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TITLE PAGE

Protocol Title:

Phase 3, Randomized, Double-Blind, Placebo-Controlled, 8-week Clinical Study to Assess the Efficacy, Safety, and Tolerability, of Intranasal Carbetocin (LV-101) in Prader-Willi Syndrome (PWS) with Long Term Follow-Up: CARE-PWS

Protocol Number:

LV-101-3-01

Protocol Version Number:

3.0

Amendment Number:

4

Compound Number:

LV-101

Study Phase:

Phase 3

Indication:

Prader-Willi syndrome

Name and Address of Sponsor:

Levo Therapeutics, Inc.
5215 Old Orchard Road
Skokie, IL 60077

Investigational New Drug Number:

[redacted]

Medical Monitor Name and Contact

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Approval Date:

19 June 2019

APPROVAL

CONTENT

SIGNATURES

Clinical Document Title:	Phase 3, Randomized, Double-Blind, Placebo-Controlled, 8-week Clinical Study to Assess the Efficacy, Safety, and Tolerability, of Intranasal Carbetocin (LV-101) in Prader Willi Syndrome (PWS) with Long Term Follow-Up: CARE-PWS
Clinical Document Version No.:	3.0/Amendment 4.0
Version Date:	19 June 2019
Type of Document:	Clinical Study Protocol

By signing this document, I certify that I have reviewed and approve the above document.

Davis C. Ryman, MD, PhD Vice President, Clinical Development Levo Therapeutics, Inc.	**Signature**	**Date**
Jay Cormier, JD, PhD Vice President, Regulatory Affairs Levo Therapeutics, Inc.	**Signature**	**Date**
Sara Cotter Chief Executive Officer Levo Therapeutics, Inc.	**Signature**	**Date**

Ronald S. Pimentel, PhD Senior Biostatistician Innovative Analytics	**Signature**	**Date**

Amendment 4

Overall Rationale for the Amendment:

The purpose of this amendment is to add an exploratory endpoint to assess changes in social behaviors [redacted] and to add an extension period to the study, allowing subjects to continue to receive the investigational product, if receiving benefit. Additionally, the previous country-specific protocols for Canada and Australia (see Document History table below) have been incorporated into one harmonized document to serve all three participating countries (Canada, Australia, and United States).

DOCUMENT HISTORY	
Document	**Date**
Amendment 4/v3.0	19 Jun 2019
Amendment 3 (AUS)/v2.2	15 Mar 2019
Amendment 2 (CAN)/v2.1	20 Dec 2018
Amendment 1/v2.0	17 Sep 2018
Original Protocol	8 Aug 2018

Please see protocol Section 13 for a summary of changes from the previous version of the protocol.

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I confirm that I have read the Investigator's Brochure.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
  I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol.
  Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

Synopsis

Protocol Title:

Phase 3, Randomized, Double-Blind, Placebo-Controlled, 8-week Clinical Study to Assess the Efficacy, Safety, and Tolerability of Intranasal Carbetocin (LV-101) in Prader-Willi Syndrome (PWS) with Long Term Follow-Up: CARE-PWS

Sponsor:

Levo Therapeutics, Inc.

Number of Sites:

Approximately 20 sites

Planned Study Period:

Enrollment time: Approximately 12 months

Study Duration: Approximately 66 weeks per subject

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of 9.6 mg intranasal carbetocin (LV-101) 3 times per day versus placebo on PWS behavioral symptoms	• Change in Hyperphagia Questionnaire for Clinical Trials (HQ-CT) total score from baseline to Week 8 • Change in Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS) Severity Rating total score from baseline to Week 8
Secondary	
• To assess the efficacy of 3.2 mg intranasal carbetocin (LV-101) 3 times per day versus placebo on PWS behavioral symptoms	• Change in HQ-CT total score from baseline to Week 8 • Change in CY-BOCS Severity Rating total score from baseline to Week 8

Objectives and Endpoints (continued):

Objectives	Endpoints
• To assess the treatment effect of intranasal carbetocin (LV-101) versus placebo on a broader range of maladaptive behavioral symptoms, first assessing 9.6 mg/dose intranasal carbetocin (LV-101) then assessing 3.2 mg/dose intranasal carbetocin (LV-101)	• Change in PWS Anxiety and Distress Questionnaire (PADQ) score from baseline to Week 8 • Clinical Global Impression – Change (CGI-C) score at Week 8
• To further characterize the treatment effect of intranasal carbetocin (LV-101) versus placebo on hyperphagia-related behavioral symptoms (as assessed by the caregiver), looking specifically at factors that may be less impacted by environmental controls (ie, food security), first assessing 9.6 mg/dose intranasal carbetocin (LV-101) then assessing 3.2 mg/dose intranasal carbetocin (LV-101)	• Change in score of a subset of HQ-CT items (Questions 1,2,5,6,8,9) from baseline to Week 8 • Change in score of Question 9 of HQ-CT from baseline to Week 8
Safety	
• To assess the safety and tolerability of intranasal carbetocin (LV-101)	• Frequency, severity, and seriousness of adverse events during the study • Clinically significant changes in physical examinations, laboratory assessments, electrocardiograms, and vital signs during the study

Objectives and Endpoints (continued):

Objectives	Endpoints
[redacted]	

Study Design:

This is a Phase 3 study to assess the efficacy, safety, and tolerability of intranasal carbetocin (LV-101) in subjects with PWS. A randomized, double-blind, placebo-controlled study with an 8-week placebo-controlled period will be conducted in subjects who are 7 to 18 years of age with genetically confirmed PWS, documented Nutritional Phase 3 criteria, screening and baseline HQ-CT total scores ≥13, and screening and baseline CY-BOCS total scores ≥9. Approximately 175 subjects will be randomized and dosed (1:1:1) to 3.2 mg intranasal carbetocin (LV-101) or 9.6 mg intranasal carbetocin (LV-101) or placebo, administered 3 times per day before meals. Safety and tolerability will be assessed by adverse events, laboratory assessments, electrocardiograms, vital signs, and physical examinations (including nasal assessments). Efficacy will be assessed using both caregiver-reported and clinician-reported outcome measures as described above. Clinical study materials (carbetocin and placebo vials) will be blinded at the study level, ensuring the blind of the subject, caregiver, and study site.

After the 8-week placebo-controlled period, there will be a long-term follow-up period of 56 weeks during which all subjects will receive active treatment with intranasal carbetocin (LV-101). At Week 8, subjects who were randomized to placebo in the placebo-controlled period will be randomized (1:1) to 9.6 mg intranasal carbetocin (LV-101) or 3.2 mg intranasal carbetocin (LV-101) 3 times per day before meals.

The study will also include an extension period, wherein subjects receiving benefit during the long-term follow-up period will have an opportunity to continue receiving intranasal carbetocin [redacted]

Number of Participants:

The study will enroll and dose approximately 175 subjects. [redacted]

Major Inclusion/Exclusion Criteria:

Inclusion Criteria

1. Age: 7 to 18 years old at screening
2. Genetically confirmed PWS
3. PWS Nutritional Phase 3

[redacted]

7. Parent or guardian is capable of giving signed informed consent.
8. Pediatric subjects capable of assent have indicated their willingness to participate in the study.

Exclusion Criteria

1. Living in a group home
2. New food-related interventions, including environment or dietary restrictions, within 1 month of screening
3. Active upper respiratory infection at screening or baseline
4. Genetically diagnosed Schaaf-Yang syndrome or other genetic, hormonal, or chromosomal cognitive impairment
5. Presence of any cardiovascular disorders, epilepsy, frequent migraines, or severe asthma
6. History of or active psychotic symptoms
7. History of venous thrombosis or pulmonary embolism or any other history consistent with thrombophilia or hypercoagulable state that is considered clinically significant by the Investigator
8. Dose of any allowed chronic concomitant medications or supplements that have not been stable for ≥3 months prior to the study or is not expected to remain stable while participating in the study; adjustments in growth hormone dose ≤10% are not exclusionary
9. Major surgery within 6 months of screening or planned during the study
10. Nasal surgery within 6 months of screening or planned during the study
11. More than 3 episodes of sinusitis in the 12 months prior to Screening Visit
12. Other nasal diseases that may affect deposition of intranasal medication
13. Known hypersensitivity to any component of investigational product
14. Diagnosis of cancer within the past 5 years, except managed basal cell carcinoma or squamous cell carcinoma of the skin are not exclusionary

15. Unwilling to abstain from nasal saline, other nasal irrigation, or other intranasal medications for 2 weeks prior to the Baseline visit and during the 8-week, placebo-controlled period of the study
[redacted]
17. Use of weight loss medication in the 6 months prior to screening
18. Use of oxytocin or carbetocin in the 3 months prior to screening
19. Use of vasopressin in the 3 months prior to screening
20. Participation in an interventional research study involving another investigational medication or device in the 6 months prior to screening or during the study
21. History of (within the 2 years prior to screening) or current abuse of/dependence on alcohol or illicit drugs
22. Unwilling to follow protocol-specified contraception requirements
23. Positive urine pregnancy test for female subjects at screening or baseline (pregnancy testing will only be conducted for females of childbearing potential, as judged by the Investigator)
[redacted]
25. Based on the judgment of the Investigator, is unsuitable for the study for any reason, including but not limited to unstable medical condition, inability to comply with the protocol, or other risk to subject or to the integrity of the study

Intervention Groups and Duration:

Subjects who meet inclusion and exclusion criteria will be randomized to receive blinded investigational product to be administered intranasally 3 times per day before meals (ie, breakfast, lunch, and dinner) for 8 weeks.

Group Number	Treatment
1	9.6 mg/dose intranasal carbetocin (LV-101)
2	3.2 mg/dose intranasal carbetocin (LV-101)
3	Placebo

After the 8-week, double-blind, placebo-controlled period, there will be a long-term follow-up period of 56 weeks during which all subjects will receive active treatment with intranasal carbetocin (LV-101). At Week 8, subjects who were randomized to placebo in the placebo-controlled period will be randomized (1:1) to 9.6 mg intranasal carbetocin (LV-101) or 3.2 mg intranasal carbetocin (LV-101) 3 times per day before meals.

The study will also include an extension period, wherein subjects receiving benefit during the long-term follow-up period will have an opportunity to continue receiving intranasal carbetocin
[redacted]

[redacted]

Statistical Analysis:

The efficacy endpoints will be evaluated using the Full Analysis Set (ie, subjects who were randomized, completed baseline assessments, and received at least 1 dose of investigational product) unless indicated otherwise. [redacted]

Adverse events, clinical laboratory assessments, electrocardiogram, vital signs, and physical examination findings will be summarized.

A detailed description of the study statistical methods will be provided in the Statistical Analysis Plan.

Data Monitoring Committee:

A Data Monitoring Committee will be convened for the study.

Schedule of Assessments

The schedule of assessments for the placebo-controlled period is provided in Table 1, the schedule of assessments for the long-term follow-up period is provided in Table 2, and the schedule of assessments for the extension period is provided in Table 5. The schedule of assessments for questionnaires is provided in Table 3 for the placebo-controlled period and in Table 4 for the long-term follow-up period.

