FERRING
PHARMACEUTICALS

Protocol

Title of trial: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Intranasal Carbetocin in Subjects with Prader-Willi Syndrome (PWS)
NCT number: NCT01968187
Sponsor trial code: 000114
Date: 10-Feb-2014

CLINICAL TRIAL PROTOCOL

A Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Intranasal Carbetocin in Subjects with Prader-Willi Syndrome (PWS)

Trial Code 000114

IND Number:	112,521
Investigational Medicinal Product:	Carbetocin (FE 992097)
Indication:	Treatment of hyperphagia behavioral symptoms in children and adults diagnosed with PWS
Phase:	2a
Name and Address of Sponsor:	Ferring International Pharmascience Center U.S., Inc. 4 Gatehall Drive, 3rd Floor Parsippany, NJ 07054 Phone: 973-796-1600 Fax: 973-796-1663
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Intranasal Carbetocin in Subjects with Prader Willi Syndrome (PWS)

SIGNATORY INVESTIGATOR(S)

No signatory investigator(s) will be appointed for this trial.

TRIAL SITE(S)

The trial will be conducted at approximately 3 sites in the United States.

PLANNED TRIAL PERIOD	**CLINICAL PHASE**
Enrollment time: Approximately 6 months Trial duration: Approximately 8 months	2a

OBJECTIVES

Primary objective

- To assess the effect of intranasal carbetocin (FE 992097) on hyperphagia behavioral symptoms in subjects with Prader-Willi Syndrome (PWS), measured by the Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness (HPWSQ-R) scale – completed by the subject's parent/caregiver

Secondary objectives

- To assess the effect of intranasal carbetocin (FE 992097) on hyperphagia behavioral symptoms in subjects with Prader-Willi Syndrome (PWS), measured by the Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness – Clinician (HPWSQ-R-C) scale – administered by the clinician
- To assess improvement of PWS symptoms, assessed by the Clinical Global Impression (CGI) scale
- To assess safety and tolerability of intranasal carbetocin
- To assess a population pharmacokinetic model for the patient population utilizing sparse data sampling
- To assess the effects of intranasal carbetocin on PWS maladaptive behaviors, assessed by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
- To assess the sensitivity of Food Domain of the Reiss Profile

ENDPOINTS

Primary endpoint

Change in HPWSQ-R total score from Visit 2 to Visit 4

Secondary endpoints

1. Clinical Global Impression-Improvement after treatment (CGI-I) at Visit 4
2. Change from Visit 2 to Visit 4 for the following measurements:
   - HPWSQ-R hyperphagia behavior, drive, and severity domain scores
   - HPWSQ-R-C total score
   - HPWSQ-R-C hyperphagia behavior, drive, and severity domain scores
3. Change from Visit 1 to Visit 4 for the following measurements:
   - CY-BOCS score
   - Food Domain of the Reiss Profile
4. Population PK/PD relationships for carbetocin

Safety endpoints:

- Frequency, severity and seriousness of adverse events
- Clinically significant changes in vital signs
- Clinically significant findings during physical and laboratory assessments
- Physical examinations, including focused nasal examinations and nasal irritation, graded 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

METHODOLOGY

This is a prospective, double-blind, placebo-controlled, parallel trial in subjects with PWS between 10 and 18 years of age with genetically confirmed diagnosis of PWS and a documented nutritional phase 3 based on the criteria of Miller et al, 2011. Since PWS is a rare condition, and individuals with PWS are generally treated at a few centers of excellence throughout the country, it is expected that a significant proportion of eligible subjects will reside at a considerable geographic distance from the investigational site(s), requiring ground or air transportation to complete trial visits. The trial design considers both the geographic challenges, as well as the need to ensure subjects' home-life "normalcy" during the trial in order to accurately assess treatment effect. The trial includes a Screening Period, a 14-day Treatment Period, and a Follow-Up Period. Subjects, along with their parent/caregiver, will be required to visit the investigational site 4 times over the course of the trial and participate in 2 phone call assessments.

- Visit 1: Screening Period (Day -7 to Day 0)
- Visit 2: Baseline 1st day dosing on site (Day 1)
- Visit 3: 2nd day dosing on site (Day 2)
- Phone call assessment (Day 8±1)
- Visit 4: End-of-Treatment Visit (Day 15)
- Follow-up phone call (Day 19±3)

Following appropriate informed consent procedures, subjects will undergo screening evaluations to determine eligibility before randomization. Screening evaluations include a physical examination, vital signs, 12-lead electrocardiogram (ECG), and laboratory assessments - hematology, clinical chemistry, hemostasis, and urinalysis. After randomization, efficacy measures and other assessments, including physical examination, vital signs, and collection of blood samples for clinical laboratory and pharmacokinetic evaluation, will be performed at selected visits according to the Trial Flow Chart (Table 1). Subjects will be closely monitored for adverse events throughout the trial.

Prior to first dosing at the investigational site, parents/caregivers will be trained on the proper use of the nasal spray device and procedures for investigational medicinal product (IMP) home delivery. Parents/caregivers will be instructed to administer 3 intranasal spray pumps of blinded IMP per nostril 3 times daily before meals within the following intervals:

Morning dose: 06:00 a.m. – 09:00 a.m.

Midday dose: 11:00 a.m. – 1:00 p.m.

Evening dose: 4:30 p.m. – 6:00 p.m.

Initial IMP dosing at Visit 2 (Day 1) and Visit 3 (Day 2) will take place under observation of the site staff at the investigational site. Subject vital signs will be monitored prior to and after IMP dosing at 30-minute intervals for 2 hours after each dose. IMP will be shipped by central pharmacy directly to the subject's residence on regular intervals as needed for the duration of the Treatment Period. IMP will be administered by parents/caregivers 3 times per day before meals within the above-specified dosing intervals. The IMP will require refrigeration during shipment to and during storage until administered.

NUMBER OF SUBJECTS

Approximately 38 male or female subjects 10-18 years of age, with genetically confirmed diagnosis of PWS and documented nutritional phase 3 PWS criteria (based on Miller et al, 2011), will be randomized.

MAIN CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria:

1. Signed informed consent by parent/caregiver
2. Signed assent by subject (if applicable)
3. Male or female 10-18 years of age (both inclusive)
4. Genetically confirmed diagnosis of PWS
5. Nutritional phase 3 PWS criteria based on Miller et al, 2011
6. HPWSQ-R score greater than 13 at screening (Visit 1)
7. Willingness and ability of the parent/caregiver to comply with the protocol and trial requirements
8. Negative urine drug and alcohol screen at screening (Visit 1)
9. Negative urine pregnancy test for female subjects of childbearing potential at screening (Visit 1).
10. Willing to use an adequate barrier method or hormonal method of contraception from informed consent to 1 week after the end of dosing of trial medication, if deemed appropriate by the investigator
11. Ability of the subject to perform procedures and assessment required of this trial, based on the investigator's judgment

Exclusion Criteria:

1. Known genetic, hormonal, or chromosomal cause of cognitive impairment other than PWS
2. Presence of currently active psychotic symptoms
3. Presence of any cardiovascular disorders, epilepsy, frequent migraines or severe asthma
4. Previous diagnosis of autism spectrum disorder by a qualified healthcare provider
5. Prior or concomitant use of a selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI), antipsychotic medication, wakefulness-promoting drug, or thyroid hormone that does not comply with the criteria in Section 4.3.1
6. Use of any of the prohibited medications or therapies listed in Section 4.3.2
7. Major surgery within 6 months of screening (Visit 1)
8. Nasal or sinus surgery within 1 year of screening (Visit 1)
9. Chronic sinusitis - more than 3 episodes per year
10. Other nasal diseases that may affect deposition of intranasal medication
11. Serum sodium < 135 mmol/L at screening (Visit 1)
12. Known hypersensitivity to any component of carbetocin or saline solution
13. History of long-term daily use of any intranasal medication
14. Cancer within the last 5 years except for adequately managed basal cell carcinoma or squamous cell carcinoma of the skin
15. History within the last 2 years or current abuse of alcohol or drugs
16. Intake of an IMP within the last 12 weeks preceding screening or longer, if judged by the investigator to possibly influence the outcome of the current trial
17. Mental incapacity or language barrier of the primary parent/caregiver precluding adequate understanding or cooperation
18. Considered by the investigator to be unsuitable to participate in the trial for any other reason

