planned to be assayed.

Bioanalytical samples collected to measure study drug concentration will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

9.6.1. Acylated-Ghrelin and Unacylated-Ghrelin

A separate PD sampling manual will detail the appropriate collection and processing procedures to be followed for this study. For all patients, blood samples for the determination of PD assessments (AG and UAG) will be collected at scheduled time points as provided in Schedule of Activities (Section 2). The blood samples should be collected in a fasted state.

9.7. Biomarkers

Not applicable.

9.8. Health Economics

Not applicable.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 34 patients will be randomized to 1 of 2 treatment sequences (GLWL-01/placebo or placebo/GLWL-01) in a 1:1 ratio. Thirty-four patients will 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.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Analysis Set	Description
Entered	All patients who sign informed consent
Randomized	All randomized patients who take at least 1 dose of double-blind study drug. Patients will be analyzed according to the treatment they actually received.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of GLWL Research Inc. or its designee.

Efficacy analyses will be conducted on the randomized analysis set. This set includes all data from all randomized patients receiving at least 1 dose of double-blind study drug. Patients will be included in the analysis if they have a postbaseline measurement for the parameter being analyzed. Safety analyses will be conducted on the randomized analysis set. Patients will be analyzed according to the study drug they actually received.

Data will be presented using summary tables by treatment, unless otherwise specified.

Continuous data will be summarized using the mean, standard deviation, median (for selected variables), minimum, and maximum. Categorical data will be summarized as frequency counts and percentages. Figures may be used to support the presentation of selected data.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

Baseline values will be defined as the last available value prior to receiving double-blind study drug for each double-blind treatment phase.

For the purposes of follow-up analyses, the first 2 weeks of the washout period will be the follow-up for the Treatment Period 1 double-blind treatment phase and the Follow-up Period will be the follow-up for the Treatment Period 2 double-blind treatment phase.

Details related to handling of missing data will be described in the statistical analysis plan (SAP).

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis

methods described in the protocol, and the justification for making the change, will be described in the SAP and/or in the clinical study report (CSR).

Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be summarized by treatment sequence. If known, a reason for their discontinuation will be given.

10.3.2.2. Patient Characteristics

Patient demographics (age, gender, race, ethnicity, height, weight, and BMI) will be summarized by treatment sequence for the safety analysis set.

10.3.2.3. Concomitant Therapy

Concomitant therapy will be listed.

10.3.2.4. Treatment Compliance

Treatment compliance will be calculated for each double-blind treatment phase as

$$Treatment\ Compliance = \frac{number\ of\ capsules\ received}{number\ of\ intended\ capsules} * 100$$

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary analysis will be conducted using a restricted maximum likelihood-based, mixed-effect model repeated measures analysis. The analysis of the primary endpoint will be the contrast between GLWL-01 and placebo at the end of the double-blind treatment phase on the posttreatment HQ-CT score.

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 double-blind Treatment Period 1 phase HQ-CT score minus the baseline double-blind Treatment Period 2 phase HQ-CT score (diff) and the interaction of period*diff (Mehrotra 2014).

An unstructured covariance structure will be used to model the within-patient errors.

Sensitivity analyses will be outlined in the SAP.

10.3.3.2. Secondary Analyses

The secondary analysis will be conducted similarly to the primary analysis, but the model will not include the baseline covariate or interaction. The secondary efficacy endpoint is the CGIC.

10.3.3.3. Exploratory Analyses

The following exploratory endpoints will be analyzed using the same methodology as for the primary efficacy analysis:

- AG
- UAG
- AG/UAG ratio
- Body weight
- Percentage fat mass
- BMI
- Waist circumference
- low-density lipoprotein
- Total cholesterol

10.3.4. Safety Analyses

The safety analyses will be conducted for the double-blind treatment phase and follow-up combined. Data will be summarized by treatment group unless otherwise noted.

The safety and tolerability of treatment will be assessed by evaluating the following:

- Treatment-emergent adverse events by Preferred Term and maximum severity
- SAEs
- AE leading to discontinuation
- Suicidal ideation and behaviours assessed by solicited questioning using the C-SSRS
- Vital signs and weight
- ECGs
- Laboratory measurements

Treatment-emergent adverse events are defined as the reported AEs that first occurred or worsened during the double-blind treatment phase and follow-up compared with baseline. The most recent version of Medical Dictionary for Regulatory Activities Lowest Level Term (LLT) will be used in the treatment-emergent computation. For each LLT, the maximum severity at baseline will be used as the baseline severity. If the maximum severity during postbaseline is greater than the maximum baseline severity, the event is considered to be treatment emergent for the specific postbaseline period. Treatment-emergent adverse events will be summarized by the number and percentage of patients with the event.

For events that are gender-specific, the denominator and computation of the percentage will include only patients from the given gender.

Suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior based on the C-SSRS will be listed.

Vital signs collected during the study include systolic and diastolic BP, pulse, and temperature. Blood pressure and pulse measurements will be taken when the patient is in a sitting position. Three measurements of sitting BP will be collected at approximately 30- to 60-sec intervals and those 3 sitting BP will be averaged and used as the value for that visit for analysis.

The incidence rates of patients with clinically significant vital sign and weight changes at any time postbaseline will be assessed using Fisher's exact test. The clinically significant criteria will be documented in the SAP.

The QT and QTcF interval will be summarized with the number and percentage of patients with values >450 msec, >480 msec, and >500 msec at any time postbaseline.

The incidence rates of patients with treatment-emergent abnormal, high, or low laboratory values at any time postbaseline will be assessed using Fisher's exact test for each laboratory test.

Patients will be defined as having a treatment-emergent low value if they have all normal or high values at baseline, followed by a value below the lower reference limit at any postbaseline visit. Patients with all normal or high values at baseline (no low values) will be included in the analysis of treatment-emergent low laboratory values. Patients will be defined as having a treatment-emergent high value if they have all normal or low values at baseline, followed by a value above the upper reference limit at any postbaseline visit. Patients with all normal or low values at baseline (no high values) will be included in the analysis of treatment-emergent high laboratory values.

For analytes simply classified as normal or abnormal, patients will be defined as having a treatment-emergent abnormal value if they have all normal values at baseline, followed by an abnormal value at any postbaseline visit. Patients with all normal values at baseline will be included in the analysis of treatment-emergent abnormal laboratory values.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Plasma GLWL-01 PK parameters will be calculated using noncompartmental methods after single and multiple dose administration (on Day 1 and Day 28 of Treatment Period 1, respectively). Additional PK parameters may be calculated if deemed appropriate.

Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Mean and individual GLWL-01 plasma concentration-time curves will be represented graphically.

Accumulation will be estimated. Additional analyses will be performed as deemed necessary upon review of the data.