Table 1. Schedule of Assessments for the Placebo-Controlled Period

Procedure	Screening (14 to 28 days prior to Baseline)	Baseline Site Visit	Week 2 Site Visit (±2 days)	Week 8 Site Visit (±2 days)
Informed consent (ICF)/assent	X			
Inclusion and exclusion criteria	X	X		
Demography	X			
Medical history	X	X		
Physical examination	X	X	X	X
Nasal assessment	X	X	X	X
Vital signs (including weight)	X	X	X	X
Height	X			
Pregnancy test[a]	X	X	X	X
Laboratory assessments (chemistry, hematology, coagulation, urinalysis)	X	X	X	X
12-lead electrocardiogram	X	X		X
Randomization, if subject qualifies		X		X[b]
Training on investigational product administration		X		
Study drug dosing		X	ongoing	ongoing
Adverse event review		X	X	X
Serious adverse event review	X	X	X	X
Concomitant medication review (including all supplements)	X	X	X	X
Caregiver training on clinical outcomes assessments	X	X		
Structured interview, including clinical outcomes assessments by caregiver and clinician[c]	X	X	X	X
[redacted]				
Archive blood/plasma samples[e]		X	X	X

[a] Pregnancy testing will be conducted only for females of childbearing potential, as judged by the Investigator.

[b] At Week 8, subjects who were randomized to placebo in the placebo-controlled period will be randomized (1:1) to 9.6 mg/dose intranasal carbetocin (LV-101) 3 times per day before meals or 3.2 mg/dose intranasal carbetocin (LV-101) 3 times per day before meals.

[redacted]

Table 2. Schedule of Assessments for the Long-Term Follow-Up Period

Procedure	Week 10 (±2 Days)	Week 16 (±1 Week)	Week 28 (±1 Week)	Week 40 (±1 Week)	Week 52 (±1 Week)	Week 64 (±1 Week)	Early Term (if required)
Physical examination	X	X	X	X	X	X	X
Nasal assessment	X	X	X	X	X	X	X
Vital signs (including weight)	X	X	X	X	X	X	X
Height						X	X
Pregnancy test[a]	X	X	X	X	X	X	X
Laboratory assessments (chemistry, hematology, coagulation, urinalysis)	X	X	X	X	X	X	X
12-lead electrocardiogram		X				X	X
Study drug dosing	ongoing	ongoing	ongoing	ongoing	ongoing	X	
Extension period determination						X	
Adverse event review	X	X	X	X	X	X	X
Serious adverse event review	X	X	X	X	X	X	X
Concomitant medication review (including all supplements)	X	X	X	X	X	X	X
Structured interview, including clinical outcomes assessments by caregiver and clinician[b]	X	X	X	X	X	X	X
[redacted]							
Archive blood/plasma samples[d]	X	X	X	X	X	X	X

[redacted]

a [redacted]

Table 3. Schedule for the Questionnaires During the Placebo-Controlled Period

Instrument	Screening (14 to 28 days prior to Baseline)	Baseline Site Visit	Week 2 Site Visit (±2 days)	Week 8 Site Visit (±2 days)
PWS Nutritional Phase Assessment	X	X		
[redacted]				
Hyperphagia Questionnaire for Clinical Trials (HQ-CT)	X	X	X	X
[redacted]				
Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS)	X	X	X	X
[redacted]				
PWS Anxiety and Distress Questionnaire (PADQ)	X	X	X	X
[redacted]				
Clinical Global Impression	X[a]	X[a]	X[a]	X[a]
[redacted]				

[redacted] PWS = Prader Willi Syndrome

[a] Screening and baseline assessments will include only Severity. Post-baseline assessments will include Severity and Change.

Table 4. Schedule for the Questionnaires During the Long-Term Follow-Up Period

Instrument	Week 10 (±2 Days)	Week 16 (±1 Week)	Week 28 (±1 Week)	Week 40 (±1 Week)	Week 52 (±1 Week)	Week 64 (±1 Week)	Early Term (if required)
PWS Nutritional Phase Assessment						X	X
[redacted]							
Hyperphagia Questionnaire for Clinical Trials (HQ-CT)	X	X	X	X	X	X	X
[redacted]							
Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS)	X	X	X	X	X	X	X
[redacted]							
PWS Anxiety and Distress Questionnaire (PADQ)	X	X	X	X	X	X	X
[redacted]							
Clinical Global Impression	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
[redacted]							

[redacted] PWS = Prader Willi Syndrome; Term = termination

[a] Screening and baseline assessments will include only Severity. Post-baseline assessments will include Severity and Change.

Table 5. Schedule of Assessments for the Extension Period

Procedure	Week 64[b] (±1 Week)	Quarterly (±3 Weeks)	End of Study (EOS)/Early Term (ET)
Physical examination	X		X
Nasal assessment	X		X
Vital signs (including weight)	X		X
Height	X		X
Pregnancy test[a]	X		X
Laboratory assessments (chemistry, hematology, coagulation, urinalysis)	X		X
12-lead electrocardiogram	X		
Study drug dosing	ongoing	ongoing	
Extension period ICF/assent	X		

Procedure	Week 64[b] (±1 Week)	Quarterly (±3 Weeks)	End of Study (EOS)/Early Term (ET)
Extension period Enrollment	X		
Safety Phone call		X	
Adverse event review	X	X	X
Serious adverse event review	X	X	X
Concomitant medication review (including all supplements)	X	X	X
Structured interview, including clinical outcomes assessments by caregiver and clinician	X		
[redacted]			
Archive blood/plasma samples	X		

[redacted]

[a] Pregnancy testing will be conducted only for females of childbearing potential, as judged by the Investigator.

[b] Week 64 Visit of long-term follow-up period will serve as first visit of extension period

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List of Abbreviations

Abbreviation	Definition
CGI-C	Clinical Global Impression – Change
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CRO	contract research organization
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
eCRF	electronic case report form
EC	ethics committee
EOS	end of study
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hERG	human-ether-a-go-go-related gene
HPWSQ-R	Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IWRS	Interactive Web Response System
PADQ	PWS Anxiety and Distress Questionnaire
PWS	Prader-Willi syndrome
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
WHO-DD	World Health Organization drug dictionary

Abbreviations that appear only in tables or figures are defined with the relevant tables and figures.

1. Introduction

Prader-Willi syndrome (PWS) is a rare, serious, and life-threatening neurodevelopmental disorder that is caused by a defect on chromosome 15. In healthy individuals, several relevant genes in the 15q11-13 locus are expressed only from the paternal allele. The corresponding maternal allele is silenced (or "imprinted"), resulting in a complete reliance on the copy inherited from the father. When an individual lacks expression of these paternal genes, he/she develops PWS.

Following birth, neonates with PWS show profound hypotonia and failure to thrive, often requiring the use of feeding tubes during the first year. Developmental delays and mild to moderate intellectual disability become apparent in the early years. Following the failure-to-thrive period, young children with PWS show rising levels of interest in food and food-related items. By 7 or 8 years of age, patients with PWS are typically fixated on food and become hyperphagic (suffering from an unrelenting hunger and excessive drive to eat). Hyperphagia in PWS is associated with the lack of a normal satiety response, in addition to a low basal metabolic rate. Despite adequate energy reserves, these patients are subjected to a false state of starvation.

If left unsupervised, patients with hyperphagia are known to eat to the point of gastric rupture. Due to irregular swallowing and rapid food consumption, patients with PWS also have a greater propensity to choke while eating. Thus, hyperphagic patients require constant supervision. Patients with PWS also show high levels of anxiety, repetitive thinking/questioning, and obsessive and compulsive symptoms; these symptoms can be food-related as well as non-food related.

Today, the only therapy currently approved by the United States Food and Drug Administration (FDA) to treat PWS is human growth hormone, which is used to increase linear growth. There are no therapies approved to treat the hallmark features of PWS, specifically hyperphagia, anxiety, and obsessive and compulsive symptoms. Prader-Willi syndrome is a uniquely complex, serious, and life-threatening syndrome with significant unmet medical need.

While better known for its role in reproductive health and social-emotional behaviors, oxytocin is a potent anorectic hormone. Low doses of oxytocin injected intraperitoneally or intracerebroventricularly reduce food intake and the propensity to initiate feeding in wild-type rats in a dose-dependent manner [Arletti 1989]. Mice that are null for either oxytocin or the oxytocin receptor develop adult-onset obesity [Sabatier 2013]. Additionally, clinicians have identified an instructive group of patients that display a PWS-like phenotype and are deficient in oxytocin. These individuals have mutations in *SIM1*, a gene expressing a transcription factor important for developing oxytocin-producing neurons [Holder 2000]. In the corresponding *SIM1*-deficiency animal models, replacement of oxytocin rescues the hyperphagic phenotype. Postmortem studies in individuals with PWS have revealed significantly decreased numbers of oxytocin-secreting neurons in the paraventricular nucleus of the hypothalamus, suggesting that defects in the normal function of oxytocin may contribute to the severe hyperphagia and other behavioral symptoms characteristic of PWS [Swaab 1995]. In the aggregate, these data

demonstrate the anorexigenic properties of oxytocin and point to the potential utility of oxytocin and similar compounds in the treatment of PWS.

Intranasal oxytocin has demonstrated excellent safety and tolerability in clinical studies of patients with PWS [Miller 2017, Tauber 2017, Kuppens 2016, Einfeld 2014, Tauber 2011]. No serious adverse events occurred in any of these studies. However, efficacy results with oxytocin have been mixed, and higher doses of oxytocin have been associated with temper tantrums. The off-target effects of oxytocin on vasopressin receptors may be limiting its therapeutic window. Specifically, excessive activation of the vasopressin V1a receptor, which is implicated in anxiety and depression, may exacerbate PWS behavioral symptoms. Additionally, excessive activation of the vasopressin V2 receptor by oxytocin may be associated with increased risks of antidiuresis and hyponatremia.

Carbetocin, an 8 amino acid analog of oxytocin, is an oxytocin receptor agonist, which has similar potency to endogenous oxytocin, but possesses greater oxytocin receptor selectivity and longer duration of action [Engstrøm 1998]. Because carbetocin has greatly improved receptor selectivity compared to oxytocin, the potential side effects of oxytocin resulting from excessive activation of vasopressin receptors could be avoided.

Carbetocin is approved in multiple countries outside the United States for the prevention of uterine atony and excessive bleeding following delivery of the infant by caesarean section under epidural or spinal anesthesia, for which it is administered as a 100 µg intravenous injection over 1 minute. Since its approval in 1997, over 10 million women have been treated with carbetocin without significant safety concerns.

The route of administration of carbetocin currently approved outside the United States is delivery by intravenous injection. However, this route of delivery would be challenging when dosing chronically 3 times per day before meals. In contrast, intranasal administration of carbetocin appears to be a suitable route of delivery for chronic use.

1.1. Background

A brief overview of nonclinical and clinical findings for carbetocin is provided below. Further details are provided in the Investigator's Brochure.

1.1.1. Nonclinical Information

[redacted]

[redacted]

1.1.2. Clinical Pharmacokinetics

[redacted]

1.1.3. Clinical Efficacy

A prospective, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study (Study 000114) of 14 days of treatment with 9.6 mg/dose of intranasal carbetocin (LV-101) 3 times per day before meals was conducted in 37 subjects with genetically confirmed PWS, between the ages of 10 to 18 years, and with documented Nutritional Phase 3 criteria. Intranasal carbetocin (LV-101) was well tolerated and improved hyperphagia and behavioral symptoms of PWS in this study [Dykens 2018]. The primary efficacy endpoint was the change in Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness (HPWSQ-R) total score from baseline to Day 15. The HPWSQ-R was completed by the caregiver. A decrease in the HPWSQ-R total score indicates improvement in hyperphagia.