MEDICINAL PRODUCTS

The IMPs to be used in this trial are:

Carbetocin intranasal spray – Carbetocin dissolved in sterile sodium chloride solution 0.9%

- Carbetocin Powder for Solution for Nasal Spray, 160 mg
- Sodium chloride solution 0.9%, sterile
- The preweighed carbetocin powder to be reconstituted with the sodium chloride solution and subsequently transferred to a nasal spray device
- Each spray pump actuation will deliver a 50 µL volume of solution containing 1.6 mg carbetocin; each dose will consist of 3 spray pump actuations in each nostril to deliver a total of 9.6 mg carbetocin

Placebo intranasal spray – sterile sodium chloride solution 0.9%

- Sterile sodium chloride solution 0.9% to be transferred to a nasal spray device
- Each spray pump actuation will deliver 50 µL volume of solution; each dose will consist of 3 spray pump actuations in each nostril

DURATION OF TREATMENT

For each subject, there will be 14 days of treatment with either intranasal carbetocin or placebo.

STATISTICAL METHODS

Sample Size:

Based on the available literature (Dykens et al 2007), the baseline HPWSQ-R total score is assumed to be normally distributed with a standard deviation of 6.12, and the standard deviation of the change between baseline (Visit 2) and Visit 4 is estimated to be between 5 and 6. With 30 subjects eligible for the primary efficacy assessment, the trial has at least 80% power to detect a borderline statistically significant difference (1-sided 10% significance) between 2 groups when the true treatment group difference is -5 under the standard deviation of 5 to 6. Subjects are randomized in a 1:1 ratio to either placebo or carbetocin.

The efficacy of carbetocin will be assessed by change in HPWSQ-R total score from Visit 2 (baseline) to Visit 4. Assuming a dropout rate of approximately 20%, at least 19 subjects per treatment arm will need to be randomized to have a total of 30 subjects eligible for the primary efficacy assessment.

Primary Analysis:

The primary endpoint will be analyzed using an analysis of covariance model with treatment and site as fixed effects and HPWSQ-R total score at Visit 2 (baseline) as a covariate. The last observation carried forward method will be used to carry forward non-missing values of HPWSQ-R total score during the phone call assessment (Day 8±1) to impute missing values of HPWSQ-R total score at Visit 4. The treatment group difference in total score between placebo and carbetocin will be calculated by subtracting the mean change from baseline in placebo from that in the carbetocin group. A borderline statistically significant difference at the 10% significant level will be achieved if the upper limit of the 90% 1-sided confidence interval for the treatment difference is less than zero.

The secondary endpoints will be analyzed using a similar model to that of the primary endpoint.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ANCOVA	Analysis of covariance
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Improvement after treatment
CGI-S	Clinical Global Impression Severity
CI	confidence interval
CL/F	apparent total clearance
C_{trough}	plasma concentration observed immediately prior to first dose of the day
CRF	case report form
CRO	contract research organization
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
DMC	Data Monitoring Committee
ECG	electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
F/U	follow-up
GCP	Good Clinical Practice
HPWSQ-R	Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness – completed by the parent/caregiver
HPWSQ-R-C	Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness-Clinician – administered by the clinician
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board

Abbreviation	Definition
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PWS	Prader-Willi syndrome
SAE	serious adverse event
SNRI	selective norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
V_zF	apparent volume of distribution

1 INTRODUCTION

1.1 Background

Prader-Willi syndrome (PWS) is a genetic disorder that occurs in approximately 1 out of every 16,000 births (1). This rare, complex, and multisystem genetic disorder is caused by the lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13 that can occur via 1 of 3 main mechanisms: paternal microdeletion, maternal uniparental disomy, and imprinting defect (2,3).

The course and natural history of PWS have classically been described as consisting of 2 distinct clinical stages. The first stage occurs during the neonatal and early infancy period, characterized by varying degrees of hypotonia, weak cry, poor suck reflex, feeding difficulties (failure to thrive), developmental delay, temperature instability, and underdeveloped sex organs (hypogonadism). Motor and language development delays are also notable during this first stage. The neonatal symptoms typically improve by 9-25 months of age, muscle tone improves, the child becomes more alert, appetite increases, and weight begins to normalize.

The second stage of PWS (beginning ~2-4 years of age) is characterized by weight gain, onset and escalation of hyperphagia, and continued growth and developmental delays. In addition, as hyperphagia emerges, a separate and distinctly negative constellation of maladaptive or problematic behaviors is observed. These maladaptive (or problematic) behaviors include temper tantrums, depression, stubbornness, obsessive compulsivity, and sudden acts of violence. By the time persons with PWS reach chronological adolescence, unless obesity is life-threatening, behavioral difficulties–often severe–become the central issue for individuals with the syndrome and their families (4).

More recently, Miller et al described the much more gradual and complex progression of the nutritional phases of PWS than that of the traditional 2 stages described in the literature (5). Miller characterized the PWS nutritional phases by assessing growth, metabolic, and laboratory changes. Miller's reporting of the progression of PWS nutritional phases is considered to be a foundation for family counseling, patient management, and development of rational therapies.

1.2 Scientific Justification for Conducting the Trial

Development of rational therapies for PWS is challenging and there are no approved drug products to treat the complex behavioral symptoms, including hyperphagia. Both children and adults with PWS can be particularly difficult to trial. Shortened attention spans and reduced tolerance for things that are difficult for the individual, combined with expressive language difficulties and slower than normal processing speeds frequently lead to behavioral refusals to complete testing protocols. Therefore, in addition to expert clinical assessment, contributory proxy or caregiver information is necessary for both clinical management and research trials.

The neurohypophyseal hormone, oxytocin, previously thought to only be responsible for milk ejection and uterine contraction during labor, has recently been identified as an important neurotransmitter and key modulator of behavior. Numerous non-clinical and clinical studies, including a small, single-dose, pilot study in PWS subjects suggest that oxytocin delivered via the nasal route will provide therapeutic benefit in treating both hyperphagia and negative behaviors in PWS (6).

Although there may be some positive clinical data, nasal oxytocin does not represent an ideal therapy. Oxytocin is not receptor-selective and, due to its considerable vasopressin V2 receptor activity, it carries the risk of prolonged antidiuresis and hyponatremia (7,8,9). Since some subjects with PWS are known to have polydipsia and low baseline serum sodium levels (10) adding an anti-diuretic increases the risk of serious complications due to hyponatremia. Therefore, a receptor-selective compound would be preferable to avoid these potential side-effects.

Carbetocin (FE 992097) is a selective oxytocin receptor agonist that has 2 amino acid substitutions from the native ligand, oxytocin. Due to the improved selectivity profile and established safety in humans, Ferring has initiated development of this molecule for the treatment of children and adults with PWS.