Pharmacokinetic data may be fit with a population PK model; and may be pooled with data from previous studies.

Pharmacodynamics of GLWL-01 will be based on plasma AG and potentially UAG measures. Raw and change from baseline values will be reported and summarized for AG and potentially UAG.

The PK/PD relationship of GLWL-01 with PD, efficacy, and/or safety measures may be explored.

10.3.6. Evaluation of Immunogenicity

Not applicable.

10.3.7. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate sponsor medical representative will be consulted to determine whether it is necessary to amend the protocol.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AG	acylated-ghrelin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice a day
blinding	A double-blind study is one in which neither the patient/caregiver nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CGIC	Caregiver Global Impression of Change
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CSR	clinical study report
C-SSRS	Columbia–Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	Electrocardiogram
EDC	electronic data capture
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.

enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GHSR-1a	growth hormone secretagogue receptor
GOAT	ghrelin-O-acyltransferase
HIV	human immunodeficiency virus
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
IWRS	interactive web-response system
LLT	Lowest Level Term
P-gp	P-glycoprotein
PI	principal investigator
PK/PD	pharmacokinetic(s)/pharmacodynamics
PWS	Prader-Willi syndrome
QD	once daily
QTcF	corrected QT interval with Frederica's correction
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

study drug	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
UAG	unacylated-ghrelin
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (red blood cell [RBC])	Potassium
Mean cell volume	Bicarbonate
Mean cell hemoglobin concentration	Chloride
Leukocytes (white blood cell [WBC])	Calcium
Cell morphology	Phosphorus
Absolute/relative/% counts of	Magnesium
Neutrophils	Glucose (fasting)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Total cholesterol
Eosinophils	Total protein
Basophils	Albumin
Platelets	Total bilirubin
	Creatinine
	Estimated glomerular filtration rate (eGFR)[d]
Urinalysis[a]	Alkaline phosphatase (ALP)
Specific gravity	Aspartate aminotransferase (AST)
pH	Alanine aminotransferase (ALT)
Protein	
Glucose	Gamma-glutamyl transferase (GGT)
Ketones	
Bilirubin	**Troponin I**
Urobilinogen	
Blood	**Additional tests**
Nitrite	High-density lipoprotein cholesterol (HDL-c)
Creatinine	Triglycerides (TG)
Ethanol testing[b,c]	Calculated low-density lipoprotein cholesterol (LDL-c)
Urine drug screen[b,c]	
Hepatitis B surface antigen[b]	
Hepatitis C antibody[b]	
Human immunodeficiency virus (HIV)[b]	
Pregnancy test (serum, in females only)	
Serum follicle-stimulating hormone (FSH; in postmenopausal females only)	
Thyroid-stimulating hormone	

[a] Results will be reported and/or validated by the Central Laboratory at the time of initial testing. If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for RBCs, WBCs, bacteria, casts, and epithelial cells) will be performed.

[b] Performed at screening only.

[c] Urine drug screen and ethanol level may be repeated as needed.

[d] eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (utilizing enzymatic creatinine).

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for

- ensuring that the patients understand the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

The sponsor or designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to the sponsor before the study may begin at the investigative sites. The sponsor or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current IB and updates during the course of the study
- ICF
- other relevant documents (e.g., curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.5. Investigator Information

Licensed physicians with a specialty in endocrinology or internal medicine will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

The sponsor's medical representative will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each PI will sign the protocol signature page and send a copy of the signed page to the sponsor representative.

Appendix 3.1.7. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study. The investigator with the most analyzable patients will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by the sponsor to serve as the CSR coordinating investigator.

The sponsor's medical representative and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the EDCs, and study procedures.
- make periodic visits to the study site

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate EDC data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, sponsor or its designee will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An EDC system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided EDC system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the sponsor.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if sponsor or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear Antibody**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth Muscle Antibody (or Anti-actin Antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by sponsor-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Sampling Summary

This table summarizes the approximate number of samples and volumes for all sampling and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol GLWL-PWS Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number of Samples	Maximum Total Amount
Screening tests[a]	Blood	21 mL	1	21 mL
Standard laboratory tests[a]	Blood	2 mL	5	10 mL
Drug concentration	Blood	2 mL	14	28 mL
AG and UAG samples	Blood	4 mL	5	20 mL
On-study serum chemistry (includes serum thyroid-stimulating hormone, lipid panel, troponin, and serum pregnancy when done at the same time)	Blood	15 mL	5	75.0 mL
Total	Blood	-	-	154.0 mL
Hepatic monitoring[b]	Blood	3 - 30 mL	-	-

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly-designated Medical Monitor.

Appendix 6. Protocol Amendment GLWL-PWS(a) Summary [A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome]

Overview

Protocol GLWL-PWS [A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome] has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Serum pregnancy test has been added at the end of the second Double Blind Treatment Phase [Visit 10 (day 112)] and Early Termination Visit for women of childbearing potential, per requested change by Health Canada.
- Exclusion criteria for family history of Long QT Syndrome, now Exclusion Criteria #19 has been added, per requested change by Health Canada .
- Now Exclusion Criteria #23(c), the use of any medications that prolong the QT/QTc interval is excluded, per requested change by Health Canada.
- In Section 7.7 Concomitant Medications, consistency sentences were added to indicate that medications that prolong the QT/QTc interval are prohibited and that a list will be provided separately and updated as data evolves, per request by Health Canada.
- In Section 8 Discontinuation Criteria, marked prolongation of the QT/QTc interval >500 ms or >60 ms over baseline, judged medically significant following repeat ECG after 5 minutes of rest from the initial ECG was added, per request by Health Canada.
- Minor textual edits were made for the purpose of clarification or correction.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

2. Schedule of Activities

Table GLWL-PWS.3. Schedule of Activities

Period	Screening[a]	Treatment Period 1				Washout (28 days)	Treatment Period 2				Follow-up	ET[c]
Phase		Single-blind Placebo Lead-in Phase (14 days)	Double-blind Treatment Phase (28 days)[b]				Single-blind Placebo Lead-in (14 days)	Double-blind Treatment Phase (28 days)[b]				
Visit No/ Type Procedure	V1	V2[d] Caregiver	V3[e]	V4[f] Phone	V5	V6 Phone	V7[d] Caregiver	V8	V9[f] Phone	V10	V11	
Day	-28 to -3	1 (±3)	14 (±2)	28 (±2)	42 (±2)	56 (±2)	70 (±2)	84 (±2)	98 (±2)	112 (±2)	126 (±3)	
Informed consent	X											
Demographics	X											
Physical examination[g]	X										X	X
Height[h]	X											
Initial history/ preexisting conditions	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg, HCAB, HIV	X											
Urinalysis[i]	X											
Substance abuse screen[j]	X											
Inclusion/exclusion review	X		X[e]									
Study drug dispensing		X	X				X	X				
Study drug administration at site			X		X							
Study drug accountability			X		X			X		X		
Efficacy and Outcome Measures												
HQ-CT		X	X	X	X	X	X	X	X	X	X	X
CGIC					X					X		X
Body weight[h]	X		X		X			X		X	X	X
Percentage fat mass (calipers)			X		X			X		X		X
BMI	X		X		X			X		X	X	X
Waist circumference			X		X			X		X		X
Vital signs[k]	X		X		X			X		X	X	X