A statistically significantly greater decrease in the HPWSQ-R total score from baseline to Day 15 was observed for intranasal carbetocin (LV-101) compared to placebo. The least squares mean change from baseline to Day 15 for the intranasal carbetocin (LV-101) and placebo groups was -15.6 and -8.9, respectively (1-sided p=0.029).

Treatment group differences for the behavior, drive, and severity domain scores of the HPWSQ-R were directionally consistent with the total score, indicating that the effect of intranasal carbetocin (LV-101) was evident across a range of hyperphagic symptoms. The remaining secondary efficacy results (Clinical Global Impression – Improvement [CGI-I]; clinician-rated version of the HPWSQ-R total and domain scores; Children's Yale-Brown Obsessive Compulsive Scale [CY-BOCS]; and food domain of Reiss Profile) also indicated a statistically significant improvement of symptoms for the subjects in the intranasal carbetocin (LV-101) group when compared to the placebo group.

1.1.4. Clinical Safety and Tolerability

In the Phase 2 study (Study 000114) in subjects with PWS, there were no deaths, serious treatment-emergent adverse events (TEAEs), or severe TEAEs. One subject in the placebo group had an adverse event that led to withdrawal. A similar percentage of subjects in the intranasal carbetocin (LV-101) and placebo groups experienced at least 1 treatment-related TEAE (35.3% and 30.0%, respectively).

Headache was the only TEAE reported for more than 2 subjects in the intranasal carbetocin (LV-101) group (5 [29.4%] subjects). In the placebo group, headache (6 [30.0%] subjects) and

medication error (2 [10.0%] subjects) were reported for 2 or more subjects. There were no clinically important treatment group differences (>1 subject) for any individual TEAE.

[redacted]

1.2. Study Rationale

There are no therapies currently approved by the FDA to treat the hallmark features of PWS, specifically hyperphagia, anxiety, and obsessive and compulsive symptoms. Intranasal oxytocin has demonstrated excellent safety and tolerability in clinical studies of patients with PWS [Miller 2017, Tauber 2017, Kuppens 2016, Einfeld 2014, Tauber 2011]. No serious adverse events occurred in any of these studies. However, efficacy results with oxytocin have been mixed, and higher doses have been associated with temper tantrums in some cases. The off-target vasopressin effects of oxytocin may be limiting its therapeutic window. Specifically, activation of the vasopressin V1a receptor, which is implicated in anxiety and depression, may exacerbate PWS behavioral symptoms. Additionally, oxytocin activation of the vasopressin V2 receptor is associated with increased risks of antidiuresis and hyponatremia.

Carbetocin, an 8 amino acid analog of oxytocin, is an oxytocin receptor agonist which has similar potency to endogenous oxytocin, but possesses greater oxytocin receptor selectivity and longer duration of action [Engstrøm 1998]. Because carbetocin has greatly improved receptor selectivity compared to oxytocin itself, it may avoid the potential side effects of oxytocin related to off-target excessive activation of vasopressin receptors, creating a strong rationale for further development of carbetocin as a potential therapy for PWS.

As further described in Section 1.1.3 and Section 1.1.4, a Phase 2 study in subjects with PWS demonstrated that 14 days of treatment with intranasal carbetocin (LV-101) was safe and well tolerated, and was associated with encouraging evidence of improvement in hyperphagia and obsessive-compulsive symptoms.

For further evaluation of efficacy and safety across a range of dose levels, the current study will evaluate the safety and efficacy of 9.6 mg/dose and 3.2 mg/dose intranasal carbetocin (LV-101). This Phase 3 study is designed to assess the efficacy and safety of intranasal carbetocin (LV-101) through 8 weeks of double-blind treatment compared to placebo, and to further assess efficacy, safety, and tolerability during longer-term treatment with active carbetocin for 56 weeks.

The study will also include an extension period, wherein subjects receiving benefit during the long-term follow-up period will have an opportunity to continue receiving intranasal carbetocin

[redacted]

[redacted]

2. Objectives and Endpoints

Objectives and endpoints for the study are summarized in Table 5.

Table 5. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of 9.6 mg intranasal carbetocin (LV-101) 3 times per day versus placebo on PWS behavioral symptoms	• Change in HQ-CT total score from baseline to Week 8 • Change in CY-BOCS Severity Rating total score from baseline to Week 8
Secondary	
• To assess the efficacy of 3.2 mg intranasal carbetocin (LV-101) 3 times per day versus placebo on PWS behavioral symptoms	• Change in HQ-CT total score from baseline to Week 8 • Change in CY-BOCS Severity Rating total score from baseline to Week 8
• To assess the treatment effect of intranasal carbetocin (LV-101) versus placebo on a broader range of maladaptive behavioral symptoms, first assessing 9.6 mg/dose intranasal carbetocin (LV-101) then assessing 3.2 mg/dose intranasal carbetocin (LV-101)	• Change in PADQ score from baseline to Week 8 • CGI-C score at Week 8
• To further characterize the treatment effect of intranasal carbetocin (LV-101) versus placebo on hyperphagia-related behavioral symptoms (as assessed by the caregiver), looking specifically at factors that may be less impacted by environmental controls (ie, food security), first assessing 9.6 mg/dose intranasal carbetocin (LV-101) then assessing 3.2 mg/dose intranasal carbetocin (LV-101)	• Change in score of a subset of HQ-CT items (Questions 1,2,5,6,8,9) from baseline to Week 8 • Change in score of Question 9 of HQ-CT from baseline to Week 8

Table 5. Objectives and Endpoints (Continued)

Objectives	Endpoints
Safety	
• To assess the safety and tolerability of intranasal carbetocin (LV-101)	• Frequency, severity, and seriousness of adverse events during the study • Clinically significant changes in physical examinations, laboratory assessments, electrocardiograms, and vital signs during the study
[redacted]	

CGI-C = Clinical Global Impression – Change; CGI-S = Clinical Global Impression – Severity; [redacted] CY-BOCS = Children's Yale Brown Obsessive Compulsive Scale; [redacted] HQ-CT = Hyperphagia Questionnaire for Clinical Trials; [redacted] PADQ = PWS Anxiety and Distress Questionnaire; PWS = Prader-Willi syndrome [redacted]

3. Study Design

3.1. Overall Design

This is a Phase 3 study to assess the efficacy, safety, and tolerability of intranasal carbetocin (LV-101) in subjects with PWS. A randomized, double-blind, placebo-controlled study with an 8-week, placebo-controlled period will be conducted in subjects who are 7 to 18 years of age with genetically confirmed PWS, documented Nutritional Phase 3 criteria [redacted]
Approximately 175 subjects will be randomized and dosed (1:1:1) to 3.2 mg intranasal carbetocin (LV-101) or 9.6 mg intranasal carbetocin (LV-101) or placebo, administered 3 times per day before meals. Safety and tolerability will be assessed by adverse events, laboratory assessments, electrocardiograms, vital signs, and physical examinations (including nasal assessments). Efficacy will be assessed using both caregiver-reported and clinician-reported outcome measures as described in Section 2. Clinical study materials (carbetocin and placebo vials) will be blinded at the study level, ensuring the blind of the subject, caregiver, and study site.

After the 8-week double-blind, placebo-controlled period, there will be a long-term follow-up period of 56 weeks during which all subjects will receive active treatment with intranasal carbetocin (LV-101). At Week 8, subjects who were randomized to placebo in the placebo-controlled period will be randomized (1:1) to 9.6 mg intranasal carbetocin (LV-101) or 3.2 mg intranasal carbetocin (LV-101) 3 times per day before meals.

The study will also include an extension period, wherein subjects receiving benefit during the long-term follow-up period will have an opportunity to continue receiving intranasal carbetocin [redacted]

3.2. Scientific Rationale for Study Design

A randomized, double-blind, placebo-controlled, parallel-group study design is considered the gold standard for clinical research because it can provide unbiased estimates of efficacy and safety.

The inclusion criteria for age at enrollment (7 to 18 years of age), genetic confirmation of PWS, and PWS Nutritional Phase 3 assure that an appropriate population of hyperphagic subjects with PWS will be enrolled. [redacted] Exclusion criteria serve to assure subject safety and to exclude potentially confounding baseline factors.

A duration of 8 weeks of double-blind treatment with intranasal carbetocin (LV-101) versus placebo, followed by longer-term follow-up of subjects receiving active intranasal carbetocin

(LV-101) for a total of 56 weeks, is considered sufficient to demonstrate the efficacy, safety, and tolerability of intranasal carbetocin (LV-101).

3.3. Justification for Dose

In Phase 2 Study 000114, intranasal carbetocin (LV-101) 9.6 mg/dose was administered 3 times per day before meals for 14 days. A statistically significantly greater decrease in the HPWSQ-R total score from baseline to Day 15 was observed for intranasal carbetocin (LV-101) compared to placebo. Treatment group differences for the behavior, drive, and severity domain scores of the HPWSQ-R were directionally consistent with the total score, indicating that the effect of carbetocin was evident across a range of hyperphagic symptoms. The remaining secondary efficacy results (CGI-I; clinician-rated version of the HPWSQ-R total and domain scores; CY-BOCS; and food domain of Reiss Profile) also indicated a statistically significant improvement of symptoms for the subjects in the intranasal carbetocin (LV-101) group when compared to the placebo group. There were no deaths, serious TEAEs, or severe TEAEs in the study. There was some variability in drug exposure between subjects, as well as in the rate and extent of absorption within subjects from one dosing occasion to another. Neither subject's body weight, age, nor sex appeared to influence the systemic disposition of carbetocin in the studied population.

4. Study Population

4.1. Inclusion Criteria

Eligible subjects must meet ALL of the following inclusion criteria:

1. Age: 7 to 18 years old at screening
2. Genetically confirmed PWS
3. PWS Nutritional Phase 3

[redacted]

7. Parent or guardian is capable of giving signed informed consent
8. Pediatric subjects capable of assent have indicated their willingness to participate in the study.

4.2. Exclusion Criteria

Subjects who meet ANY of the following exclusion criteria are NOT eligible:

1. Living in a group home
2. New food-related interventions, including environment or dietary restrictions, within 1 month of screening
3. Active upper respiratory infection at screening or baseline
4. Genetically diagnosed Schaaf-Yang syndrome or other genetic, hormonal, or chromosomal cognitive impairment
5. Presence of any cardiovascular disorders, epilepsy, frequent migraines, or severe asthma

[redacted]

8. Dose of any allowed chronic concomitant medications or supplements that have not been stable for ≥3 months prior to the study or is not expected to remain stable while

participating in the study; adjustments in growth hormone dose ≤10% are not exclusionary
9. Major surgery within 6 months of screening or planned during the study
10. Nasal surgery within 6 months of screening or planned during the study
11. More than 3 episodes of sinusitis in the 12 months prior to Screening Visit
12. Other nasal diseases that may affect deposition of intranasal medication
13. Known hypersensitivity to any component of investigational product
14. Diagnosis of cancer within the past 5 years, except managed basal cell carcinoma or squamous cell carcinoma of the skin are not exclusionary
15. Unwilling to abstain from nasal saline, other nasal irrigation, or other intranasal medications for 2 weeks prior to the Baseline visit and during the 8-week, placebo-controlled period of the study
[redacted]
17. Use of weight loss medication in the 6 months prior to screening
18. Use of oxytocin or carbetocin in the 3 months prior to screening
19. Use of vasopressin in the 3 months prior to screening
20. Participation in an interventional research study involving another investigational medication or device in the 6 months prior to screening or during the study
21. History of (within the 2 years prior to screening) or current abuse of/dependence on alcohol or illicit drugs
22. Unwilling to follow protocol-specified contraception requirements
23. Positive urine pregnancy test for female subjects at screening or baseline (pregnancy testing will only be conducted for females of childbearing potential, as judged by the Investigator)
[redacted]
25. Based on the judgment of the Investigator, is unsuitable for the study for any reason, including but not limited to unstable medical condition, inability to comply with the protocol, or other risk to subject or to the integrity of the study

4.3. Lifestyle Considerations

There should be no new food-related interventions or restrictions from 1 month before screening until the end of the study.