1.3 Benefit / Risk Aspects

Carbetocin injection was first approved in Canada in June 1997. As of March 2013, the cumulative patient exposure for carbetocin is estimated to be more than 3.5 million patients in 71 countries outside the United States, where carbetocin is approved as DURATOBAL, DURATOCIN, LONACTENE, and PABAL for 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. No important safety concerns have been identified in non-clinical safety studies designed for the trial population and the route of administration or with the use of carbetocin in clinical trials or in post-marketing exposure.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary objective

- To assess the effect of intranasal carbetocin (FE 992097) on hyperphagia behavioral symptoms in subjects with PWS, measured by the Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness (HPWSQ-R) scale – completed by the subject's parent/caregiver

Secondary objectives

- To assess the effect of intranasal carbetocin (FE 992097) on hyperphagia behavioral symptoms in subjects with PWS, measured by the Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness-Clinician (HPWSQ-R-C) scale – administered by the clinician
- To assess improvement of PWS symptoms, assessed by the Clinical Global Impression (CGI) scale
- To assess safety and tolerability of intranasal carbetocin
- To assess a population pharmacokinetic model for the patient population utilizing sparse data sampling
- To assess the effects of intranasal carbetocin on PWS maladaptive behaviors, assessed by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
- To assess the sensitivity of Food Domain of the Reiss Profile

2.2 Endpoints

Primary endpoint

- Change in HPWSQ-R total score from Visit 2 to Visit 4

Secondary endpoints

1. Clinical Global Impression-Improvement after treatment (CGI-I) score at Visit 4
2. Change from Visit 2 to Visit 4 for the following measurements:
    - HPWSQ-R hyperphagia behavior, drive, and severity domain scores
    - HPWSQ-R-C total score
    - HPWSQ-R-C hyperphagia behavior, drive, and severity domain scores
3. Change from Visit 2 to Visit 4 for the following measurements:
    - CY-BOCS score

- Food Domain of the Reiss Profile

4. Population PK/PD relationships for carbetocin

Safety endpoints

- Frequency, severity and seriousness of adverse events
- Clinically significant changes in vital signs
- Clinically significant findings during physical and laboratory assessments
- Physical examinations, including focused nasal examinations and nasal irritation, graded 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

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Overall Design and Control Methods

This is a prospective, randomized, double-blind, placebo-controlled parallel trial in subjects with PWS between the ages of 10 and 18 years of age with genetically confirmed diagnosis of PWS and a documented nutritional phase 3 symptom criteria as defined by Miller et al 2011.[5] The trial includes a Screening Period, a 14-day Treatment Period, and a Follow-Up Period. Subjects, along with their parent/caregiver, will be required to visit the investigational site 4 times over the course of the trial, and participate in 2 phone call assessments.

- Visit 1: Screening Period (Day -7 to Day 0)
- Visit 2: Baseline 1st day dosing on site (Day 1)
- Visit 3: 2nd day dosing on site (Day 2)
- Phone call assessment (Day 8)
- Visit 4: End-of-Treatment Visit (Day 15)
- Follow-up phone call (Day 19±3)

Following appropriate informed consent procedures, subjects will undergo screening evaluations to determine eligibility before randomization. Screening evaluations include a physical examination, vital signs, height, weight, 12-lead electrocardiogram (ECG), nasal examination, and laboratory assessments - hematology, clinical chemistry, hemostasis, and urinalysis. Approximately 38 eligible male or female subjects will be randomized at Visit 2 to 1 of 2 treatment groups for 14 days:

- Carbetocin: each spray pump actuation will deliver a 50 µL volume of solution containing 1.6 mg carbetocin; each dose will consist of 3 spray pump actuations in each nostril to deliver a total of 9.6 mg carbetocin
- Placebo: each spray pump actuation will deliver a 50 µL volume of sterile sodium chloride solution 0.9%; each dose will consist of 3 spray pump actuations in each nostril

After randomization, efficacy measures and other assessments, including physical examination, vital signs, nasal examination, and collection of blood samples for clinical laboratory and pharmacokinetic (PK) evaluation, will be performed at selected visits according to Table 1. Subjects will be closely monitored for adverse events throughout the trial following informed consent.

Prior to first dosing at the investigational site, parents/caregivers will be trained on the proper use of the nasal spray device and procedures for IMP home delivery. Parents/caregivers will be instructed to administer 3 intranasal spray pumps of blinded IMP per nostril 3 times daily before meals within the following intervals:

Morning dose: 06:00 a.m. – 09:00 a.m.

Midday dose: 11:00 a.m. – 1:00 p.m.

Evening dose: 4:30 p.m. – 6:00 p.m.

Initial IMP dosing at Visit 2 (Day 1) and Visit 3 (Day 2) will take place under observation of the site staff at the investigational site. Subject vital signs will be monitored prior to and after IMP dosing at 30-minute intervals for 2 hours after each dose. IMP will be shipped by central pharmacy directly to the subject's residence on regular intervals as needed for the duration of the Treatment Period. IMP will be administered by parents/caregivers 3 times per day before meals within the above specified dosing intervals. The IMP will require refrigeration during shipment to and during storage at the investigational site or subject's residence until administered.

3.1.2 Trial Schedule

For each subject, there will be a Screening period and a 14-day Treatment period. An End-of-Treatment Visit will be conducted on Day 15 and a Follow-up phone call will be conducted 4 days (±3 days) after the End-of-Treatment Visit.

3.2 Planned Number of Trial Sites and Subjects

Approximately 38 male or female subjects 10-18 years of age with genetically confirmed diagnosis of PWS and documented nutritional phase 3 PWS symptom criteria will be randomized at approximately 3 sites. It is expected that 30 subjects will complete the trial.

3.3 Interim Analysis

No interim analysis is planned.

3.4 Data Monitoring Committee (DMC)

No DMC will be established for this trial.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

Placebo is a standard control used to ensure unbiased estimates for the effects of active treatment. The 14-day duration of treatment was considered sufficient to observe the onset of efficacy for an active treatment of PWS.

Since PWS is a rare condition, and subjects with PWS are generally treated at a few centers of excellence throughout the country, it is expected that a significant proportion of eligible subjects will reside at a considerable geographic distance from the investigational site(s), requiring ground or air transportation to complete trial visits. The trial design considers both the geographic challenges, as well as the need to ensure subjects' home-life "normalcy" during the trial in order to accurately assess treatment effect.

3.5.2 Selection of Endpoints

HPWSQ-Responsiveness (HPWSQ-R)

The Hyperphagia in Prader-Willi Syndrome questionnaire (HPWSQ) is an informant-based measure originally developed by Elisabeth Dykens (Vanderbilt) as a comprehensive tool to examine the psychological, developmental and neurobiological correlates of hyperphagia in PWS (11). HPWSQ-R represents all 11 items from the original HPWSQ, structured to include a 1-week recall period. The HPWSQ-R is designed to be used for repeated measures to evaluate the change in hyperphagia severity after intervention.

CGI

CGI rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of subjects with psychiatric, neurological or behavioral disorders (12). CGI is an overall clinician-determined summary measure that takes into account all available information including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function (13). The CGI measures 3 components: 1) severity of illness, 2) global improvement, and 3) efficacy index (comparison of subject's baseline condition with a ratio of current therapeutic benefit to severity of side effects).

The rationale for using CGI in an interventional trial of subjects with PWS is supported by a body of evidence and its usefulness in determining baseline functioning prior to starting a treatment and in evaluating treatment effect with the CGI-Improvement score (CGI-I). Given its ease of use and ability to capture behavior that has occurred in the last 7 days, it is an effective tool for clinicians. It also allows for sizable amounts of information to be summarized and yields an easily understood score as well as the potential for benchmarking PWS against several pediatric maladaptive behavioral type indications.

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

People with PWS often have obsessive compulsive symptoms, both food and non-food related, including repeated questioning, insistence on sameness, re-arranging items until they are "just right" and hoarding. The CY-BOCS is a clinician rated, semi-structured inventory of specific symptoms and

symptom severity in pediatric obsessive-compulsive disorder (OCD) (14). 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). CY-BOCS is well researched in psychometric studies with reported treatment sensitivity (14,15,16,17,18).

Food Domain of the Reiss Profile

Several indications may encompass hyperphagic behavior as part of the constellation of maladaptive behaviors encountered. However, unlike PWS, these indications are not considered "hyperphagia centric". In unpublished pilot work, Dykens used the Food Domain of the Reiss Profile to simply document the frequency distribution of the 5 items in 64 people with PWS. The mean BMI of the subjects was 30.82 (SD, 10.31; range: 16.6-64.4), and mean age was 17.33 (SD, 10.79; range: 4.25-48.6). The majority of participants (from 81% to 97%) enjoyed eating, always thought about food, became upset if meals were delayed, and had hearty appetites. Parents endorsed the "always eating" item less frequently (55%), due to the needs for food limits, diets and supervision around food in PWS. In a second, published study by Dykens and Rosner [19], the 5 items that comprise the Food Domain from the Reiss Profile was used to evaluate 94 subjects with PWS, Williams syndrome or Down syndrome. Subjects were evaluated at 3 time points, tested 2 years apart. The results showed that persons with PWS had significantly higher scores in the Reiss Profile food domain than either score for subjects with Williams syndrome or Down syndrome at all measurement time points.