Period	Screening[a]	Treatment Period 1			Washout (28 days)	Treatment Period 2				Follow-up	ET[c]
Phase		Single-blind Placebo Lead-in Phase (14 days)	Double-blind Treatment Phase (28 days)[b]			Single-blind Placebo Lead-in (14 days)	Double-blind Treatment Phase (28 days)[b]				
Visit No/ Type Procedure	V1	V2[d] Caregiver	V3[e]	V4[f] Phone	V5	V6 Phone	V7[d] Caregiver	V8	V9[f] Phone	V10	V11	
Day	-28 to -3	1 (±3)	14 (±2)	28 (±2)	42 (±2)	56 (±2)	70 (±2)	84 (±2)	98 (±2)	112 (±2)	126 (±3)	
12-lead ECG[l]	X		X		X			X		X	X	X
Serum pregnancy test[m]	X									X		X
Urine pregnancy test[m]			X					X				
Clinical chemistry and hematology[i]	X		X		X			X		X		X
Lipid panel			X		X			X		X		X
AG and UAG[n]			X		X			X		X		X
Plasma sample collection for PK analysis[o]			X		X							X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AG = acylated-ghrelin; BMI = body mass index; CGIC = Caregiver Global Impression of Change; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; EDC = electronic data capture; ET = early termination; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; HBsAg = hepatitis B surface antigen; HCAB = hepatitis C antibody; HIV = human immunodeficiency virus; PK = pharmacokinetic; UAG = unacylated-ghrelin; V = Visit.

[a] Screening visit must occur between -28 days to -3 days of V2.

[b] Double-blind Treatment Phase must not exceed 28 days and patients must not take the study drug beyond 28 days. For example, if the V3 occurs on Day 14, then corresponding V5 would occur on Day 42. Similarly, if V3 occurs on Day 15 (Day 14 +1), then corresponding V5 would occur on Day 43 (Day 42 +1).

[c] The primary reason for early termination of the patient will be entered in EDC and recorded in the patient's source documents. The patient will attend an early termination visit as soon as possible after participation ceases.

[d] Caregiver only visit; patient does not need to attend in person.

[e] Confirm that the patient has met all inclusion/exclusion criteria. Patients will only be dosed after the investigator has completed the appropriate protocol assessments and determined that it is acceptable to dose the patient.

[f] Patients/caregivers will receive phone calls from the site; no visit required.

[g] A full physical examination with neurological assessments should be performed at Visit 1. Symptom-driven physical examinations should be performed at V3, V5, and V8, V10,V11, and at ET.

[h] Height will only be measured at Visit 1. Patients should be instructed to wear lightweight clothing and remove shoes during weighing.

[i] Refer to Appendix 2 for details on serum chemistry, hematology, and urinalysis clinical laboratory tests.

[j] Substance abuse screen test to be performed at Visit 1 and additionally at any visit per investigator's discretion.

[k] Vital sign assessments will include triplicate sitting blood pressure, and single pulse and body temperature. Additional vital sign assessments may be performed as clinically indicated. For visits in which both vital signs and blood samples are collected, vital signs should be obtained prior to blood collection. Any clinically significant result of vital sign assessment will be documented in the source documentation and EDC as an AE.

[l] Single 12-lead ECGs to be collected according to the schedule and may be collected at any time if deemed clinically necessary. Patients must be supine for at least 5 minutes prior to ECG collection. When ECG collections are scheduled at the same time point as any other tests, ECGs, followed by vital signs, should be recorded prior to any clinical laboratory or PK blood sampling.

[m] For all female patients, the investigator will document potential childbearing status. For women who are postmenopausal, a confirmatory test of serum follicule-stimulating hormone and estradiol levels will be done at Visit 1. For all women of childbearing potential, a pregnancy serum test will be done at Visit 1, which must be negative to enroll. Subsequently, urine pregnancy tests will be done for all women of childbearing potential as indicated in the schedule; the results must be confirmed negative. In case of a positive urine pregnancy test, the serum pregnancy test must be performed to confirm the pregnancy results.

[n] The blood samples for AG and UAG should be collected in the fasted state.

[o] On Day 14 and Day 42, a total of 7 PK samples each day will be taken at the following times: pre-dose, and 0.5, 1, 2, 4, 6, and between 8 and 12 hours postdose. Times of sampling are intended as a guide and can be modified to accommodate clinical procedures. Actual time of sample must be collected, as well as date and time of dosing on the day of PK sample collection. For patients who discontinue early, a sample should be obtained at the ET visit.

6.2 Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

9. Are Eli Lilly and Company, GLWL Research Inc. (sponsor hereafter), contract research organization employees, investigator or site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
10. Are currently enrolled in any other clinical trial involving a study drug or off-label use of a drug or device, or any other type of medical research judged not to be scientifically or medically compatible with this study.
11. Participated in a clinical trial within 30 days (defined as last dose of study drug), prior to the GLWL-PWS first dose.
12. Are currently living in a group home for more than 50% of the time.
13. Have a HQ-CT total score at Visit 3 <13.
14. Have clinical laboratory test results outside normal reference range, or any clinically significant laboratory abnormality, that in the judgment of the investigator, indicates a medical problem that would preclude study participation. Values for aspartate aminotransferase (AST)/alanine aminotransferase (ALT)/gamma-glutamyl transferase (GGT)/alkaline phosphatase (ALP) >3X upper limit of normal (ULN).
15. Have an estimated glomerular filtration rate <60 mL/minute/1.73 m2. Have macroalbuminuria (defined as spot urine albumin to creatinine ratio of >300 µg/mg) or hematuria.
16. Are hypertensive (defined as sitting systolic BP ≥140 mmHg and diastolic BP ≥90 mmHg) on or off medications for the treatment of hypertension. Blood pressure may be re-tested up to 2 additional times, under well-rested conditions.
17. In addition to conditions described below, have a history or presence of any other medical illness including but not limited to any autoimmune disorder, cardiovascular, hepatic, respiratory, hematological, or uncontrolled neurological disease.
    a) Have a history of clinically overt uncontrolled or untreated endocrine illness such as growth hormone insufficiency, adrenal gland, or thyroid illness.
    b) Have evidence of other chronic liver disease, including but not limited to chronic alcoholic disease, cirrhosis of any cause, recent history (within 3 months of screening) of acute viral hepatitis or chronic autoimmune hepatitis. Patients with a history of biliary disease, including primary sclerosing cholangitis, must be excluded. Patients with a history of cholecystectomy longer than 6 months prior to screening could be enrolled.
    c) Have evidence of significant active or unstable/uncontrolled psychiatric disease by medical history, such as bipolar disorder, schizophrenia, personality disorders, or other serious mood or anxiety disorders. Note: Patients whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