All medications the subject is receiving (including over-the-counter therapies such as vitamins, herbal, and nutritional supplements) during the study will be recorded in the medical source data and the electronic case report form (eCRF).

5. Treatments

5.1. Treatments Administered

Subjects who meet inclusion and exclusion criteria will be randomized to receive blinded investigational product to be administered intranasally 3 times per day before meals (ie, breakfast, lunch, and dinner) for 8 weeks.

Group Number	Treatment
1	9.6 mg/dose intranasal carbetocin (LV-101)
2	3.2 mg/dose intranasal carbetocin (LV-101)
3	Placebo

After the 8-week, double-blind, placebo-controlled period, there will be a long-term follow-up period of 56 weeks during which all subjects will receive active treatment with intranasal carbetocin (LV-101). At Week 8, subjects who were randomized to placebo in the placebo-controlled period will be randomized (1:1) to 9.6 mg intranasal carbetocin (LV-101) or 3.2 mg intranasal carbetocin (LV-101) administered 3 times per day before meals.

Study drug should be administered with a minimum of 2.5 hours between each dose.

The study will also include an extension period, wherein subjects receiving benefit during the long-term follow-up period will have an opportunity to continue receiving intranasal carbetocin [redacted]

5.1.1. Investigational Product

Blinded investigational product, intranasal carbetocin or placebo, will be supplied [redacted] Each vial will provide 3 doses of investigational product for use in a 24-hour period.

[redacted]

The blinded doses of investigational product are described in Table 6.

Table 6. Investigational Product

Blinded Dose Group	9.6 mg/dose	3.2 mg/dose	Placebo
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

5.1.2. Placebo

Matching placebo will be provided for dosing during the 8-week placebo-controlled period. Placebo formulation will be identical to carbetocin formulations with the exceptions that carbetocin will not be present and the formulation will be adjusted to be isotonic (buffer will be increased to account for lack of carbetocin in the formulation).

5.1.3. Spray Pumps

Spray pumps [redacted] will also be provided for investigational product dosing. Instructions for spray pump use are provided in Section 5.2.

Spray pump incidents, including those resulting from malfunctions of the spray pump, must be detected, documented, and reported by the Investigator throughout the study (see Section 7.4).

5.2. Preparation/Handling/Storage/Accountability

5.2.1. First Dose of Investigational Product on Day 1 (Baseline Visit)

Starter packs (containing vials and spray pumps) will be provided to the study site. [redacted] Spray pumps will be stored [redacted] at room temperature.

The first dose of investigational product will be dispensed by the study site for observed dosing on Day 1. The Investigator, or trained and qualified designee, will train the caregiver on the process of assembly, priming, dosing, and storage.

[redacted]

Assembly: Just prior to dosing, the crimp seal and stopper must be removed from the [redacted] vial. The spray pump must be snapped into place, using the vial holder provided to prevent spilling. The Investigator or designee can demonstrate assembly using the first vial and the caregiver can assemble the second vial.

Priming: Once assembled, the spray pump must be primed by holding the vial upright and spraying it [redacted] into the bag provided or a plastic bag with a paper towel inside. After priming, close the bag and throw the bag away. The spray pump does not require additional priming before the second and third doses.

Dosing: Prior to dosing, the subject should blow his or her nose. Following priming, each dose of investigational product will be administered via 2 sprays into each nostril, administered alternating between nostrils (ie, left nostril, then right nostril, then left nostril, then right nostril), for a total of 4 sprays.

Study drug should be administered before meals with a minimum of 2.5 hours between each dose.

The Investigator, caregiver, or designee will record the dose of investigational product administered to the subject on a paper dosing diary. Caregivers will be trained that completed dosing diaries must be returned to the site staff at study visits.

[redacted] The clinical site is required to maintain current drug storage, dispensation, and accountability logs throughout the study.

5.2.2. Subsequent Doses of Investigational Product

Subsequent supplies of investigational product may be shipped to the caregiver's home or dispensed by the study site. [redacted]

Assembly: Prior to dosing, the crimp seal and stopper must be removed from the [redacted] vial. The spray pump must be snapped into place, using the vial holder provided to prevent spilling.

Priming: Once assembled, the spray pump must be primed by holding the vial upright and spraying it [redacted] into the bag provided or a plastic bag with a paper towel inside. After priming, close the bag throw the bag away. The spray pump does not require additional priming before the second and third doses.

Dosing: Prior to dosing, the subject should blow his or her nose. Following priming, each dose of investigational product will be administered via 2 sprays into each nostril, administered alternating between nostrils (ie, left nostril, then right nostril, then left nostril, then right nostril), for a total of 4 sprays.

Study drug should be administered before meals with a minimum of 2.5 hours between each dose.

The caregiver or designee will record all doses of investigational product administered to the subject on a paper dosing diary. Completed dosing diaries must be returned to the site staff at study visits.

5.3. Randomization and Blinding

Investigational product will be labelled with a unit number, such that the investigational product is blinded at the study level, preserving the blind for the Investigator, caregiver, and subject.

Subjects will be randomized (1:1:1) to 9.6 mg/dose intranasal carbetocin (LV-101), 3.2 mg/dose intranasal carbetocin (LV-101), or placebo. Subjects will be randomized on the day prior to Day 1 (first dose day) using the Interactive Web Response System (IWRS) according to instructions provided to the study site. The IWRS will provide a subject number and a unit number to be dispensed, maintaining the study blind for the Investigator, caregiver, and subject during the 8-week placebo-controlled period.

Subjects randomized to placebo in the placebo-controlled period will be randomized (1:1) to intranasal carbetocin at the 9.6 mg/dose or 3.2 mg/dose in the long-term follow-up period. Subjects will be randomized at the Week 8 site visit using the IWRS according to instructions provided to the study site. Subjects randomized to 9.6 mg/dose or 3.2 mg/dose intranasal carbetocin (LV-101) in the placebo-controlled period will continue on that same dose throughout the long-term follow-up period. Thus, all subjects will receive intranasal carbetocin (LV-101) during the long-term follow-up period; however, the actual investigational product dose will remain blinded to the Investigator, caregiver, and subject throughout the long-term follow-up period.

After all subjects complete Week 8, the database will be locked and treatment assignments will be unblinded for the purpose of analysis of study endpoints. Unblinded information will not be disclosed to investigators, caregivers, or patients during or following the Week 8 analysis.

5.4. Treatment Compliance

The investigational product will be dispensed only for subjects who meet the eligibility criteria and are randomized to a treatment in the study. The Investigator or his/her designated personnel

(eg, study nurse) will maintain a drug dispensing log detailing the dates and quantities of investigational products dispensed to, and used by, each subject, as well as the batch numbers.

The caregiver or designee will record all doses of investigational product administered to the subject on a paper dosing diary. Completed dosing diaries must be returned to the site staff at study visits.

Caregivers will be asked to return all used and unused investigational product containers to the study site or clinical study material management company.

5.5. Concomitant Therapy

At screening, use of any intranasal therapies (including nasal saline) during the preceding 6 months, any use of oxytocin or carbetocin, and all medications (including over-the-counter therapies such as vitamins, herbal, and nutritional supplements) within the preceding 30 days will be recorded in the medical source data and the eCRF.

Use of any concomitant therapy will be recorded in the medical source data and the eCRF, following the subject interview at each visit. Required information includes the drug name, strength, formulation, route of administration, dosing frequency, indication for use, start date, and stop date. Any changes (including new therapies) must be recorded at each subsequent study visit.

Every effort should be made to maintain concomitant medications at stable doses, if clinically possible. During the placebo-controlled period, if any change of dose of concomitant medication is judged medically necessary in the opinion of the Investigator, this should be discussed with Sponsor's medical monitor. During the active treatment period, changes to concomitant medications should be recorded in the medical source data and the eCRF.

During the active treatment period, if nasal saline, other nasal irrigation, or other intranasal medications are resumed, these treatments should be administered 1 hour before or after intranasal carbetocin (LV-101) administration. For once-daily administration of these treatments, bedtime dosing is recommended to separate dosing of nasal saline, other nasal irrigation, or other intranasal medications from intranasal carbetocin (LV-101) administration.

5.6. Prohibited Therapies

Prohibited therapies per exclusion criteria include:

- New food-related interventions, including environment or dietary restrictions, within 1 month of screening
- Unwilling to abstain from nasal saline, other nasal irrigation, or intranasal medications for 2 weeks prior to the Baseline visit and during the 8-week placebo-controlled period of the study

[redacted]

- Use of weight loss medication
- Use of oxytocin or carbetocin in the 3 months prior to screening
- Use of vasopressin

6. Discontinuation of Treatment and Withdrawal from Study

Every subject has the right to refuse further participation in the study at any time and without providing reasons. A subject's participation will be terminated immediately upon his/her request. The Investigator should obtain and document the reason for the subject's withdrawal, if possible.

If, at the time of refusal, a dose of investigational product has already been administered, the subject will be advised to agree to follow-up safety investigations, which will include all procedures outlined for the early termination visit, before withdrawal from the study. All adverse events will be monitored to resolution, and the subject will be monitored for new adverse events that may be related to withdrawal or are otherwise clinically important.

The subject may be withdrawn from the study at any time at the discretion of the Investigator; the reason should be discussed with the Sponsor prior to discontinuing the subject and fully documented in the site source documents. Should the subject, during the course of the study, develop conditions, which would have prevented his/her entry into the study according to the exclusion criteria, the Investigator should discuss with the Sponsor the risks and benefits to remaining in the study.

Subjects who withdraw from the study will not be replaced.

Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and the caregiver is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the caregiver and reschedule the missed visit as soon as possible, counsel the caregiver on the importance of maintaining the assigned visit schedule, and ascertain whether or not the family wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the caregiver (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the caregiver continue to be unreachable, the subject will be considered to have withdrawn from the study.

7. Study Assessments and Procedures

The schedule of assessments for the 8-week, placebo-controlled period is provided in Table 1, the schedule of assessments for the long-term follow-up period is provided in Table 2, and the schedule of assessments for the extension period is provided in Table 5. The schedule of assessments for questionnaires during the placebo-controlled period is provided in Table 3 and during the long-term follow period in Table 4.

During the first 16 weeks of the study, the visit window is ±2 days, measured from the baseline visit (not as measured from the previous visit). From Week 16 until the end of the study, the visit window is ±1 week (±7 days) as measured from the baseline visit (not as measured from the previous visit). During the extension period, the visit window is ±3 weeks (±21 days) as measured from the baseline visit (not as measured from the previous visit).

7.1. Efficacy and Pharmacokinetic Assessments

7.1.1. Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

The HQ-CT is a 9-item questionnaire designed to be completed by caregivers of subjects with PWS. It is a revision of the 11-item HPWSQ-R and has been further validated. The Foundation for Prader-Willi Research has made the HQ-CT available for clinical studies in PWS. As a result, it is the consensus instrument within the PWS research community. The HQ-CT is useful in measuring observable behaviors that stem from subjects' excessive drive to eat, but it is limited in its ability to assess the other important psychiatric symptoms and distress experienced in PWS. Given that some questions may be more sensitive to environmental controls, subsets of questions will also be analyzed.