3.5.3 Blinding

Blinding

The trial treatment(s) will be allocated according to computer-generated randomization codes prepared for all trial sites. The randomization assignment will be available to the unblinded pharmacist (at the site and central pharmacy), but not to any other person involved in the conduct and evaluation of the trial, until the trial database is locked.

Prior to the start of the trial, the investigator will assign a pharmacist to act as the unblinded site pharmacist. This person will be the only person unblinded to the subject's treatment group at the site and will be responsible for randomization, mixing, and distribution of the trial drug at Visits 2 & 3.

A central pharmacy will be utilized by Ferring to prepare and distribute unmixed drug kits to trial sites (to be mixed and administered by the site during Visit 2 & 3) and to provide pre-mixed trial drug to subjects and their parent/caregiver once the at-home portion of the trial commences.

The coordinator will instruct each subject's parent/caregiver as to the proper administration and the timing of the drug administration. This person will be available to answer the subject's and parent's/caregiver's questions regarding the trial drug and its administration.

Unblinding of Individual Subject Treatment

In case of an emergency, the emergency decoding envelope will be available to the investigator and the sponsor's medical officer. Breaking of the blind in individual subjects is only permitted in case of a serious, unexpected or other important adverse event, when the knowledge of the investigational medicinal product in question is required for therapeutic decisions for the management of the subject.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and the sponsor. The investigator should document why, when and by whom the blind is broken.

In case of accidental unblinding, the same documentation as for emergency unblinding must be obtained, i.e., the code envelope must be opened and why, when, and by whom must be noted both on the code envelope and the subject's medical records.

It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities and/or IRBs. In that situation, every effort will be made to maintain blinding of sponsor personnel involved in trial conduct, data analysis and interpretation. Only those individuals within Ferring Pharmaceuticals whose responsibility it is to report this information will know the identity of the IMP. Every attempt will be made to ensure that all other trial and site personnel will continue to remain blinded throughout the course of the trial. Information on whether the blind has been broken for any subjects must be collected before the database is declared clean and is released to the statistician.

3.5.4 Selection of Doses in the Trial

A non-clinical program designed to address the safety of the pediatric trial population and the route of administration, comprising chronic 6 months juvenile repeated dose toxicity studies after intranasal administration in both rat and dog, and reproductive toxicity studies investigating fertility and embryo-fetal development, demonstrated satisfactory exposure margins and was considered sufficient to support commencement of the planned Phase 2a trial.A placebo-controlled combined single ascending dose and multiple-dose trial, with a crossover intravenous and nasal administration portion, in healthy adult human subjects to determine the pharmacokinetics, safety, tolerability and absolute bioavailability of nasal carbetocin was completed in December 2012. The absolute bioavailability was 2.5%. No safety signals were observed up to the highest dose tested (9.6 mg) in either the single ascending dose or multiple-dose part. Pharmacokinetic data indicate linear pharmacokinetics over the dose range with respect to area under the concentration-time curve and maximum observed plasma concentration tested.

Thus, the existing non-clinical and clinical safety documentation with carbetocin and the results from the Phase 1 trial supports the choice of dose and dose regimen for the proposed Phase 2a trial.

3.5.5 Selection and Timing of Dose for Each Subject

Prior to first dosing at the investigational site, parents/caregivers will be trained on the proper use of the nasal spray device and procedures for IMP home delivery. Parents/caregivers will be instructed to administer 3 intranasal spray pumps of blinded IMP per nostril 3 times daily before meals within the following intervals:

Morning dose: 06:00 a.m. – 09:00 a.m.

Midday dose: 11:00 a.m. – 1:00 p.m.

Evening dose: 4:30 p.m. – 6:00 p.m.

Initial IMP dosing at Visit 2 (Day 1) and Visit 3 (Day 2) will take place under observation of the site staff at the investigational site. Subject vital signs will be monitored prior to and after IMP dosing at 30-minute intervals for 2 hours after each dose. Subsequent IMP will be administered by parents/caregivers 3 times per day before meals within the above specified dosing intervals.

3.5.6 Withdrawal Criteria

Every subject has the right to refuse further participation in the trial at any time and without providing reasons. A subject's participation is to terminate 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 the IMP has already been administered, the subject must be advised to agree to follow-up safety investigations, which will include all procedures outlined for the End-of-Treatment Visit (Visit 4) – before withdrawal/discontinuation of the trial.

The subject may be withdrawn from the trial 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 trial, develop conditions, which would have prevented his/her entry into the trial according to the exclusion criteria, the subject must be withdrawn immediately.

The withdrawal of subjects from the trial will be agreed upon by the investigator and the sponsor.

3.5.7 Follow-up Procedures

There will be a follow-up/End-of-Treatment visit at Visit 4 (Day 15) and a follow-up phone call on Day 19 (±3 days) (Table 1).

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible for the trial:

1. Signed informed consent by parent/caregiver
2. Signed assent by subject (if applicable)
3. Male or female 10-18 years of age (both inclusive)
4. Genetically confirmed diagnosis of PWS
5. Nutritional phase 3 PWS criteria based on Miller et al, 2011 (5) (see Appendix VI)
6. HPWSQ-R score greater than 13 at screening, Visit 1 (see Appendix II)
7. Willingness and ability of the parent/caregiver to comply with the protocol
8. Negative urine drug and alcohol screen at screening (Visit 1)
9. Negative urine pregnancy test for female subjects of childbearing potential at screening (Visit 1).
10. Willing to use an adequate barrier method or hormonal method of contraception from informed consent to 1 week after the end of dosing of trial medication, if deemed appropriate by the investigator
11. Ability of the subject to perform procedures and assessment required of this trial, based on the investigator's judgment

4.1.2 Exclusion Criteria

The presence of any of the following excludes a subject from trial enrollment:

1. Known genetic, hormonal, or chromosomal cause of cognitive impairment other than PWS
2. Presence of currently active psychotic symptoms
3. Presence of any cardiovascular disorders, epilepsy, frequent migraines or severe asthma

4. Previous diagnosis of autism spectrum disorder by a qualified healthcare provider
5. Prior or concomitant use of a selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI), antipsychotic medication, wakefulness-promoting drug, or thyroid hormone that does not comply with the criteria in Section 4.3.1
6. Use of any of the prohibited medications or therapies listed in Section 4.3.2
7. Major surgery within 6 months of screening (Visit 1)
8. Nasal or sinus surgery within 1 year of screening (Visit 1)
9. Chronic sinusitis - more than 3 episodes per year
10. Other nasal diseases that may affect deposition of intranasal medication
11. Serum sodium < 135 mmol/L at screening (Visit 1)
12. Known hypersensitivity to any component of carbetocin or saline solution
13. History of long-term daily use of any intranasal medication
14. Cancer within the last 5 years except for adequately managed basal cell carcinoma or squamous cell carcinoma of the skin
15. History within the last 2 years or current abuse of alcohol or drugs
16. Intake of an IMP within the last 12 weeks preceding screening or longer, if judged by the investigator to possibly influence the outcome of the current trial
17. Mental incapacity or language barrier of the primary parent/caregiver precluding adequate understanding or cooperation
18. Considered by the investigator to be unsuitable to participate in the trial for any other reason

4.2 Method of Assigning Subjects to Treatment Groups

Approximately 38 subjects meeting the eligibility requirements will be randomized in this trial. At each trial site, subjects will be assigned sequentially, in the order in which they are enrolled, to receive their allocated treatment according to a computer-generated randomization schedule prepared by Ferring or designee prior to trial initiation.

Eligible subjects will be assigned to 1 of 2 treatments (carbetocin or placebo) in a sequential order, based on their expected arrival to the trial site for the baseline Visit 2 (Day 1)

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

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

Prior and concomitant use of growth hormone is permitted.

Prior and concomitant use of the following types of medications is permitted only if the prescribed dosage of the medication has been stable for ≥ 6 months at time of screening:

- A single selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI)
- An antipsychotic medication
- A wakefulness-promoting drug
- A thyroid hormone

The table below lists examples of some common SSRIs, SNRIs, antipsychotics, wake promoting agents, and hypothyroid medications.