18. Have an abnormality in the 12-lead electrocardiogram (ECG), including corrected QT interval with Frederica's correction (QTcF) >450 msec for men and >470 msec for women or an abnormality that, in the opinion of the investigator, increases the risks associated with participating in the study. If QTcF does not meet criteria, ECGs may be repeated once after 5 minutes of rest.
19. Have a family history of Long QT Syndrome.
20. Have evidence of human immunodeficiency virus (HIV) infection, hepatitis B, hepatitis C and/or positive results at screening for the respective antibodies for HIV, hepatitis B surface antigen, or hepatitis C antibodies.
21. Patients who, in the clinician's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or those who have answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the Columbia–Suicide Severity Rating Scale (C-SSRS), or answer "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C–SSRS; and the ideation or behavior occurred within a month of Visit 1.
22. Patients on weight loss medications within 30 days of dosing. Patients with a history of bariatric surgery should also be excluded.
23. Unable to refrain from or anticipates the use of
    a) Any drugs known to be significant inhibitors of cytochrome P450 (CYP)3A enzymes and/or P-glycoprotein (P-gp) including regular consumption of grapefruit or grapefruit juice for 14 days prior to the first dose of study medication and throughout the study. Appropriate sources will be consulted by the principal investigator (PI) or designee to confirm lack of PK or pharmacodynamic (PD) interaction with study medication. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study.
    b) Any drugs known to be significant inducers of CYP3A enzymes and/or P-gp, including St. John's Wort, for 28 days prior to the first dose of study medication and throughout the study. Appropriate sources will be consulted by the PI or designee to confirm lack of PK/PD interaction with study medication.
    c) Any medications that prolong the QT/QTc interval.
24. Currently taking simvastatin >10 mg per day, atorvastatin >20 mg per day, or lovastatin >20 mg per day. The doses of these statins in combination products should not exceed these defined dose levels. Patients with a history of statin-induced myopathy/rhabdomyolysis should also be excluded.
25. Current smokers, or any use of tobacco and nicotine products within 3 months of dosing.
26. Regular user of known drugs of abuse and/or shows positive findings on urinary drug screening.
27. An average weekly alcohol intake that exceeds 21 units per week (males ≤65 years of age) and 14 units per week (females and males >65 years of age), or is unwilling to stop alcohol consumption for the duration of the study (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
28. Venous access insufficient to allow for blood sampling as per the protocol.

29. Any major surgery within 60 days prior to the first dose or has planned elective surgeries to occur during the study.
30. Unsuitable for inclusion in the study in the opinion of the investigator.

7.7 Concomitant Therapy

Patients may not take any medication (including over-the-counter products), herbal products, or vitamin supplements, which are CYP3A and/or P-gp inhibitors for 14 days prior to dosing and throughout the study. In cases that require the use of such medication for the treatment of an AE or comorbidity, GLWL-01 dosing must be terminated before the CYP3A inhibitor can be started.

Medications that prolong the QT/QTc interval are prohibited. A list will be provided separately and updated as data evolves.

If the need for the initiation of other medication arise during the study, the investigator must consult with sponsor medical representative and such medication change must be reported in the EDC.

All medications taken by patients during the course of the study will be recorded. Concomitant medications will be listed by treatment and coded using the most current World Health Organization drug dictionary.

8. Discontinuation Criteria

Patient participation in the study may be discontinued for any of the following reasons:

- Enrolment in any other clinical study involving an study drug or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- **Investigator's decision**: the investigator decides that the patient should be discontinued from the study.
- **Patient's/caregiver's decision**: the patient or caregiver requests to be discontinued from the study.
- **Sponsor's decision**: GLWL stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
- **Adverse event**: any SAE or a significant change in a laboratory value occurs that merits the study drug being discontinued and necessitates appropriate measures being taken. In this case, the sponsor is to be notified immediately.
- **Hepatic event or liver test abnormality**: Patients who are discontinued from using study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via electronic data entry.
  Discontinuation of the study drug for abnormal liver test results **should be** considered by the investigator when a patient meets 1 of the following conditions after consultation with the sponsor medical representative:

  - ALT or AST >5X ULN
  - ALT or AST >3X ULN along with 1 of the following criteria:
    - sustained for more than 2 weeks or
    - total bilirubin level (TBL) >2X ULN or
    - prothrombin time >1.5X ULN or
    - the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - ALP >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Marked prolongation of the QT/QTc interval >500 ms or >60 ms over baseline, judged medically significant following repeat ECG after 5 minutes of rest from the initial ECG.
- A clinically significant systemic hypersensitive reaction occurs following administration of the study drug (e.g., study drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension), that requires parenteral medication, does not respond to symptomatic medication, or result in clinical sequelae or an anaphylactic reaction.
- Requirement of prohibited concomitant medication.
- Patient failure to comply with protocol requirements or study-related procedures.

- Termination of the study by the sponsor or regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal.

Patient discontinuing from the study prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Appendix 7. Protocol Amendment GLWL-PWS(b) Summary [A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome]

Overview

Protocol GLWL-PWS [A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome] has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Troponin I testing has been added to Visits 3, 4, 5, 8, 9, and 10 as requested by FDA
- ECGs 2 hours post-dose have been added at Visits 3 and 8 as requested by FDA
- ECGs have been added to Visits 4 and 9 as requested by FDA
- Visit 4 occurs on Day 21 and visit 9 occurs on Day 91 as requested by FDA
- Visits 2 and 7 will be phone visits due to change of Visits 4 and 9 to in-person visits
- The following discontinuation criteria have been added as requested by FDA:
    - Patients with elevated troponin I level (greater than 0.04 ng/mL) must be withdrawn from the study. Elevations must be referred for further evaluation.
    - Patients who have stopped eating or drinking for more than 24 hours must be withdrawn from the study.
- Minor textual edits were made for the purpose of clarification or correction.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

1. Synopsis

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

Rationale:
The aim of this study is to evaluate efficacy, safety, and pharmacokinetics of GLWL-01 in the treatment of patients with Prader-Willi Syndrome (PWS).