The HQ-CT should be completed by the same caregiver throughout the study. A copy of the HQ-CT is provided in Section 12.1.

7.1.2. Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS)

The CY-BOCS is a validated, clinician rated, semi-structured inventory of specific symptoms and symptom severity in pediatric obsessive-compulsive disorder [Scahill 1997]. It is also commonly used in related disorders and performed well in the Phase 2 study of intranasal carbetocin (LV-101) in PWS. It includes 2 primary components: the symptom checklist and severity scale. The 10 severity items are summed to produce an obsessions severity score (5 items), compulsions severity score (5 items), and total score (sum of all 10 severity items). The symptom checklist contains common obsessions and compulsions seen in classical obsessive-compulsive disorder, but it also offers flexibility with the "other" write-in fields to enable the clinician to capture the unique obsessive and compulsive symptoms seen in PWS.

The scale will be administered by the Investigator or a designated rater (trained and qualified). For a given subject, the same person should perform this task around the same time throughout the study. A copy of the CY-BOCS is provided in Section 12.2.

7.1.3. PWS Anxiety and Distress Questionnaire (PADQ)

The PADQ is a caregiver-reported instrument designed to capture observable signs of anxiety and distress common among subjects with PWS. It has been developed in collaboration with a working group of 3 experienced researchers who are also parents of individuals with PWS. [redacted]

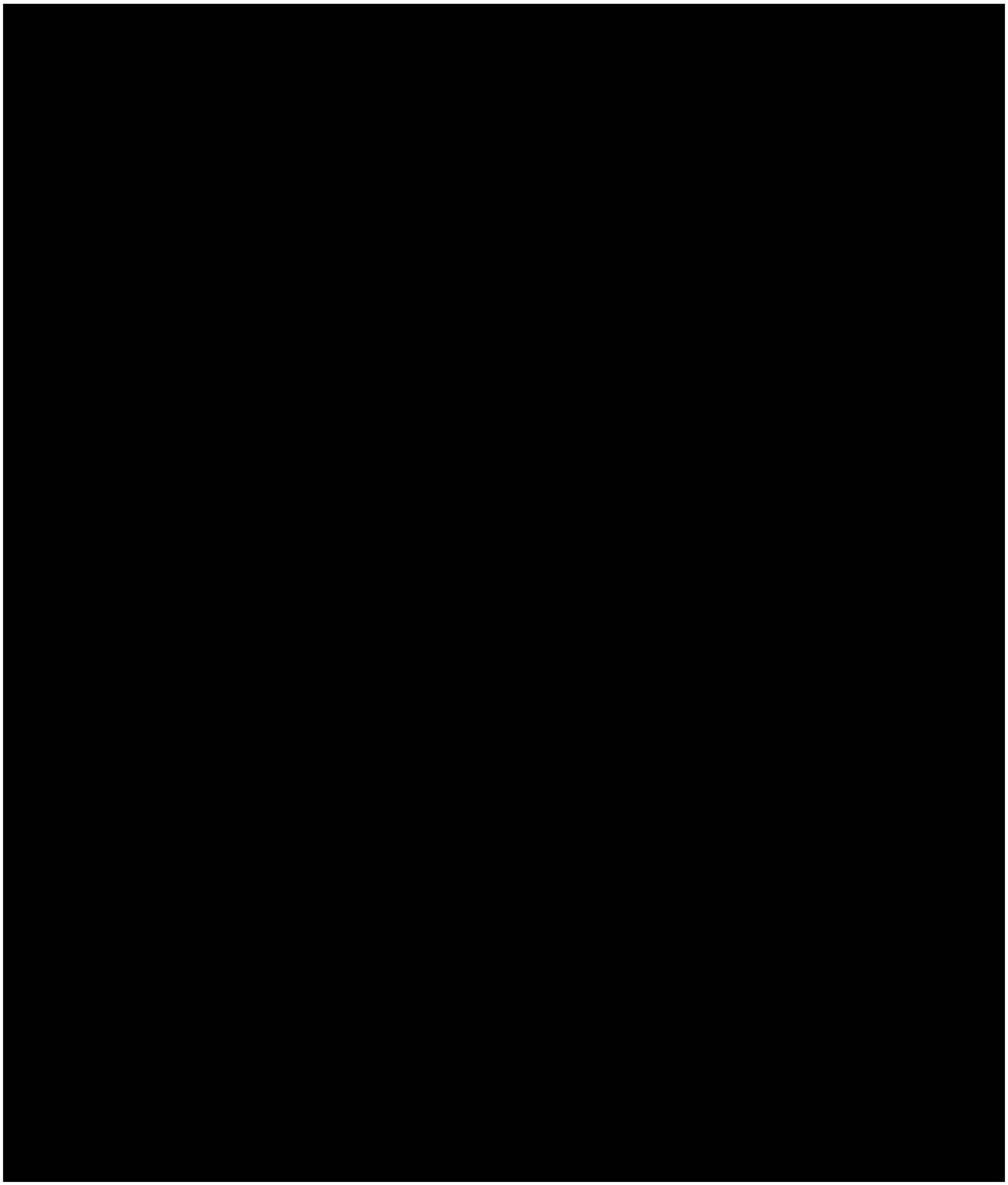
The PADQ should be completed by the same caregiver throughout the study. [redacted]

7.1.4. Clinical Global Impression – Severity (CGI-S) and Clinical Global Impression - Change (CGI-C)

The CGI-S is a rating scale which records a clinician's global impression of the current severity of illness on a 7-point scale, using a range of responses from 1 (normal) to 7 (among the most severely ill patients). The CGI-C is a similar rating scale which records a clinician's global impression of change in severity of illness, using a range of responses from 1 (very much improved) to 7 (very much worse) [Guy 1976].

The scale will be administered by the Investigator or a designated rater (trained and qualified). For a given subject, the same person should perform this task throughout the study. A copy of the CGI-S and CGI-C is provided in Section 12.4.

[redacted]



7.2. Safety Assessments

7.2.1. Medical History

A complete medical history will be obtained and documented. The history will include current conditions, and substance usage.

7.2.2. Physical Examinations

A complete physical examination including general appearance, head, eyes, ears, nose, and throat, neck, cardiovascular, thorax/lungs, breasts, abdomen, genitourinary, musculoskeletal, lymph nodes, skin, neurological and mental status examination, will be performed by the Investigator or a delegated Sub-Investigator (a medically licensed, qualified study team member). A thorough examination of the lower extremities for potential signs of deep venous thrombosis should be performed with each physical examination.

At screening and baseline, each category will be evaluated as normal, abnormal not clinically significant, or abnormal clinically significant. Abnormal clinically significant changes from baseline will be recorded as adverse events. Tanner staging will be recorded at the Screening Visit and the Week 64 or Early Termination visit.

7.2.3. Nasal Assessment

Grading will be conducted according to the following scale:

Grade 0 = no abnormal findings

Grade 1A = focal nasal mucosal inflammation, erythema, or hyperemia

Grade 1B = superficial nasal mucosal erosion

Grade 2 = moderate nasal mucosal erosion

Grade 3 = nasal mucosal ulceration

Grade 4 = nasal septum perforation

After randomization, Grades 3 and 4 will be documented as adverse events. If deemed appropriate, additional follow-up examinations will be performed at the discretion of the Investigator.

7.2.4. Vital Signs

Pulse, respiration rate, and body temperature will be measured under resting conditions while the subject is seated. All blood pressure measurements should be made using the same arm while the subject is in the supine position after resting for 3 minutes, and prior to any scheduled blood draws. Weight should be measured consistently for each subject with regard to time of day and time since last meal. Subjects should wear a hospital gown or underwear for weight and height measurements.

7.2.5. Electrocardiograms

A 12-lead electrocardiogram will be obtained after at least a 5-minute rest in a supine position, and prior to any scheduled blood draws. The baseline electrocardiogram must be measured prior to administration of investigational product.

7.2.6. Clinical Safety Laboratory Assessments

Samples may be drawn non-fasting and can be repeated fasting if judged necessary by the Investigator. Specific instructions for blood collection will be provided in a central laboratory manual to the study site for the United States and Canada. Clinical safety laboratory samples will be processed by each site's local laboratory in Australia.

Hematology, Coagulation, Serum Chemistry, and Urinalysis

Hematology: Platelet count, red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)

Coagulation: Prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen

Note: d-dimer (during placebo-controlled period only)

Serum chemistry: Calcium, chloride, sodium, potassium, glucose, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin (reflex to direct), creatinine, blood urea nitrogen, total protein, alkaline phosphatase, and albumin

Urinalysis: specific gravity, pH, glucose, protein, blood, urobilinogen by dipstick, and microscopic examination (if blood or protein is abnormal)

The Investigator will review laboratory results for abnormalities and clinical significance.

Pregnancy Testing

Urine pregnancy tests (ß-human chorionic gonadotropin) will be performed on females of childbearing potential, as assessed by the Investigator or a Sub-Investigator.

[redacted]

7.2.7. Extension Period Determination

During the Week 64 Visit and following consultation with the subject and caregiver, the investigator will make a determination whether continuing on intranasal carbetocin (LV-101) would be in the subject's best health interest by weighing the subject's documented clinical benefit against any safety concerns. Subjects for whom the investigator determines continuation would be appropriate will complete the extension period informed consent process and will be enrolled into the extension period to continue intranasal carbetocin (LV-101) treatment.

7.2.8. Safety Phone Call

Caregivers will be contacted by phone at least quarterly during the extension period. Clinical sites will document discussion of any adverse events and/or serious adverse events, concomitant medications, and any missed doses.

7.3. Adverse Events and Serious Adverse Events

7.3.1. Adverse Event Definition

An adverse event is any untoward medical occurrence in a subject participating in a clinical study.

A TEAE is any adverse event that begins or worsens after the first administration of investigational product. An unexpected adverse event is an adverse event not identified in nature, severity, or frequency in the Sponsor's current Investigator's Brochure.

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a subject suffers from the same adverse event more than once and the subject recovers in between the events, the adverse events should be recorded separately. If an adverse event

changes in intensity, a worst-case approach should be used when recording the event (ie, record the highest intensity and the longest duration of the event. However, if an adverse event with onset before the first investigational product administration (ie, a pre-treatment adverse event) changes in intensity, this must be recorded as 2 separate events. The initial adverse event should be recorded with outcome "not yet recovered" and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

Pre-existing conditions are not adverse events, but become adverse events if worsening occurs after investigational product administration during the study. Pre-existing clinically significant conditions diagnosed or observed as a result of the screening procedures must be recorded as medical history.

A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalization is not an adverse event; the reason for hospitalization is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

7.3.2. Collection and Recording of Adverse Events

The Investigator must monitor the condition of the subject throughout the study from the time of obtaining informed consent until 30 days after the last dose of study medication.

All serious adverse events will be collected from the signing of the informed consent form until 30 days after the last dose of study medication. Other adverse events will be collected from the Baseline Visit until 30 days after the last dose of study medication.