Class of Drug	**Examples of Common Drugs in each Class**
SSRIs	Citalopram
	Sertraline
	Paroxetine
	Fluoxitene
SNRIs	Duloxetine
	Venlafaxine
	Desvenlafaxine
Antipsychotics	Respiridone
Wakefulness-promoting drugs	Amphetamine
	Modafinil (Provigil)
	Armodafinil (Nuvigil)
Thyroid hormones	Levothyroxine
	Lyothyronine

4.3.2 Prohibited Therapy

Concomitant use of any intranasal therapies, including nasal saline is prohibited.

Concomitant use of any products containing prostaglandins (for a complete list see Appendix VII) is prohibited.

Occasional use of over-the-counter medications may be permitted with prior approval from the investigator and sponsor.

5 TREATMENTS

5.1 Treatments Administered

The 2 treatments are:

- Carbetocin: each spray pump actuation will deliver a 50 µL volume of solution containing 1.6 mg carbetocin; each dose will consist of 3 spray pump actuations in each nostril to deliver a total of 9.6 mg carbetocin
- Placebo: each spray pump actuation will deliver a 50 µL volume of sterile sodium chloride solution 0.9%; each dose will consist of 3 spray pump actuations in each nostril

Carbetocin is a peptide comprising 8 amino acids. All amino acids, except glycine, which is achiral, are present as L-enantiomers. The 2 amino acids, L-O-methyl tyrosine and L 1-carboxypropylcysteine, are unnatural. The drug product for nasal administration is a solution consisting of the drug substance carbetocin dissolved in 5 mL of sterile 0.9% sodium chloride.

Placebo will be a sterile sodium chloride solution 0.9% to be transferred to a nasal spray device.

Carbetocin Powder for Solution for Nasal Spray, 160 mg is preweighed in a glass vial for reconstitution with sterile sodium chloride solution 0.9%, and subsequent transfer to a nasal spray device.

5.2 Characteristics and Source of Supply

All medicinal drug products are provided by Ferring Pharmaceuticals/Ferring entity and will be handled according to the principles of Good Manufacturing Practice (GMP).

The IMP components will be delivered to the central pharmacy as pre-weighed carbetocin in vials and sterile 0.9% sodium chloride solution for reconstitution. After reconstitution, the IMP will be transferred to the glass container of the metered-dose nasal spray device, and the spray pump will be attached.

A central pharmacy will prepare/ship intranasal IMP kits for onsite mixing/dosing followed by preparing/shipping reconstituted IMP for off-site dosing.

IMP kits for mixing and dosing will be delivered to the investigational site for dosing on Visit 2 (Day 1), Visit 3 (Day 2), and to provide IMP for off-site dosing on Day 3.

Reconstituted IMP shipments to the subject's home for subsequent dosing will be made via special courier arrangements to ensure regular and timely shipment of blinded IMP to the subject's home for use over the remainder of the treatment period.

5.3 Packaging and Labeling

Packaging and labeling of the medicinal products will be performed under the responsibility of the IMP Department at Ferring Pharmaceuticals A/S in accordance with GMP and national and local regulatory requirements.

The content on the labels will be in accordance with Annex 13, Eudralex, volume 4 and national regulatory requirements.

Date and Clock time (example: 01Jan2013, 9:00 am EST) will be provided on reconstituted drug labels to indicate time of expiration.

5.4 Blinding / Unblinding

5.4.1 Blinding

The randomization list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and is released to the statistician.

The randomization list will be available only to the unblinded pharmacist(s) preparing the diluted solutions in the spray vial.

5.4.2 Unblinding of Individual Subject Treatment

An emergency decoding envelope will be available to the investigator and designated persons at Ferring.

Breaking of the blind for individual subjects in emergency situations is only permitted in case of a suspected unexpected serious adverse reaction (SUSAR) or in case of an important adverse event where the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and Ferring. The person who opens a code envelope must record the reason and the date of opening, and then sign and date the opened envelope. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

In case of accidental unblinding, the same documentation as for emergency unblinding must be obtained, i.e. the code envelope must be opened and why, when and by whom must be noted.

It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities and Institutional Review Boards (IRBs). In that situation, every effort will be made to maintain blinding of sponsor personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial site staff as well as staff acting on behalf of Ferring.

Information on whether the blind has been broken for any subjects must be collected before the database is declared clean and is released to the statistician.

5.5 Conditions for Storage and Use

The IMP will require refrigeration during shipment to and during storage at the investigational site or subject's residence for the duration of the trial.

The investigator will ensure that IMP is stored in appropriate conditions in a reasonably secure, substantially constructed locked cabinet with controlled access. The substance (powder form) is stable for 24 months when stored at 2 - 8°C. The sterile sodium chloride solution 0.9% should be stored at 2 - 8°C. The expiry date is documented on the package. The temperature in the storage compartment shall be regularly monitored with a min/max thermometer and the values documented.

The shelf life of the nasal spray solutions and the placebo for carbetocin nasal solution after reconstitution/transfer to the nasal spray is 48 hours. After reconstitution the solution must be stored at 2 - 8°C when it is not used for administration.

5.6 Treatment Compliance

5.6.1 Preparation

The IMP will be shipped from an External Packaging Facility / central pharmacy as follows:

- IMP kits will be sent to site(s) to be prepared on-site for dosing during on-site Visit 2 (Day 1) and Visit 3 (Day 2), and for off-site dosing on Day 3
- Fully reconstituted IMP in the nasal spray device will be sent directly to subject's residence for remainder of dosing period

5.6.2 Dispensing and Accountability

The investigator or parent/caregiver will dispense the medication only to the identified subjects of this trial, following the procedures described in this trial protocol and dispensing instructions. Subject dosing will be documented in a subject dispensing log.

Drug inventory/dispensing will be documented in the source documents for each subject and the drug accountability binder. The investigator is responsible for all drug supplies. Written documentation is mandatory. After completion of the trial, all unused IMP will be returned to the sponsor.

5.6.3 Assessment of Compliance

The IMP will be dispensed only to subjects who meet the eligibility criteria and are randomized to a treatment in the trial. The investigator or his/her designated personnel (e.g., trial nurse) and parent/caregiver will maintain a drug dispensing log detailing the dates and quantities of IMPs dispensed to, and used by, each subject, as well as the batch numbers. The monitor will verify drug accountability during the trial.

Subjects will be asked to return used IMP containers. Treatment compliance will be verified by reviewing the containers, any unused nasal spray bottles, and/or subject's statements documented in the source documents, in case the nasal spray device is lost.

5.7 Return and Destruction of Medicinal Products

After completion of the trial, all used and unused investigational product (and Temperature Monitoring Devices) will be returned to the sponsor.

6 TRIAL PROCEDURES

6.1 Trial Flow Chart

The schedule of activities for the trial is presented in Table 1.

Table 1 Schedule of Activities

Period:	Screening	Treatment					F/U	
		Baseline			1-Week Assessment		End of Treatment Visit / Early termination visit	F/U phone call
Visit:	1	2	3				4	
Days:	-7 to 0	1	2	3-7	8 (+/-1)	9-14	15	19 (+/-3)
IMP Dosing:	NA	On site	On site	Off site			On site	NA
Assessments								
Written informed consent and assent	X							
Inclusion/exclusion criteria	X							
Prior/concomitant medication	X	X	X		X		X	
Physical examination	X						X	
Nasal examination[a]	X	X	X				X	
Medical history	X							
Demographics	X							
Urine drug and alcohol screen	X						X	
Urine pregnancy test	X						X	
Height and Weight	X						X	
Vital signs[b]	X	X	X				X	
Electrocardiogram[c]	X	X	X				X	
Blood samples for clinical chemistry, hematology, hemostasis, and urinalysis	X		X				X	
Blood samples for pharmacokinetics[d]		X	X					
Nutritional phase assessment	X							
Randomization[e]		X[e]						
HPWSQ-R and HPWSQ-R-C	X	X			X		X	
CGI-S		X						
CGI-I					X		X	
CY-BOCS	X				X		X	
Food Domain of Reiss Profile	X				X		X	
IMP administration training		X						
Dispense IMP		X	X	X	X	X		
Return IMP							X	
IMP dosing		X	X	X	X	X		
Adverse events	X	X	X		X		X	X

CGI-I=Clinical Global Impression-Improvement after treatment; CGI-S=Clinical Global Impression-Severity; CY-BOCS= Children's Yale-Brown Obsessive-Compulsive scale; F/U=follow-up; HPWSQ-R=Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness; HPWSQ-R-C=Hyperphagia in Prader-Willi Syndrome Questionnaire-Clinician ; IMP=investigational medicinal product

[a] Nasal examinations to be done at Visit 1 (anytime), within 1 hour prior to each dose at Visit 2 and Visit 3, and at Visit 4 (anytime).