Objectives/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)	• Posttreatment HQ-CT total score
Secondary • Evaluate the safety and tolerability of GLWL-01 after 28 days of treatment in patients with PWS • 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) • Evaluate the pharmacokinetics after single and multiple oral dosing of GLWL-01 in patients with PWS	• Treatment-emergent adverse events • CGIC score • GLWL-01 o Area under the concentration versus time curve from time zero to 12 hours (AUC_{0-12}) o Maximum observed drug concentration (C_{max})
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	Posttreatment: • AG • UAG • AG/UAG • Body weight • Percentage fat mass • Body mass index • Waist circumference • Low-density lipoproteins • Total cholesterol

Summary of Study Design:

Study GLWL-PWS is a multicenter, double-blind, randomized, placebo-controlled, crossover study of GLWL-01 in patients with PWS.

The study consists of 5 periods, including 2 active treatment periods, as depicted below:

Period	Phase	Duration
Screening	NA	28 days
Treatment Period 1	Single-blind placebo lead-in[a]	14 days
	Double-blind treatment phase[b]	28 days
Washout	NA	28 days
Treatment Period 2	Single-blind placebo lead-in[a]	14 days
	Double-blind treatment phase[b]	28 days
Follow-up	NA	14 days

Abbreviation: NA = not applicable

[a] Only patient/caregiver will be blinded.

[b] Both investigator and patient/caregiver will be blinded.

Patients and caregivers will be required to visit the site on ~~6~~8 occasions at Visits 1, 3, 4, 5, 8, 9, 10, and 11. Patients and caregivers ~~(but not the patients) will be required to visit the site on 2 additional occasions at Visits 2 and 7~~ will be required to participate in phone calls with the site at Visits 2, ~~4,~~ 6, and 7~~9~~.

Treatment Arms and Duration:

Patients will be randomized to 1 of 2 treatment sequences; GLWL-01/placebo or placebo/GLWL-01 (Treatment Period 1 double-blind treatment phase/Treatment Period 2 double-blind treatment phase). During single-blind placebo lead-in phases, patients will receive 3 capsules of 150-mg placebo twice daily (BID) for 14 days. During double-blind treatment phases, patients will receive 3 capsules of 150-mg GLWL-01 (450 mg total dose) BID or identical placebo BID for 28 days.

Number of Patients:

Approximately 34 patients with PWS will be randomized.

Statistical Analysis:

Efficacy: Efficacy analyses will be conducted on the randomized analysis set. The primary analysis will be conducted using a restricted maximum likelihood-based, mixed-effect model repeated measures analysis. The analysis will be the contrast between GLWL-01 and placebo at the end of the double-blind treatment phase on the primary endpoint of the posttreatment HQ-CT score.

The secondary analysis will be conducted similar to the primary analysis. The secondary efficacy endpoint is the CGIC.

Safety: Safety analyses will be conducted on the safety analysis set. Safety data will be summarized by treatment group. Safety parameters that will be assessed include adverse events, clinical laboratory parameters, C-SSRS, vital signs, electrocardiogram parameters, and weight. The parameters will be listed and summarized using standard descriptive statistics.

Pharmacokinetics/Pharmacodynamics: Plasma GLWL-01 pharmacokinetic (PK) parameters will be calculated using noncompartmental methods after single and multiple dose administration. Additional PK parameters may be calculated if deemed appropriate. Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Mean and individual GLWL-01 plasma concentration-time curves will be represented graphically.

Pharmacodynamics of GLWL-01 will be based on plasma AG and potentially UAG measures. Raw and change from baseline values will be reported and summarized for AG and potentially UAG.

The PK/PD relationship of GLWL-01 with PD, efficacy, and/or safety measures may be explored.

2. Schedule of Activities

Table GLWL-PWS.1. Schedule of Activities

Period	Screening[a]	Treatment Period 1				Washout (28 days)	Treatment Period 2				Follow-up	ET[c]
Phase		Single-blind Placebo Lead-in Phase (14 days)	Double-blind Treatment Phase (28 days)[b]				Single-blind Placebo Lead-in (14 days)	Double-blind Treatment Phase (28 days)[b]				
Visit No/ Type Procedure	V1	V2[de] ~~Caregiver~~Phone	V3[e]	V4[f] ~~Phone~~	V5	V6[e] Phone	V7[de] ~~Caregiver~~Phone	V8	V9[f] ~~Phone~~	V10	V11	
Day	-28 to -3	1 (±3)	14 (±2)	2~~1~~8 (±2)	42 (±2)	56 (±2)	70 (±2)	84 (±2)	9~~1~~8 (±2)	112 (±2)	126 (±3)	
Informed consent	X											
Demographics	X											
Physical examination[gf]	X		X	X	X			X	X	X	X	X
Height[hg]	X											
Initial history/ preexisting conditions	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg, HCAB, HIV	X											
Urinalysis[ih]	X											
Substance abuse screen[ji]	X											
Inclusion/exclusion review	X		X[e]									
Study drug dispensing		X	X				X	X				
Study drug administration at site			X		X							
Study drug accountability			X		X			X		X		
Efficacy and Outcome Measures												
HQ-CT		X	X	X	X	X	X	X	X	X	X	X
CGIC					X					X		X
Body weight[hg]	X		X		X			X		X	X	X
Percentage fat mass (calipers)			X		X			X		X		X
BMI	X		X		X			X		X	X	X
Waist circumference			X		X			X		X		X
Vital signs[kj]	X		X		X			X		X	X	X
12-lead ECG[lk]	X		X	X	X			X	X	X	X	X
12-lead ECG 2 hours post-dose[k]			X					X				

Period	Screening[a]	Treatment Period 1				Washout (28 days)	Treatment Period 2				Follow-up	ET[c]
Phase		Single-blind Placebo Lead-in Phase (14 days)	Double-blind Treatment Phase (28 days)[b]				Single-blind Placebo Lead-in (14 days)	Double-blind Treatment Phase (28 days)[b]				
Visit No/ Type Procedure	V1	V2[d~~e~~] ~~Caregiver~~Phone	V3[e]	V4[f] ~~Phone~~	V5	V6[~~e~~] Phone	V7[d~~e~~] ~~Caregiver~~Phone	V8	V9[f] ~~Phone~~	V10	V11	
Day	-28 to -3	1 (±3)	14 (±2)	2~~1~~8 (±2)	42 (±2)	56 (±2)	70 (±2)	84 (±2)	9~~1~~8 (±2)	112 (±2)	126 (±3)	
Serum pregnancy test[~~m~~l]	X									X		X
Urine pregnancy test[~~m~~l]			X					X				
Clinical chemistry and hematology[~~i~~h]	X		X		X			X		X		X
Lipid panel			X		X			X		X		X
AG and UAG[~~n~~m]			X		X			X		X		X
Plasma sample collection for PK analysis[~~o~~n]			X		X							X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; AG = acylated-ghrelin; BMI = body mass index; CGIC = Caregiver Global Impression of Change; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; EDC = electronic data capture; ET = early termination; HQ-CT = Hyperphagia Questionnaire for Clinical Trials; HBsAg = hepatitis B surface antigen; HCAB = hepatitis C antibody; HIV = human immunodeficiency virus; PK = pharmacokinetic; UAG = unacylated-ghrelin; V = Visit.