Investigators are not obligated to actively seek adverse events or serious adverse events after conclusion of study participation. However, if the Investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and the event is considered to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

7.3.3. Evaluation of Adverse Events

The Investigator must record all adverse events in the eCRF with information about:

- Date and time of onset (time can be omitted, if applicable)
- Severity/intensity
- Causal relationship to investigational product
- Action taken
- Outcome
- Date and time of outcome (time can be omitted, if applicable)
- Seriousness

7.3.3.1. Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

7.3.3.2. Severity/Intensity

The intensity of an adverse event must be classified using the following 3-point scale:

Mild:	Awareness of signs or symptoms, but no disruption of usual activity
Moderate:	Event sufficient to affect usual activity (disturbing)
Severe:	Inability to perform usual activities (unacceptable)

7.3.3.3. Relationship to Investigational Product

The possibility of whether the investigational product caused the adverse event must be classified as one of the following:

Possibly related: There is evidence or argument to suggest a causal relationship between the investigational product and the adverse event. The adverse event may occur as part of the pharmacological action of the investigational product or may be unpredictable in its occurrence. Examples may include:

- Adverse events that are uncommon but are known to be strongly associated with investigational product exposure
- Adverse events that are not commonly associated with investigational product exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association or the event recurs on rechallenge

Not related: There is no reasonable evidence or argument to suggest a causal relationship between the investigational product and the adverse event. Examples may include:

- Known consequences of the underlying disease or condition under investigation
- Adverse events common in the study population, which are also anticipated to occur with some frequency during the course of the study, regardless of investigational product exposure

7.3.3.4. Action Taken

The action taken with the investigational product in response to an adverse event must be classified as one of the following:

- No change (medication schedule maintained or no action taken)
- Study medication temporarily held
- Study medication discontinued

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the adverse event, this medication should be recorded (Section 5.5).

7.3.3.5. Outcome

The outcome of an adverse event will be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of study treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Not yet recovered
- Fatal

7.3.3.6. Date and Time of Outcome

The date that the subject recovered or died will be recorded. If the subject has not recovered or died at the time of study completion, the date of last adverse event follow-up will be recorded.

7.3.3.7. Serious Adverse Events

A serious adverse event is defined as an adverse event meeting any of the criteria in Table 8.

Table 8. Definition of Serious Adverse Event

Serious Adverse Event Criteria	Guidance
Results in death	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within 4 weeks after the treatment ends and irrespective of the causal relationship to the investigational product. The death of a subject enrolled in a study is per se not an event, but an outcome.
Is life-threatening	The term life-threatening refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Overnight stay for observation, stay at emergency room, or treatment on an outpatient basis do not constitute a hospitalization. However, medical judgment must always be exercised and when in doubt the case should be considered serious (ie, if case fulfills the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute a serious adverse event. Hospital admissions and/or surgical operations planned before study inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the study, provided that the condition did not deteriorate during the study.
Results in persistent or significant disability/incapacity	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgment by the Investigator.
Is a congenital anomaly/birth defect	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the investigational product.
Is an important medical event	Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include adverse events that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a medicinal product.

7.3.4. Follow-up of Adverse Events and Serious Adverse Events

During the study, the Investigator must follow each adverse event until it is resolved or until the medical condition of the subject is stable.

After the subject's last visit, the Investigator must follow any adverse event classified as serious or considered to have a reasonable possible causality to the investigational product until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to the Sponsor. If the event is a chronic condition, the Investigator and the Sponsor may agree that further follow-up is not required.

7.3.5. Reporting Requirements for Serious Adverse Events

All serious adverse events must be reported immediately to Levo Therapeutics, Inc. as soon as it becomes known to the Investigator and not later than within 24 hours of their knowledge of the occurrence of a serious adverse event.

The Investigator is responsible for submitting the completed Serious Adverse Event Report Form with the fullest possible details within 24 hours of his/her knowledge of the serious adverse event. The site will notify the Institutional Review Board (IRB)/Ethics Committee (EC) according to its guidelines.

The Serious Adverse Event Report Form must be completed and submitted according to the instructions provided on the form, using the email address below:

[redacted]

Demographic characteristics, adverse event information, medical history, and concomitant medication information are mandatory for initial reports and for follow-up reports if any relevant changes have been made since the initial report.

Additional information relevant to the serious adverse event such as hospital records, results from investigations (eg, laboratory parameters, invasive procedures, scans and x rays, and autopsy results) can sent to Levo Therapeutics, Inc. using the contact details above. In any case this information must be supplied by the Investigator upon request from Levo Therapeutics, Inc. On any copies provided, such details such as subject's name, address, and hospital identification number should be concealed and instead subject number should be provided.

The Investigator will supply Levo Therapeutics, Inc. and the IRB with any additional requested information, such as results of post-mortem examinations and hospital records.

Expedited Reporting by Levo Therapeutics, Inc.

Levo Therapeutics, Inc. will report to the relevant parties within the stipulated timelines all adverse events that are serious, unexpected (according to the Investigator's Brochure) and with a reasonable possible causality to the investigational product as judged by either the Investigator or Levo Therapeutics, Inc. Levo Therapeutics, Inc. will submit serious, unexpected, causally-related adverse event reports to Health Canada, the Australian Therapeutic Goods Administration (TGA), and the FDA within the timelines required by each regulatory authority.

Serious adverse events will be considered reportable regardless of whether or not the investigational product was used in accordance with the provisions in the protocol and Investigator's Brochure.

7.3.6. Pregnancy

Because of the young age of study subjects and the nature of the syndrome, it is considered likely that the majority of study subjects will not be sexually active. In the event that a subject is sexually active, the Investigator will confirm that the subject will, throughout participation in the study and at least 30 days following the last dose of study drug, either (1) remain abstinent from sexual intercourse or (2) use an effective barrier method or hormonal method of contraception. In such cases, the Investigator will discuss use of effective contraception with the subject and caregiver and the study medical monitor.

If a pregnancy occurs, the investigational product should be immediately stopped and the Sponsor must be informed. The mother and the fetus must be followed at least until the birth of the infant and 1 month after the birth of the infant. In general, the follow-up will include the course, duration, and the outcome of the pregnancy, as well as neonatal health.

While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy will be reported as an adverse event or serious adverse event. A spontaneous abortion is always considered to be a serious adverse event and will be reported as such. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly), this must be reported as a serious adverse event.

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. After obtaining signed informed consent from the pregnant female partner, the female partner will also be followed to determine the outcome of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure. A spontaneous abortion is always considered to be a serious adverse event and will be reported as such. If the pregnancy results in an abnormal outcome (birth defect/congenital anomaly this must be reported as a serious adverse event.

7.4. Intranasal Spray Pump Incidents (Including Malfunctions)

Intranasal spray pumps are being provided for use in this study for administration of investigational product. In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with the spray pumps.

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

A serious deterioration in state of health can include any of the following:

- life-threatening illness

- permanent impairment of body function or permanent damage to body structure
- condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death, or any congenital abnormality or birth defect

Examples of medical device incidents include:

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

NOTE: Incidents fulfilling the definition of an adverse event/serious adverse event will also follow the processes outlined in Section 7.3.

7.4.1. Time Period for Detecting Medical Device Incidents

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used. If the Investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

Documenting of medical device incidents include:

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the eCRF.
- For incidents fulfilling the definition of an adverse event or a serious adverse event, the appropriate adverse event/serious adverse event eCRF page will be completed.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the Sponsor) at the time of the initial adverse event or serious adverse event report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

7.4.2. Follow-up of Medical Device Incidents

All medical device incidents involving an adverse event will be followed and reported in the same manner as other adverse events (see Section 7.3). This applies to all participants, including those who discontinue study intervention.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident. New or updated information will be provided by the Investigator.

7.4.3. Prompt Reporting of Medical Device Incidents to the Sponsor

Medical device incidents will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device incident. Information regarding the medical device incident will be collected using a Spray Pump Incident Report Form. Medical device incidents should be emailed to: [redacted]

7.4.4. Regulatory Reporting Requirements for Medical Device Incidents

The Investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. The Investigator, or designee, will comply with the applicable local regulatory requirements relating to the reporting of medical device incidents to the IRB/EC.

7.5. Treatment of Overdose

No specific antidote is available. In the case of severe pharmacologic effects, intravenous infusion of hypotonic solutions should be avoided.

The size of the vial provided in this study helps to limit risk of overdose. If an overdose occurs, contact the Investigator and/or study coordinator. The subject should be monitored for seizures and behavioral changes (eg, aggressive behavior, temper tantrums, or other behavioral change).

8. Statistical Considerations

8.1. General Considerations

The objectives of this study are to evaluate the efficacy, safety and tolerability of intranasal carbetocin (LV-101) administered 3 times per day before meals in patients with PWS. The detailed description of the study statistical methods is provided in the Statistical Analysis Plan. Any deviations from the Statistical Analysis Plan will be described and justified in the final clinical study report.

8.2. Sample Size Determination

The study will enroll and dose approximately 175 subjects. The study alpha is specified to be 2-sided 0.05 with multiplicity control for the primary outcomes, thereby leading to study success if either outcome meets the statistical criterion. [redacted]

8.3. Analysis Sets

The following analysis sets will be defined for the study:

Intent-to-Treat Analysis Set: Subjects who were randomized. Subjects will be summarized in the treatment in which they were randomized.

Safety Analysis Set: Subjects who received at least 1 dose of investigational product. Subjects will be summarized according to the treatment actually received.

Full Analysis Set (FAS): Subjects in the Safety Analysis Set who completed baseline assessments.

[redacted]

8.4. Statistical Analyses

8.4.1. Efficacy Analyses

The efficacy endpoints will be evaluated using the FAS dataset unless indicated otherwise.

8.4.1.1. Primary Efficacy Endpoints

The primary efficacy endpoints are the HQ-CT total score change from baseline to Week 8 and the CY-BOCS total score change from baseline to Week 8 for 9.6 mg intranasal carbetocin (LV-101) versus placebo.

[redacted]

8.4.1.2. Secondary Efficacy Endpoints

The first secondary efficacy evaluation will be an analysis of the primary outcomes of HQ-CT total score change from baseline to Week 8 and the CY-BOCS total score change from baseline to Week 8 for the 3.2 mg intranasal carbetocin (low dose LV-101) group versus placebo, using the same model in Section 8.4.1.1. This first secondary efficacy assessment will act as a gatekeeper to subsequent secondary evaluations. If the first secondary evaluation fails, then subsequent secondary evaluations will become descriptive.

A fixed-sequence test procedure will then be performed to assess the following additional secondary efficacy endpoints in the order specified (hierarchical alpha protection).

- PADQ score change from baseline at Week 8
- CGI-C score at Week 8
- HQ-CT total score for Questions 1,2,5,6,8, and 9 change from baseline at Week 8
- HQ-CT score for Question 9 change from baseline at Week 8.

The previously described mixed model repeated measures analysis will be used when appropriate, with the comparison 9.6 mg intranasal carbetocin (LV-101) versus placebo tested first for each endpoint, followed by 3.2 mg intranasal carbetocin (LV-101) versus placebo.

[redacted]

8.4.2. Safety Analyses

Safety parameters will be listed and summarized for the safety population.

8.4.2.1. Adverse Events

Directly observed and spontaneously reported adverse events will be recorded from time of signing informed consent (serious adverse events only) through 30 days after the last dose of study medication. Adverse events will be coded using Medical Dictionary for Regulatory Activities, in which each reported event is mapped to a preferred term and a system organ class. A TEAE will be defined as an adverse event that was not present prior to the first investigational product administration or was present but worsened in intensity or frequency. All reported adverse events will be listed. Both TEAEs and non-TEAEs will be summarized, overall and by severity and seriousness. For each system organ class and preferred term within system organ classes, the numbers and percentages of subjects reporting an event, as well as the number of events that were reported, will be calculated. Deaths, adverse events that resulted in study discontinuation, severe adverse events, and serious adverse events will be listed and summarized separately.