[b] Includes pulse, respiration rate, blood pressure and body temperature. At Visit 2 and 3, vital signs will be monitored prior to and after IMP dosing at 30-minute intervals for 2 hours after each dose.

[c] ECG to be done within 1 hour after morning dose at Visit 2 and 3.

[d] Three blood samples to be collected at Visit 2 and Visit 3, according to the schedule specified in section 7.2.6 Clinical Laboratory Tests/Pharmacokinetic Assessments. All PK labs are to be done prior to subsequent dose.

[e] Randomization will be done within 24 hours prior to the Visit 2, morning dose.

6.1.1 Screening (Visit 1: Days -7 through 0)

Prior to or at the Screening Visit, the parent or caregiver must receive a detailed explanation of the trial and must sign the Informed Consent Form after having sufficient time to consider his/her child's participation in the trial. After the parent or caregiver has signed the Informed Consent Form and the subject has signed the Assent Form (if applicable), the following will be collected and/or performed:

- Inclusion/exclusion criteria
- Use of prior/concomitant medication up to 14 days prior to first dose of trial medication
- Parent/caregiver training on completion of HPWSQ-R
- HPWSQ-R followed by HPWSQ-R-C
- CY-BOCS (Symptoms Checklist & Severity Rating Scale)
- Food Domain of Reiss Profile
- Physical examination
- Nasal examination (See scale listed in 7.2.3)
- Medical history and demographic data
- Urine drug and alcohol screen
- Urine pregnancy test for females of childbearing potential
- Vital signs (pulse, respiration rate, blood pressure, and body temperature)
- Height and Weight
- ECG
- Clinical safety laboratory assessment: chemistry, hematology, hemostasis, urinalysis
- Nutritional phase assessment
- Adverse events

6.1.2 Treatment Period

Baseline 1st day of Dosing On Site (Visit 2: Day 1)

The following will be collected and/or performed at Visit 2:

- Record use of concomitant medications
- Nasal examinations to be done within 1 hour prior to each dose (See scale listed in 7.2.3)
- Vital signs (pulse, respiration rate, blood pressure, and body temperature) will be monitored prior to and after IMP dosing at 30-minute intervals for 2 hours after each dose.
- ECG (to be done within 1 hour after morning dose)
- Laboratory samples for:
    - Pharmacokinetic sampling (3 blood samples according with the schedule specified in section 7.2.6 Clinical Laboratory Tests/Pharmacokinetic Assessments)
- Randomization (done within 24 hours prior to Visit 2 morning dose)
- HPWSQ-R followed by HPWSQ-R-C (prior to dose)
- CGI-S (prior to dose)
- IMP administration training
- Dispense IMP
- Blinded, randomized IMP dosed 3 times daily (before meals)
- Adverse events

Visit 3: 2nd day of Dosing On Site (Visit 3: Day 2)

The following will be collected and/or performed at Visit 3:

- Record use of concomitant medications
- Nasal examinations to be done within 1 hour prior to each dose (See scale listed in 7.2.3)
- Vital signs (pulse, respiration rate, blood pressure, and body temperature) will be monitored prior to and after IMP dosing at 30-minute intervals for 2 hours after each dose.

- ECG (to be done within 1 hour after morning dose)
- Laboratory samples for:
    - Clinical safety laboratory assessment (chemistry, hematology, hemostasis, urinalysis) to be drawn post-morning dose (pre-meal)
    - Pharmacokinetic sampling (3 blood samples according with the schedule specified in section 7.2.6 Clinical Laboratory Tests/Pharmacokinetic Assessments)
- Dispense IMP
- IMP dosed 3 times daily
- Adverse events

3rd through 7th day of Dosing Off Site (Day 3 through Day 7)

The following will be performed on Day 3 through Day 7 by the parent/caregiver:

- Receive/Dispense IMP
- IMP dosed 3 times daily (before meals)

1-Week Assessment: 8th day (±1 day) of Dosing Off Site (Phone Call, Day 8)

The following will be collected and/or performed on Day 8:

- Record use of concomitant medications
- HPWSQ-R, followed by HPWSQ-R-C CGI-I
- CY-BOCS Severity Rating Scale
- Food Domain of Reiss Profile
- Receive/Dispense IMP (not part of phone call)
- IMP dosed 3 times daily (not part of phone call)
- Adverse events

9th through 14th day of Dosing Off Site (Day 9 through Day 14)

The following will be performed on Day 9 through Day 14:

- Receive/Dispense IMP
- IMP dosed 3 times daily (before meals)

6.1.3 Follow-up

End-of-Treatment Visit (Visit 4: Day 15)

The following will be collected and/or performed at Visit 4:

- Record use of concomitant medications
- HPWSQ-R, followed by HPWSQ-R-C
- CGI-I
- CY-BOCS Severity Rating Scale
- Food Domain of Reiss Profile
- Physical examination
- Nasal examination (See scale listed in 7.2.3)
- Height and Weight
- Vital signs (pulse, respiration rate, blood pressure, and body temperature)
- ECG
- Urine drug and alcohol screen

- Urine pregnancy test for females of childbearing potential
- Clinical safety laboratory assessment: chemistry, hematology, hemostasis, urinalysis
- Return IMP
- Adverse events

Follow-up Phone Call (Day 19 ±3 days)

Each subject will be contacted by telephone on Day 19 (±3 days) and assessed for adverse events.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Endpoints

7.1.1 Clinical Global Impression Scales

The CGI scale (Appendix I) is a 7-point clinician rating of illness severity (0 = no illness, 6 = extremely ill), at the beginning of the trial and a 7-point clinician rating of improvement of patient condition, during and at the end of the trial (13). The scales will be administered by the Investigator or a delegated Sub-Investigator (trained and qualified by Investigator).

The CGI scales should be administered around the same time, by the same person, throughout the trial.

7.1.2 Hyperphagia in PWS Questionnaires

The HPWSQ-R (Appendix II) consists of 11 questions that rate the food-seeking behavior of subjects with PWS (11). The scale will be administered by the parent/caregiver. HPWSQ-R-C (Appendix III) consists of the same 11 questions that rate the food-seeking behavior of subjects with PWS, administered by the Investigator or a delegated Sub-Investigator (trained and qualified by Investigator). The HPWSQ-R-scale should be administered by the same parent/caregiver throughout the trial. The HPWSQ-R-C-scale should be administered by the same clinician throughout the trial.

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

The CY-BOCS (Appendix IV) is a clinician rated, semi-structured inventory of specific symptoms and symptom severity in pediatric obsessive-compulsive disorder (OCD) (14). 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 scale will be administered by the Investigator or a delegated Sub-Investigator (trained and qualified by Investigator). Same person should perform this task around the same time, throughout the trial.

7.1.4 Food Domain From the Reiss Profile

The food domain of the Reiss Profile (Appendix V) consists of 7 questions that pertain to food seeking behavior. The scale will be administered by the Investigator or a delegated Sub-Investigator (trained and qualified by Investigator), around the same time throughout the trial. It should be administered by the same person.

7.2 Safety and Other Assessments

7.2.1 Medical History

A complete medical history will be obtained and documented at screening.

7.2.2 Physical Examination

A complete physical examination including general appearance, head, eyes, ears, nose, and throat (HEENT), 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 trial team member) at Visits 1 and 4.