[a] Screening visit must occur between -28 days to -3 days of V2.

[b] Double-blind Treatment Phase must not exceed 28 days and patients must not take the study drug beyond 28 days. For example, if the V3 occurs on Day 14, then corresponding V5 would occur on Day 42. Similarly, if V3 occurs on Day 15 (Day 14 +1), then corresponding V5 would occur on Day 43 (Day 42 +1).

[c] The primary reason for early termination of the patient will be entered in EDC and recorded in the patient's source documents. The patient will attend an early termination visit as soon as possible after participation ceases.

[d] ~~Caregiver only visit; patient does not need to attend in person.~~

[e~~d~~] Confirm that the patient has met all inclusion/exclusion criteria. Patients will only be dosed after the investigator has completed the appropriate protocol assessments and determined that it is acceptable to dose the patient.

[f~~c~~] Patients/caregivers will receive phone calls from the site; no visit required. Both patient and caregiver should be on the phone in order for the site to conduct AE assessments and the C-SSRS.

[g~~f~~] A full physical examination with neurological assessments should be performed at Visit 1. Symptom-driven physical examinations should be performed at V3, V4, V5, and V8, V9, V10,V11, and at ET.

[h~~g~~] Height will only be measured at Visit 1. Patients should be instructed to wear lightweight clothing and remove shoes during weighing.

[i~~h~~] Refer to Appendix 2 for details on serum chemistry, hematology, and urinalysis clinical laboratory tests.

[ji] Substance abuse screen test to be performed at Visit 1 and additionally at any visit per investigator's discretion.

[kj] Vital sign assessments will include triplicate sitting blood pressure, and single pulse and body temperature. Additional vital sign assessments may be performed as clinically indicated. For visits in which both vital signs and blood samples are collected, vital signs should be obtained prior to blood collection. Any clinically significant result of vital sign assessment will be documented in the source documentation and EDC as an AE.

[lk] Single 12-lead ECGs to be collected according to the schedule and may be collected at any time if deemed clinically necessary. Patients must be supine for at least 5 minutes prior to ECG collection. When ECG collections are scheduled at the same time point as any other tests, ECGs, followed by vital signs, should be recorded prior to any clinical laboratory or PK blood sampling.

[ml] For all female patients, the investigator will document potential childbearing status. For women who are postmenopausal, a confirmatory test of serum follicule-stimulating hormone and estradiol levels will be done at Visit 1. For all women of childbearing potential, a pregnancy serum test will be done at Visit 1, which must be negative to enroll. Subsequently, urine pregnancy tests will be done for all women of childbearing potential as indicated in the schedule; the results must be confirmed negative. In case of a positive urine pregnancy test, the serum pregnancy test must be performed to confirm the pregnancy results.

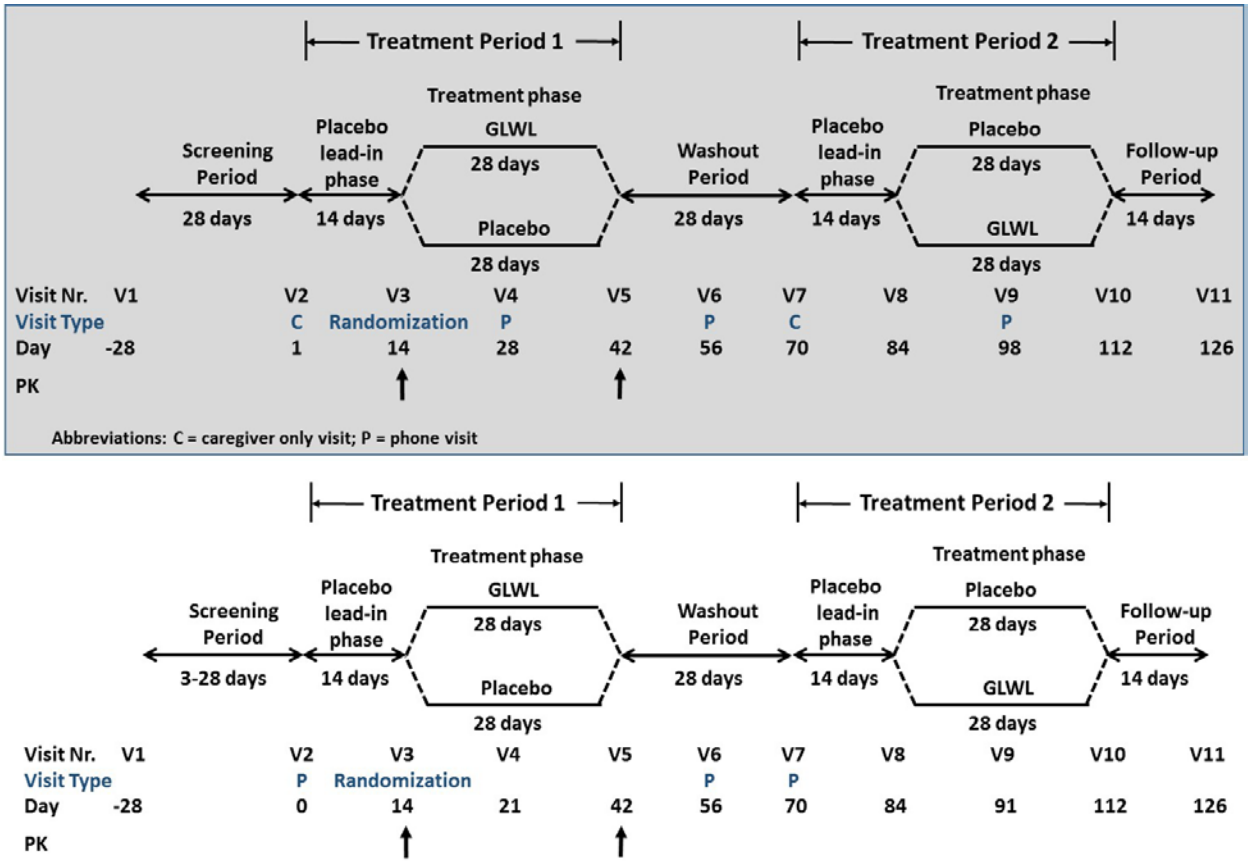
[nm] The blood samples for AG and UAG should be collected in the fasted state.