8.4.2.2. Concomitant Medications

Prescription, over-the-counter, and alternative medication use will be coded to drug class, preferred drug name, and generic/trade drug name using the World Health Organization drug dictionary (WHO-DD). Medications that were stopped before the start of the investigational product administration procedure will be considered "pre-treatment." All other medications will be considered "concomitant." Medications that were started or ongoing at the time the investigational product administration procedure was started will be considered "baseline" (a subset of "concomitant"). All reported medications will be listed. Frequencies and percentages of subjects reporting or receiving each medication will be summarized by WHO-DD drug class and preferred name within drug class. Pre-treatment and baseline medications will be summarized separately.

8.4.2.3. Clinical Laboratory Assessment

Laboratory assessments will be listed and summarized by visit within each panel (eg, chemistry, hematology, etc.). Summary tables will show means of observed values and changes from baseline for observations on a continuous scale and distributions of categorical observations. Shift tables will be produced that will show frequencies and percentages of subjects who shift from one out-of-range category at baseline to another out-of-range category at subsequent visits.

8.4.2.4. Physical Examination

Observed status (eg, normal, abnormal) and changes from baseline in body system-specific physical examination findings will be summarized by visit within each body system.

8.4.2.5. Electrocardiogram, Vital Signs, and Weight

Observed values and changes from baseline will be summarized by visit.

8.5. Interim Analyses

After all subjects have completed the Week 8 visit (excluding drop-outs), the database will be locked and treatment assignments through Week 8 will be unblinded.

8.6. Data Monitoring Committee

A Data Monitoring Committee will be convened for the study.

9. Supporting Documentation and Operational Considerations

9.1. Data Handling

9.1.1. Source Data and Source Documents

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Source documents are defined as original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

The Investigator shall retain the source records for a period of 5 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or such longer period as required by regulatory authorities such as Health Canada, TGA, or FDA; or, if no application is to be filed or if the application is not approved for such indication, until 5 years after the investigation is discontinued and the FDA is notified. For each subject enrolled, the Investigator will indicate in the source record(s) that the subject participates in this study and will record all study-specific information including: any adverse event, any concomitant therapy, primary response variable(s), date of informed consent/assent, progress notes and status at treatment end, and the end of the subject's participation.

9.1.2. Electronic Case Report Form

An eCRF system provided by an independent third-party CRO will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Levo Therapeutics, Inc. and vendor procedures, in accordance with regulatory and system requirements.

Data should be entered into the system within 5 days after the subject has attended a visit or after the data become available, as applicable. Data entry of serious adverse events will be within 24 hours of the Investigator becoming aware. Also, applicable data (demographics, medical history, concomitant medication, etc.) must be entered at the time of entry of serious adverse event. The Investigator will approve/authorize the eCRF entries for each subject with an electronic signature which is equivalent to a handwritten signature.

Errors occurring in the eCRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

9.1.3. Data Management

A data management plan will be created and issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The data management plan will include who is authorized to enter the data, decisions about ownership of data, source data storage, which data will be transferred (including timing of transfers), the origin and destination of the data, and who will have access to the data at all times.

9.2. Monitoring Procedures

9.2.1. Periodic Monitoring

The monitor will contact and visit the Investigator periodically to ensure adherence to the protocol, International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP), standard operating procedures and applicable regulatory requirements, maintenance of study-related source records, and completeness, accuracy and verifiability of all eCRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies that may be identified are resolved. A monitoring visit will take place shortly after the first subject is enrolled at the site.

9.2.2. Audit and Inspection

The Investigator will make all the study-related source data and records, both paper and electronic, available to a quality assurance auditor mandated by the Sponsor, or to domestic or foreign regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects have been adequately protected, the protocol and standard operating procedures have been adhered to, and that all data relevant for the evaluation of the investigational product have been processed and reported in compliance with ICH-GCP and applicable regulatory requirements.

The Investigator should notify the Sponsor without any delay of an announced inspection by a regulatory authority.

9.2.3. Confidentiality of Subject Data

The Investigator will ensure that the confidentiality of the subject data will be preserved. In the eCRF or any other documents submitted to the Sponsor, the subjects will not be identified by their names, but by an identification system consisting of their initials and assigned number in the study. Documents not intended for submission to the Sponsor (eg, the confidential subject identification code and the signed informed consent forms) will be maintained by the Investigator in strict confidence.

9.3. Changes in the Conduct of the Study

9.3.1. Protocol Amendment

Any change to this protocol will be documented in a protocol amendment, issued by the Sponsor, and agreed upon by the Investigator and the Sponsor prior to its implementation.

Significant amendments will be submitted for consideration to the approving IRB(s)/ECs, and regulatory authorities, in accordance with local regulations.

An approval is required for a significant amendment (eg, one that could affect the safety of the subjects, or that entails a significant change of the scope/design of the study).

9.3.2. Deviations from the Protocol

Deviations from the protocol are discouraged. If deviations do occur, the Investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented with the visit number and type of violation. Any significant violations as determined by the Sponsor and/or IRB/EC must be reported to the IRB/EC. Any paper documentation must be kept in the Investigator's file and in the Trial Master File.

9.3.3. Early Termination of the Study

Both the Investigator (with regard to his/her participation) and the Sponsor reserve the right to terminate the study at any time. Should this become necessary, the procedures will be agreed upon after consultation between the 2 parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IRB(s)/ECs will be informed.

9.4. Publication Policy

Submission of data for journal publication and/or presentation of data to scientific audiences may be considered by Levo Therapeutics, Inc. The details of specific journal authorship will be discussed by the Investigator(s) and the Sponsor, with the final decision at the discretion of the Sponsor. If the Sponsor prepares a publication based on the results of this study, a copy of the manuscript will be provided to the Investigator(s) prior to publication. Investigator(s) may not separately publish data from the study without written authorization from the Sponsor.

Any external CRO or laboratory involved in the conduct of this study has no publication rights regarding this study.

10. Regulatory and Ethical Considerations

The responsibilities of Levo Therapeutics, Inc., the monitor, and the Investigator will be as defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the study takes place. The Investigator is responsible for adhering to the ICH-GCP responsibilities of Investigators, for dispensing the investigational product in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the study.

10.1. Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, ICH-GCP, and applicable regulatory requirements.

The regulatory permission to perform the study will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a subject is exposed to any study-related procedure, including screening tests for eligibility.

10.2. Informed Consent/Assent

The Investigator or designee will obtain a freely given written informed consent from each subject's caregiver, and signed assent by the subject (if applicable) after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the study that are relevant to the subject's decision to participate. The consent form must be signed and dated by the caregiver before the subject is exposed to any study-related procedure, including screening tests for eligibility. The assent form (if applicable) must also be signed and dated by the subject before exposure to any study-related procedure, including screening tests for eligibility.

The Investigator or designee will explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify their decision.

The subject and caregiver will receive a copy of any available subject information and signed consent/assent.

The subject and caregiver should be informed if new information becomes available that may be relevant to their willingness to continue participation in the study. The communication of this information should be documented and a new version of the informed consent and subject information form be prepared, if applicable.

Each subject and caregiver will be informed that the monitor, a quality assurance auditor mandated by the Sponsor, or a health authority inspector, in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with local and national regulations.

For subjects not qualified to give their legal consent, the written informed consent must be obtained from the legal caregiver in accordance with national regulations. If such subjects can

understand the risks and benefits of the study, they should also be informed and provide their written consent.

10.3. Institutional Review Board/Ethics Committee (EC)

An IRB or EC will review the protocol and any amendments and advertisements used for recruitment. The IRB/EC will review the informed consent/assent form, their updates (if any), and any written materials given to the subjects. A list of all IRBs/ECs consulted and the name of the committee chair(s) will be included in the study report.

At the end of the study the IRB/EC will be notified in writing.

10.4. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11. References

First Author, Year	Publication
Arletti, 1989	Arletti R, Benelli A, Bertolini A. Influence of oxytocin on feeding behavior in the rat. Peptides. 1989;10(1):89-93.
[redacted]	
Dykens, 2018	Dykens EM, Miller J, Angulo M, et al. Intranasal carbetocin reduces hyperphagia in individuals with Prader-Willi syndrome. JCI Insight. 2018 Jun 21;3(12). pii: 98333. doi: 10.1172/jci.insight.98333.
Einfeld, 2014	Einfeld SL, Smith E, McGregor IS, et al. A double-blind randomized controlled trial of oxytocin nasal spray in Prader Willi syndrome. Am J Med Genet A. 2014;164A(9):2232-9.
Engstrøm, 1998	Engstrøm T, Barth T, Melin P, Vilhardt H. Oxytocin receptor binding and uterotonic activity of carbetocin and its metabolites following enzymatic degradation. Eur J Pharmacol. 1998;355:203-10.
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Holder, 2000	Holder JL Jr, Butte NF, Zinn AR. Profound obesity associated with a balanced translocation that disrupts the *SIM1* gene. Hum Mol Genet. 2000;9(1):101-8.
Kuppens, 2016	Kuppens RJ, Donze SH, Hokken-Koelega AC. Promising effects of oxytocin on social and food-related behaviour in young children with Prader–Willi syndrome: a randomized, double-blind, controlled crossover trial. Clin Endocrinol (Oxf). 2016;85(6):979-87.
Miller, 2017	Miller JL, Tamura R, Butler MG, et al. Oxytocin treatment in children with Prader-Willi syndrome: a double-blind, placebo-controlled, crossover study. Am J Med Genet A. 2017;173(5):1243-50.
Sabatier, 2013	Sabatier N, Leng G, Menzies J. Oxytocin, feeding, and satiety. Front Endocrinol (Lausanne). 2013;4:35.
Scahill, 1997	Scahill L, Riddle MA, McSwiggin-Hardin M, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry. 1997;36:844–52.

Swaab, 1995	Swaab DF, Purba JS, Hofman MA. Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. J Clin Endocrinol Metab. 1995;80(2):573-9.
Tauber, 2017	Tauber M, Boulanouar K, Diene G, et al. The use of oxytocin to improve feeding and social skills in infants with Prader-Willi syndrome. Pediatrics. 2017;139(2).
Tauber, 2011	Tauber M, Mantoulan C, Copet P, et al. Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with Prader-Willi syndrome: a randomised placebo-controlled trial in 24 patients. Orphanet J Rare Dis. 2011;6:47.