At screening, each category will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant findings at screening must be reported on the Medical History Log.

At end-of-trial, potential changes from screening to end-of-trial will be evaluated for each category. In case of changes, these will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant changes from screening to end-of trial must be recorded as AEs.

7.2.3 Nasal Examination

Nasal examinations will be done at Visit 1, within 1 hour prior to each dose at Visit 2 and Visit 3, and at Visit 4 (anytime).

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

*Note: After randomization, grading of 3 or 4 will be documented as an adverse event. If deemed appropriate, additional follow-up examinations will be performed at the discretion of the Investigator.

7.2.4 Height, Weight and Vital Signs

Height and weight will be measured at Visit 1 and Visit 4.

Pulse, respiration rate, blood pressure, and body temperature will be measured at each visit (or at early termination) under resting conditions while the subject is seated. All blood pressure measurements should be made using the same arm while the subject is in supine position after resting for 3 minutes, and prior to any scheduled blood draws. At Visit 2 and Visit 3 - vital signs will be monitored prior to and after IMP dosing at 30-minute intervals for 2 hours after each dose.

7.2.5 12-Lead Electrocardiogram

After at least a 5-minute rest in a supine position, a 12-lead ECG will be obtained at each visit (or at early termination). Additional ECGs may be obtained if clinically indicated.

7.2.6 Clinical Laboratory Tests

Hematology, Hemostasis, Serum Chemistry, and Urinalysis

The following safety laboratory tests will be performed at the times specified in Table 1. A 10-hour overnight fast is required prior to collecting the blood samples. Specific instructions for blood collection will be provided in a laboratory manual to the trial site.

Hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count.

Hemostasis: prothrombin time, activated partial thromboplastin time, thrombin time, and fibrinogen

Serum chemistry: glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase.

Urinalysis: blood, pH, specific gravity, protein, glucose, urobilinogen, and microscopic if positive for blood or protein.

The investigator is to review laboratory results for abnormalities and clinical significance.

Pharmacokinetic Assessments

Blood samples for PK testing will be obtained according with the following schedule:

At a Given Site	Visit 2 (Day 1) morning dose	Visit 3 (Day 2) midday dose
1st randomized patient and every third thereafter (1, 4, 7, 10, etc.)	Pre-dose, 15, and 60 min	5, 20, and 120 min
2nd randomized patient and every third thereafter (2, 5, 8, 11, etc.)	10, 30, and 180 min	Pre-dose, 15, and 60 min
3rd randomized patient and every third thereafter (3, 6, 9, 12, etc.)	5, 20, and 120 min	10, 30, and 180 min

All PK samples must be drawn prior to thenext dose.:

- Visit 2 (Day 1) morning dose PK samples must be drawn prior to midday dose
- Visit 3 (Day 2) midday dose PK samples must be drawn prior to evening dose

Specific instructions for blood collection will be provided to the trial site.

Drug and Alcohol Screen

At screening and End of Treatment/Early Termination visit, a urine drug screen and alcohol test will be performed.

Pregnancy Testing

Urine pregnancy tests will be performed on females of childbearing potential at Screening (Visit 1) and End of Treatment/Early Termination visit (Visit 4). Negative results are required for trial admission and/or administration of IMP.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign or finding from physical (or gynecological) examination assessed as clinically significant by the investigator (note: findings from assessments and examinations done during screening are not adverse events, but are recorded as medical history).
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

An adverse drug reaction is an adverse event evaluated by the investigator as being probably or possibly causally related to treatment with the IMP.

A serious adverse drug reaction is a serious adverse event (SAE) evaluated by the investigator and/or by Ferring as having a reasonable possibility of causal association with IMP.

An unexpected adverse event is an adverse event not identified in nature, severity, or frequency in the section “Undesirable Effects” in the sponsor’s current Investigator’s Brochure.

A treatment-emergent adverse event is any adverse event that begins during the Treatment Period or worsening of a pre-existing medical condition. The Treatment Period is the period during which a subject receives IMP.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the Day 19 follow-up phone call.

The sources of adverse events cover:

- The subject's response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
- Symptoms spontaneously reported by the subject.
- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
- Other information relating to the subject's health becoming known to the investigator (e.g., hospitalization).

8.2.2 Recording of Adverse Events

The investigator must record all adverse events in the Adverse Event Log provided in each subject's eCRF with information about:

- Adverse event
- Date and time of onset (time can be omitted, if applicable)
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- Outcome
- Seriousness

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event

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, i.e. the highest intensity and the longest duration of the event.[a]

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

Note: 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).

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.

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 work or perform usual activities (unacceptable).

[a] Exception: if an adverse event with onset before the first IMP administration (i.e., 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.

Causal Relationship to IMP

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

Reasonable possibility:

There is evidence or argument to suggest a causal relationship between the IMP and the adverse event. The adverse event may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

- Adverse events that are uncommon but are known to be strongly associated with IMP exposure.
- Adverse events that are not commonly associated with IMP 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.

No reasonable possibility:

There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the adverse event.

Examples:

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

Action Taken to IMP

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

- No change (medication schedule maintained or no action taken)
- Withdrawn
- Interrupted
- Dose reduced
- Dose increased

Other Action Taken

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 entered in the Concomitant Medication Log.

Date and Time of Outcome

The date the subject recovered or died.

Outcome

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

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

8.3 Pregnancy and Pregnancy Outcome

If a pregnancy occurs, the IMP should be immediately stopped and Pharmacovigilance at Ferring Pharmaceuticals must be informed and a SAE form completed. 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. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly), this must be reported as an SAE to Pharmacovigilance at Ferring Pharmaceuticals.

In cases in which a fetus may have been exposed through transmission of the IMP via semen following paternal exposure and the pregnancy results in an abnormal outcome (birth defect/congenital anomaly), this must be reported as a serious adverse event to Pharmacovigilance at Ferring Pharmaceuticals.

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event if it:	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 IMP. The death of a subject enrolled in a trial 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. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgment must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfills the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute a serious adverse event (SAE). Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
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 IMP.
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 (e.g. 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.

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to Ferring Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 24 hours** of his/her knowledge of the SAE.

The SAE Report Form must be completed and submitted according to the instructions provided on the form, using the contact details below:

Pharmacovigilance, Ferring Pharmaceuticals Inc.
Fax: 1-973-796-1791

Email: Safety.fax@ferring.com

Completion of the Demographics, Adverse Event Log, Medical History Log and Concomitant Medication Log 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 SAE such as hospital records, results from investigations, e.g., laboratory parameters, invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, such details such as subject's name, address, and hospital ID number should be concealed and instead subject number should be provided.

The investigator will supply Ferring and the IRB with any additional requested information such as results of post-mortem examinations and hospital records.

Expedited Reporting by Ferring

Ferring will report all adverse events that are **serious, unexpected (according to the Investigator Brochure) and with a reasonable possible causality to the IMP** as judged by either the investigator or Ferring to the relevant parties within the stipulated timelines. Ferring will submit serious, unexpected, causally-related adverse event reports to the US Food and Drug Administration and other applicable Health Authorities according to local reporting requirements.

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

8.5 Follow-up of Adverse Events and Serious Adverse Events

8.5.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the investigator must follow-up on 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-up on any adverse event classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.5.2 Collection of Serious Adverse Events with Onset after Last Trial Visit

If an investigator becomes aware of an SAE after the subject's last visit and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

Details of the statistical methodology will be provided in a separate Statistical Analysis Plan. All individual subject data will be listed by domain.

9.1 Determination of Sample Size

Based on available literature (Dykens et al 2007), the HPWSQ-R total score at baseline (Visit 2) is assumed to be normally distributed with a standard deviation of 6.12, and the standard deviation of the change between baseline (Visit 2) and Visit 4 is estimated to be between 5 and 6 (11). With 30 subjects eligible for the primary efficacy assessment, the trial has at least 80% power to detect a borderline statistically significant difference (1-sided 10% significance) between 2 groups when the true treatment group difference is -5 under the standard deviation of 5 to 6. Subjects are randomized in a 1:1 ratio to either placebo or carbetocin.