[on] On Day 14 and Day 42, a total of 7 PK samples each day will be taken at the following times: pre-dose, and 0.5, 1, 2, 4, 6, and between 8 and 12 hours postdose. Times of sampling are intended as a guide and can be modified to accommodate clinical procedures. Actual time of sample must be collected, as well as date and time of dosing on the day of PK sample collection. For patients who discontinue early, a sample should be obtained at the ET visit.

5. Study Design

5.1 Overall Design

This is a multicenter, double-blind, randomized, placebo-controlled, crossover study to evaluate the efficacy of GLWL-01 in patients with PWS. The study consists of 5 periods, including 2 active treatment periods, as depicted below:



Abbreviations: P = phone visit; PK = pharmacokinetic sample
Note: Placebo lead-in phases will be single-blinded (patient/caregiver) and treatment phases will be double-blinded (investigator and patient/caregiver)

Figure GLWL-PWS.2. Illustration of study design for Clinical Protocol GLWL-PWS.

The Screening Period allows for evaluation of inclusion/exclusion criteria. Treatment Period 1 consists of 2 phases: a 14-day single-blind (patient/caregiver) placebo lead-in phase followed by a 28-day double-blind treatment phase. At the conclusion of the single-blind placebo lead-in phase, eligible patients will be randomly assigned (in 1:1 ratio) to 1 of 2 treatment sequences: GWLW-01/placebo or placebo/GLWL-01 (Treatment Period 1 double-blind treatment phase/Treatment Period 2 double-blind treatment phase). Following Treatment Period 1, there will be a 28-day Washout Period. Treatment Period 2 also consists of 2 phases: a 14-day single-blind (patient/caregiver) placebo lead-in followed by a 28-day double-blind treatment phase. Following Treatment Period 2, there will be a 14-day Follow-up Period (see Figure GLWL-PWS.1).

Patients and caregivers will be required to visit the site on ~~6~~8 occasions at Visits 1, 3, 4, 5, 8, 9, 10, and 11. Patients and caregivers ~~(but not the patients) will be required to visit the site on 2 additional occasions at Visits 2 and 7~~ will be required to participate in phone calls with the site at Visits 2, ~~4,~~ 6, and 7~~9~~.

Study governance considerations are described in detail in 3.1 Appendix 3.

6.3 Lifestyle Restrictions

Consumption of foods and beverages containing the following substances will be limited or prohibited as indicated:

- xanthine/caffeine: throughout the study, patients are required to maintain their regular intake of caffeinated beverages for the duration of the study
- Alcohol: an average weekly alcohol intake should not exceed 21 units per week (males ≤65 years of age) and 14 units per week (females and males >65 years of age).
- Grapefruit/Seville orange: 14 days before first dosing and throughout the study.

Following the morning dose on Day 14 and Day 42, and on Day 84 and Day 112, patients will remain ambulatory or seated upright for the first 4 hours, except when they are supine or semi-reclined for study procedures.

Patients will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from Visit 1 until completion of the study participation. Patients should otherwise minimize changes in their activity levels during study participation.

6.4 Screen Failures

Patients who do not meet the criteria for participation in this study (screen failure) at Visit 1 may be rescreened. Individuals may be rescreened up to 1 time. The rescreen should be at the discretion of the PI after discussion with sponsor medical representative. If a rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatments

7.1 Treatments Administered

GLWL-01 drug product is supplied for clinical trial use as size 0 dark blue opaque capsules for oral administration. Capsules will contain 150 mg of GLWL-01. No additional excipients are used, with the exception of the capsule itself.

The GLWL-01 drug product placebo will consist of microcrystalline cellulose and magnesium stearate filled directly into size 0 dark blue opaque capsules, identical in appearance to GLWL-01 150-mg capsules.

Capsules must be taken whole.

In Treatment Period 1, all eligible patients will undergo a single-blind (patients/caregiver) placebo lead-in phase, wherein they will receive 3 capsules of placebo BID for 14 days. Following this, patients will be randomly assigned to either GLWL-01 450 mg BID/placebo or placebo/GLWL-01 450 mg BID treatment sequence. During Treatment Period 1, patients will receive 3 capsules of 150-mg GLWL-01 (450-mg total dose) or identical matching placebo BID for 28 days.

Before Treatment Period 2, patients will undergo a 28-day Washout Period following which all patients will receive 3 capsules of placebo BID during the 14-day single-blind placebo lead-in phase.

During Treatment Period 2 double-blind treatment phase, patients will receive 3 capsules of 150-mg GLWL-01 (450-mg total dose) or identical matching placebo BID for 28 days. The double-blind treatment phases in both treatment periods must not exceed 28 days and patients must not administer the double-blind study drug beyond 28 days. The study drugs can be administered in fed or fasted conditions.

The investigator or designee is responsible for

- explaining the correct use of the study drug to patients and caregivers;
- verifying that instructions are followed properly;
- maintaining accurate records of study drug dispensation and collection;
- and returning all unused medications to sponsor or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

8. Discontinuation Criteria

Patient participation in the study may be discontinued for any of the following reasons:

- Enrollment in any other clinical study involving any study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- **Investigator's decision**: the investigator decides that the patient should be discontinued from the study.
- **Patient's/caregiver's decision**: the patient or caregiver requests to be discontinued from the study.
- **Sponsor's decision**: GLWL stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
- **Adverse event**: any SAE or a significant change in a laboratory value occurs that merits the study drug being discontinued and necessitates appropriate measures being taken. In this case, the sponsor is to be notified immediately.
- **Hepatic event or liver test abnormality**: Patients who are discontinued from using study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via electronic data entry.
  Discontinuation of the study drug for abnormal liver test results **should be** considered by the investigator when a patient meets 1 of the following conditions after consultation with the sponsor medical representative:

  - ALT or AST >5X ULN
  - ALT or AST >3X ULN along with 1 of the following criteria:
    - sustained for more than 2 weeks or
    - total bilirubin level (TBL) >2X ULN or
    - prothrombin time >1.5X ULN or
    - the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - ALP >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Marked prolongation of the QT/QTc interval >500 ms or >60 ms over baseline, judged medically significant following repeat ECG after 5 minutes of rest from the initial ECG.
- A clinically significant systemic hypersensitive reaction occurs following administration of the study drug (e.g., study drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension), that requires parenteral medication, does not respond to symptomatic medication, or result in clinical sequelae or an anaphylactic reaction.
- An elevated troponin I level (greater than 0.04 ng/mL); the patient must be referred for further evaluation.

- Patient has stopped eating or drinking for more than 24 hours.
- Requirement of prohibited concomitant medication.
- Patient failure to comply with protocol requirements or study-related procedures.
- Termination of the study by the sponsor or regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal.