12. Questionnaires

12.1. Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12.2. Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS)

Children's Yale-Brown Obsessive Compulsive Scale

CY-BOCS Obsessions Checklist

Check all symptoms that apply (items marked "*" may or may not be OCD Phenomena)

Current	Past	Contamination Obsessions
☐	☐	Concern with dirt, germs, certain illnesses (e.g., AIDS)
☐	☐	Concerns or disgust with bodily waste or secretions (e.g. urine, feces, saliva)
☐	☐	Excessive concern with environmental contaminants (e.g., asbestos, radiation, toxic waste)
☐	☐	Excessive concern with household items (e.g., cleaners, solvents)
☐	☐	Excessive concern about animals / insects
☐	☐	Excessively bothered by sticky substances or residues
☐	☐	Concerned will get ill because of contaminant
☐	☐	Concerned will get others ill by spreading contaminant (aggressive)
☐	☐	No concern with consequences of contamination other than how it might feel *
☐	☐	Other (describe) _____
		Aggressive Obsessions
☐	☐	Fear might harm self
☐	☐	Fear might harm others
☐	☐	Fear harm will come to self
☐	☐	Fear harm will come to others (maybe because of something child did or did not do)
☐	☐	Violent or horrific images
☐	☐	Fear of blurting out obscenities or insults
☐	☐	Fear of doing something embarrassing *
☐	☐	Fear will act on unwanted impulses (e.g., to stab a family member)
☐	☐	Fear will steal things
☐	☐	Fear will be responsible for something else terrible happening (e.g. ,fire, burglary, flood)
☐	☐	Other (describe) _____

Current	Past	Sexual Obsessions
☐	☐	Forbidden or perverse sexual thoughts, images, impulses
☐	☐	Content involves homosexuality
☐	☐	Sexual behavior towards others (aggressive)
☐	☐	Other (describe) _____
		Hoarding / Saving Obsessions
☐	☐	Fear of losing things
☐	☐	Other (describe) _____
		Magical Thoughts / Superstitious Obsessions
☐	☐	Lucky / unlucky numbers, colors, words
☐	☐	Other (describe) _____
		Somatic Obsessions
☐	☐	Excessive concern with illness or disease *
☐	☐	Excessive concern with body part or aspect of appearance (e.g. dysmorphophobia) *
☐	☐	Other (describe) _____
		Religious Obsessions
☐	☐	Excessive concern or fear of offending religious objects
☐	☐	Excessive concern with right / wrong morally
☐	☐	Other (describe) _____
		Miscellaneous Obsessions
☐	☐	The need to know or remember
☐	☐	Fear of saying certain things
☐	☐	Fear of not saying just the right thing
☐	☐	Intrusive (non-violent) images
☐	☐	Intrusive sounds, words, music or numbers
☐	☐	Other (describe) _____

Target Symptom List for Obsessions

OBSESSIONS (describe, listing by order of severity, with #1 being the most sever, #2 second most severe, etc):

1. _____
2. _____
3. _____
4. _____

CY-BOCS Compulsions Checklist

Check all symptoms that apply (items marked "*" may or may not be OCD Phenomena)

Current	Past	Washing / Cleaning Compulsions
☐	☐	Excessive or ritualized hand washing
☐	☐	Excessive or ritualized showering, bathing, tooth brushing, grooming, toilet routine
☐	☐	Excessive cleaning of items, such as personal clothes or important objects
☐	☐	Other measures to prevent or remove contact with contaminants
☐	☐	Other (describe)_____
		Checking Compulsions
☐	☐	Checking locks, toys, school books / items, etc.
☐	☐	Checking associated with getting washed, dressed, or undressed
☐	☐	Checking that did not / will not harm others
☐	☐	Checking that did not / will not harm self
☐	☐	Checking that nothing terrible did / will happen
☐	☐	Checking that did not make mistake
☐	☐	Checking tied to somatic obsessions
☐	☐	Other (describe)_____
		Repeating Rituals
☐	☐	Rereading, erasing, or rewriting
☐	☐	Need to repeat activities (e.g. In / out of doorway, up / down from chair)
☐	☐	Other (describe)_____
		Counting Compulsions
☐	☐	Objects, certain numbers, words, etc.
☐	☐	Other (describe)_____
		Ordering / Arranging
☐	☐	Need for symmetry / evening up (e.g. lining items up a certain way or arranging personal items in specific patterns)
☐	☐	Other (describe)_____

Current	Past	Hoarding / Saving Compulsions
		Distinguish from hobbies and concern with objects of monetary or sentimental value.
☐	☐	Difficulty throwing things away, saving bits of paper, string, etc.
☐	☐	Other (describe)_____
		Excessive Games / Superstitious Behaviors
☐	☐	Distinguish from age appropriate magical games (e.g. array of behavior, such as sleeping over certain spots on a floor, touching an object / self certain number of times as a routine game to avoid something bad from happening
☐	☐	Other (describe)_____
		Rituals Involving Other Persons
☐	☐	The need to involve another person (usually a parent) in ritual (e.g. asking a parent to repeatedly answer the same question, making mother perform certain mealtime rituals involving specific utensils) *
☐	☐	Other (describe)_____
		Miscellaneous Compulsions
☐	☐	Mental rituals other than checking / counting
☐	☐	Need to tell, ask or confess
☐	☐	Measures (not checking) to prevent :
☐	☐	harm to self
☐	☐	harm to others
☐	☐	terrible consequences
☐	☐	Ritualized eating behaviors *
☐	☐	Excessive list making *
☐	☐	Need to touch, tap, rub *
☐	☐	Need to do things (e.g. touch or arrange until it feels just right) *
☐	☐	Rituals involving blinking or staring *
☐	☐	Trichotillomania (hair-pulling)
☐	☐	Other self-damaging or self-mutilating behaviors *
☐	☐	Other (describe)_____

Administering the CY-BOCS Symptom Checklist and CY-BOCS Severity Ratings

1. Establish the diagnosis of obsessive compulsive disorder.
2. Using the CY-BOCS Symptom Checklist (other form), ascertain current and past symptoms.
3. Next, administer the 10-item severity ratings (below) to assess the severity of the OCD during the last week.
4. Readminister the CY-BOCS Severity Rating Scale to monitor progress.

Patient _____

Date 1st Report _____ Date This Report _____

Obsession Rating Scale (circle appropriate score)

Note: Scores should reflect the composite effect of all the patient's obsessive compulsive symptoms.
Rate the average occurrence of each item during the prior week up to and including the time of interview.

QUESTIONS ON OBSESSIONS (ITEMS 1-5) *"I AM NOW GOING TO ASK YOU QUESTIONS ABOUT THE THOUGHTS YOU CANNOT STOP THINKING ABOUT."*
(Review for the informant(s) the Target Symptoms and refer to them while asking questions 1-5).

1. Time Occupied by Obsessive Thoughts [Be sure to exclude ruminations and preoccupations which, unlike obsessions, are ego-syntonic and rational (but exaggerated)]	None	Mild less than 1 hr/day or occasional intrusion	Moderate 1 to 3 hrs/day or frequent intrusion	Severe greater than 3 and up to 8 hrs/day or very frequent intrusion	Extreme greater than 8 hrs/day or near constant intrusion
Score	0	1	2	3	4
2. Interference Due to Obsessive Thoughts • How much do these thoughts get in the way of school or doing things with friends? • Is there anything that you don't do because of them? (If currently not in school, determine how much performance would be affected if patient were in school)	None	Mild slight interference with social or school activities, but overall performance not impaired	Moderate definite interference with social or school performance, but still manageable	Severe causes substantial impairment in social or school performance	Extreme incapacitating
Score	0	1	2	3	4
3. Distress Associated with Obsessive Thoughts	None	Mild infrequent, and not too disturbing	Moderate frequent, and disturbing, but still manageable	Severe very frequent, and very disturbing	Extreme near constant, and disabling distress/frustration
Score	0	1	2	3	4
4. Resistance Against Obsessions • How hard do you try to stop the thoughts or ignore them? (Only rate effort made to resist, not success or failure in actually controlling the obsessions. If the obsessions are minimal, the patient may not feel the need to resist them. In such cases, a rating of "0" should be given.)	None makes an effort to always resist, or symptoms so minimal doesn't need to actively resist	Mild tries to resist most of the time	Moderate makes some effort to resist	Severe yields to all obsessions without attempting to control them, but does so with some reluctance	Extreme completely and willingly yields to all obsessions
Score	0	1	2	3	4
5. Degree of Control Over Obsessive Thoughts	Complete Control	Much Control usually able to stop or divert obsessions with some effort and concentration	Moderate Control sometimes able to stop or divert obsessions	Little Control rarely successful in stopping obsessions, can only divert attention with difficulty	No Control experienced as completely involuntary, rarely able to even momentarily divert thinking
Score	0	1	2	3	4

Obsession subtotal (add items 1-5) _____

QUESTIONS ON COMPULSIONS (ITEMS 6-10) *"I AM NOW GOING TO ASK YOU QUESTIONS ABOUT THE HABITS YOU CAN'T STOP"*
(Review for the informant(s) the Target Symptoms and refer to them while asking questions 6-10)

6. Time Spent Performing Compulsive Behaviors

	None	Mild less than 1 hr/day	Moderate 1 to 3 hrs/day	Severe greater than 3 & up to 8 hrs/day	Extreme greater than 8 hrs/day
Score	0	1	2	3	4

7. Interference Due to Compulsive Behaviors
- How much do these habits get in the way of school or doing things with friends?
- Is there anything you don't do because of them? (If currently not in school, determine how much performance would be affected if patient were in school.)

	None	Mild slight interference with social or school activities, but overall performance not impaired	Moderate definite interference with social or school performance, but still manageable	Severe causes substantial impairment in social or school performance	Extreme incapacitating
Score	0	1	2	3	4

8. Distress Associated with Compulsive Behavior
- How would you feel if prevented from carrying out your habits? How upset would you become?

	None	Mild only slightly anxious if compulsions prevented	Moderate anxiety would mount but remain manageable if compulsions prevented	Severe prominent and very disturbing increase in anxiety if compulsions interrupted	Extreme incapacitating anxiety from any intervention aimed at modifying activity
Score	0	1	2	3	4

9. Resistance Against Compulsions
- How much do you try to fight the habits? (Only rate effort made to resist, not success or failure in actually controlling the compulsions.)

	None makes an effort to always resist, or symptoms so minimal doesn't need to actively resist	Mild tries to resist most of the time	Moderate makes some effort to resist	Severe yields to all obsessions without attempting to control them, but does so with some reluctance	Extreme completely and willingly yields to all obsessions
Score	0	1	2	3	4

10. Degree of Control Over Compulsive Thoughts
- How strong is the feeling that you have to carry out the habit(s)?
- When you try to fight them, what happens?

	Complete Control	Much Control experiences pressure to perform the behavior, but usually able to exercise voluntary control over it	Moderate Control moderate control, strong pressure to perform behavior, can control it only with difficulty	Little Control little control, very strong drive to perform behavior, must be carried to completion, can only delay with difficulty	No Control no control, drive to perform behavior experienced as completely involuntary and overpowering, rarely able to delay activity [even momentarily]
Score	0	1	2	3	4

Compulsion subtotal (add items 6-10) _____

CY-BOCS total (add items 1-10) ☐

Total CY-BOCS score: range of severity for patients who have both obsessions and compulsions

0-7	**Subclinical**	**24-31**	**Severe**
8-15	**Mild**	**32-40**	**Extreme**
16-23	**Moderate**		

12.4. Clinical Global Impression – Severity (CGI-S) and Clinical Global Impression Change (CGI-C)

Clinical Global Impression-Severity Rating
Subject Number_____ Rater_____
Age_____ Genetic subtype of PWS_____ Date of visit_____

The CGI is usually rated relative to the past seven days (including the day of the visit up to and through the visit).

CGI-Severity (CGI-S) Considering your total clinical experience with Prader-Willi syndrome population; how ill is this patient at this time? *(Which is rated on a 7 point scale-circle one answer)*

1=Normal, Not at all ill
2=Borderline ill
3=Mildly ill
4=Moderately ill
5=Markedly ill
6=Severely ill
7=Among the most extremely ill patients

CGI-Improvement (CGI-I) Compared to the patient's condition at baseline visit, this patient's condition is: (circle one) Minimal amount of improvement needed for clinical meaningfulness.

1=Very Much Improved since baseline (initiation of treatment)
2=Much Improved
3=Minimally Improved
4=No Change from baseline
5=Minimally worse
6=Much Worse
7=Very Much Worse from baseline