Patient discontinuing from the study prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Appendix 5. Sampling Summary

This table summarizes the approximate number of samples and volumes for all sampling and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol GLWL-PWS Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number of Samples	Maximum Total Amount
Screening tests[a]	Blood	21 mL	1	21 mL
Standard laboratory tests[a]	Blood	2 mL	5	10 mL
Drug concentration	Blood	2 mL	14	28 mL
AG and UAG samples	Blood	4 mL	5	20 mL
On-study serum chemistry (includes serum thyroid-stimulating hormone, lipid panel, troponin, and serum pregnancy when done at the same time)	Blood	15 mL	5	75.0 mL
Total	Blood	-	-	154.0 mL
Hepatic monitoring[b]	Blood	3 - 30 mL	-	-

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly-designated Medical Monitor.

Appendix 8. Protocol Amendment GLWL-PWS(c) Summary [A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome]

Overview

Protocol GLWL-PWS [A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome] has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Troponin has been listed separately in the Schedule of Activities for clarification purposes; no changes have been made to laboratory draws
- Exclusion Criterion #23c flexibility added. The previous language explicitly prohibited enrolling patients on "any medications that prolong the QT/QTc interval."
    - The original request for adding the QTc prolonging medications to the exclusion criteria came from HC (Control #208160, CR File Number: HC6-24-c208160); and prompted amendment (a). However, the suggested wording from Health Canada stated the medications could be used "with caution," which was not accurately reflected in the amended protocol.
    - In addition, the criterion was prior to availability of QT/QTc data. We currently have data from 9 enrolled Prader-Willi patients that have completed between 5 and 9 visits in this study, in addition to 38 diabetes patients that received GLWL in a previous study (GLWL-SMP).
    - There has been no QT/QTc prolongation observed to date.
        1. In addition to regular ECGs to assess intervals, we are measuring troponins
        2. Prolongation of the QT/QTc interval >500 ms or >60 ms over baseline, judged medically significant following repeat ECG after 5 minutes of rest from the initial ECG remains a discontinuation criterion.
    - At this time, we feel there is enough evidence to proceed with the new wording for Exclusion Criteria #23c of, "Any medications that prolong the QT/QTc interval will be excluded, unless the patient has been stable on the medication for at least 3 months and has a QTc <450 msec at Visit 1 and Visit 3."

- Section 7.7 Concomitant Therapy verbiage has been updated to allow inclusion of patients on stable doses of medications that have been publicly noted to potentially cause QTc prolongation.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

Table GLWL-PWS.4. Schedule of Activities

Period	**Screening[a]**	**Treatment Period 1**			**Washout (28 days)**	**Treatment Period 2**				**Follow-up**	**ET[c]**
Phase		**Single-blind Placebo Lead-in Phase (14 days)**	**Double-blind Treatment Phase (28 days)[b]**			**Single-blind Placebo Lead-in (14 days)**	**Double-blind Treatment Phase (28 days)[b]**				
Visit No/ Type Procedure	**V1**	**V2[e] Phone**	**V3[d]**	**V4**	**V5**	**V6[e] Phone**	**V7[e] Phone**	**V8**	**V9**	**V10**	**V11**	
Day	**-28 to -3**	**0 (±3)**	**14 (±2)**	**21 (±2)**	**42 (±2)**	**56 (±2)**	**70 (±2)**	**84 (±2)**	**91 (±2)**	**112 (±2)**	**126 (±3)**	
12-lead ECG 2 hours post-dose[k]			X					X				
Serum pregnancy test[l]	X									X		X
Urine pregnancy test[l]			X					X				
Clinical chemistry and hematology[h]	X		X	X	X			X	X	X		X
Troponin			X	X	X			X	X	X		
Lipid panel			X		X			X		X		X
AG and UAG[m]			X		X			X		X		X
Plasma sample collection for PK analysis[n]			X		X							X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

6.2 Exclusion Criteria

23. Unable to refrain from or anticipates the use of

    a. Any drugs known to be significant inhibitors of cytochrome P450 (CYP)3A enzymes and/or P-glycoprotein (P-gp) including regular consumption of grapefruit or grapefruit juice for 14 days prior to the first dose of study medication and throughout the study. Appropriate sources will be consulted by the principal investigator (PI) or designee to confirm lack of PK or pharmacodynamic (PD) interaction with study medication. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study.
    b. Any drugs known to be significant inducers of CYP3A enzymes and/or P-gp, including St. John's Wort, for 28 days prior to the first dose of study medication and throughout the study. Appropriate sources will be consulted by the PI or designee to confirm lack of PK/PD interaction with study medication.
    c. Any medications that prolong the QT/QTc interval, unless the patient has been on a stable dose of said medication for at least 3 months and has a QTc <450 msec at Visit 1 and Visit 3.

7.7 Concomitant Therapy

Patients may not take any medication (including over-the-counter products), herbal products, or vitamin supplements, which are CYP3A and/or P-gp inhibitors for 14 days prior to dosing and throughout the study. In cases that require the use of such medication for the treatment of an AE or comorbidity, GLWL-01 dosing must be terminated before the CYP3A inhibitor can be started.

Medications that prolong the QT/QTc interval are ~~prohibited~~ acceptable, per the investigator's judgement. A list of medications with a potential for QTc prolongation will be provided separately ~~and updated as data evolves~~ to the investigators.

If the need for the initiation of other medication arises during the study, the investigator must consult with sponsor medical representative and such medication change must be reported in the EDC.

All medications taken by patients during the course of the study will be recorded. Concomitant medications will be listed by treatment and coded using the most current World Health Organization drug dictionary.

Appendix 9. Protocol Amendment GLWL-PWS(d) Summary [A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome]

Overview

Protocol GLWL-PWS [A Phase 2 Study to Evaluate Efficacy, Safety, and Pharmacokinetics of GLWL-01 in the Treatment of Patients with Prader-Willi Syndrome] has been amended. The new protocol is indicated by amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Language regarding QTc prolongation medications in Section 7.7, Concomitant Therapy, has been clarified at the request of Health Canada.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore.

7.7 Concomitant Therapy

Patients may not take any medication (including over-the-counter products), herbal products, or vitamin supplements, which are CYP3A and/or P-gp inhibitors for 14 days prior to dosing and throughout the study. In cases that require the use of such medication for the treatment of an AE or comorbidity, GLWL-01 dosing must be terminated before the CYP3A inhibitor can be started.

Medications that prolong the QT/QTc interval are allowed provided the patient has been on a stable dose of said medication for at least 3 months and has a QTc < 450 msec at Visit 1 and Visit 3.~~acceptable, per the investigator's judgement.~~ A list of medications with a potential for QTc prolongation will be provided separately to the investigators.

If the need for the initiation of other medication arises during the study, the investigator must consult with sponsor medical representative and such medication change must be reported in the EDC.

All medications taken by patients during the course of the study will be recorded. Concomitant medications will be listed by treatment and coded using the most current World Health Organization drug dictionary.