The efficacy of carbetocin will be assessed by change in HPWSQ-R total score from Visit 2 to Visit 4. Assuming a dropout rate of approximately 20%, at least 19 subjects per treatment arm will need to be randomized to have a total of 30 subjects eligible for the primary efficacy assessment.

9.2 Subject Disposition

The number of subjects randomized into the trial will be summarized overall. Subjects who discontinue IMP or are removed from the trial permanently will also be reported by the treatment received immediately prior to discontinuation. Randomization errors, reasons for trial discontinuation, and time of withdrawal from the trial will be reported. No formal statistical analysis will be performed.

9.3 Protocol Deviations

Major or minor protocol deviations will be defined and documented prior to database lock.

9.4 Analysis Sets

9.4.1 Safety Population

All subjects who received at least 1 dose of IMP will be included in the safety population.

9.4.2 Full Analysis Set (FAS) Population

The FAS population will include all subjects in the safety population who have the primary efficacy endpoint measured.

9.4.3 Pharmacokinetic Population

The PK population will include all subjects in the safety population who have sufficient plasma carbetocin concentrations for inclusion in population PK modeling.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Subject characteristics at trial entry will be summarized overall in frequency tables for qualitative variables, and descriptive statistics will be provided for quantitative variables. No formal statistical analysis will be performed.

9.5.2 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history obtained at screening will be listed by subject. Physical examination results, including nasal examinations and nasal irritation, will be listed by subject. Concomitant medications will be listed by subject.

9.6 Endpoint Assessments

9.6.1 Efficacy Analyses

The primary endpoint will be analyzed in the FAS population using an analysis of covariance (ANCOVA) model with treatment and site as fixed effects and HPWSQ-R (completed by the parent/caregiver) total score at Visit 2 (baseline) as a covariate. The last observation carried forward (LOCF) method will be used to carry forward non-missing values of HPWSQ-R total score during the phone call assessment (Day 8±1) to impute missing values of HPWSQ-R total score at Visit 4. The treatment group difference in total score between placebo and carbetocin will be calculated by subtracting the mean change from baseline in placebo from that in the carbetocin group. A borderline statistically significant difference at the 10% significant level will be achieved if the upper limit of the 90% 1-sided confidence interval for the treatment difference is less than zero.

The secondary endpoints will be analyzed using a similar model to that of the primary endpoint.

9.7 Extent of Exposure

The total trial treatment exposure will be summarized and listed by treatment group for the safety population.

9.8 Safety

9.8.1 General Considerations

Safety parameters will be evaluated for the safety analysis data set.

Complete listings and summary tables for all safety information, including adverse events, clinical laboratory safety data, physical examination, nasal examination, vital signs, and ECG will be presented. No formal statistical analysis will be performed.

9.8.2 Adverse Events

All adverse events will be listed by subject using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary for system organ class and preferred term.

Treatment-emergent adverse events will be listed by subject, and the incidence of treatment-emergent adverse events will be presented by treatment. In addition, treatment-emergent adverse events will be presented by causality (relationship to the trial medication) and intensity (severity) and seriousness. Deaths, serious adverse events, and adverse events leading to discontinuation will be listed.

9.8.3 Safety Laboratory Variables

Clinical safety laboratory values for each subject will be listed by test, and all values outside the normal range will be identified. Mean laboratory values will be summarized by treatment group and visit using descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum values.

9.8.4 Other Safety Variables

Vital Signs

Vital signs will be summarized by treatment and visit using descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum values.

Electrocardiograms

Subjects with clinically significant deteriorations in ECG findings will be identified.

9.9 Population Pharmacokinetic Modeling

Plasma carbetocin PK parameters will be estimated from serum carbetocin concentrations using population analysis. The following carbetocin PK parameters will be estimated:

C_{trough}: Observed plasma concentration prior to dosing

CL/F: Apparent total clearance

V_z/F: Apparent volume of distribution

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

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 trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - ICH Definition

Source documents are defined as original documents, data, and records (e.g. 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 trial).

Trial-specific Source Data Requirements – Ferring

An 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, 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 Food and Drug Administration (FDA) is notified. For each subject enrolled, the investigator will indicate in the source record(s) that the subject participates in this trial, and will record all trial 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.

10.2 eCRF

An eCRF system provided by an independent third-party contract research organization (CRO) will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Ferring 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.

The eCRF system and the database will be hosted at the independent third party CRO. After the trial, the database is declared clean and released to the statistician, a final copy of the database will be stored at Ferring. The investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by the independent third party CRO. The PDF-files will be stored on a CD and will be provided to the investigator before access to the eCRF is revoked.

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.

10.3 Data Management

A data management plan will be created under the responsibility of Ferring's Biometrics Department. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation.

The data management plan will describe captured methods, 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.

10.4 Provision of Additional Information

On request, the investigator will provide the sponsor with additional data relating to the trial, or copies of relevant source records, duly anonymized. This is important when errors in data transcription are encountered. In case of particular issues or governmental queries, it may be necessary to have access to the complete trial documents, provided that the subjects' confidentiality is maintained and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 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 trial-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 a subject is enrolled at the site.

11.2 Audit and Inspection

The investigator will make all the trial-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.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' 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 trial. Documents not intended for submission to the sponsor (e.g., the confidential subject identification code and the signed informed consent forms) will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

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) and regulatory authorities, in accordance with local regulations.

An approval is required for a significant amendment, e.g., one that could affect the safety of the subjects, or that entails a significant change of the scope/design of the trial.

12.2 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 must be reported to the IRB. Any paper documentation must be kept in the Investigator's File and in the Trial Master File.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and the sponsor reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the 2 parties. In terminating the trial, 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) will be informed.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a trial report prepared by the sponsor. The final report may be used for the further development of the IMP as considered necessary by the sponsor.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial, will be the exclusive property of the sponsor. The investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring Pharmaceuticals, Inc.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

Submission of data for journal publication and/or presentation of data to scientific audiences may be considered by Ferring Pharmaceuticals Inc. and the investigator(s). Submission of a manuscript for publication will be considered based on the merits of the trial results. 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. The investigator(s) agrees that the sponsor will have the opportunity to review all manuscripts and abstracts (at least 30 days) related to this trial prior to any submission for presentation or publication. Likewise, if the sponsor prepares a publication based on the results of this trial, a copy of the manuscript will be provided to the investigator(s) prior to publication.

Any external contract research organization or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate registry, i.e. clinicaltrials.gov, which is sponsored by the National Institutes of Health.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

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

14.2 Regulatory Authority(ies) Authorization / Approval / Notification

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

14.3 End-of-Trial and End-of-Trial Notification

At the end of the trial, the IRB will be notified in writing.

14.4 Ethical Conduct of the Trial

This trial 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.

14.5 Subject Information and Consent

The investigator or designee will obtain a freely given written informed consent from each subject's parent or 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 trial that are relevant to the subject's decision to participate. The consent form must be signed and dated by the parent or caregiver before the subject is exposed to any trial-related procedure, including screening tests for eligibility.

The investigator or designee will explain that the subjects are completely free to refuse to enter the trial 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 parent or caregiver will receive a copy of any available subject information and her signed consent.

The subject and parent or caregiver should be informed if new information becomes available that may be relevant to their willingness to continue participation in the trial. 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 parent or 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 parent or caregiver in accordance with national regulations. If such subjects can understand the risks and benefits of the trial, they should also be informed and provide their written consent.

14.6 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP, and the national law in the United States of America shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor and the investigator will be as defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the trial takes place. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

In case of any damage or injury occurring to a subject in association with the IMP or the participation in the trial, Ferring has contracted an insurance which covers the liability of Ferring, the investigator and other persons involved in the trial in compliance with the laws in the countries involved.

16 ARCHIVING

16.1 Investigator File

To enable evaluations and/or audits from regulatory authorities or Ferring Pharmaceuticals, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, and detailed records of treatment disposition. The records shall be retained 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, 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 FDA is notified.

If the investigator relocates, retires, or for any reason withdraws from the trial, the trial records may be transferred to an acceptable designee, such as another investigator, another institution, or to Ferring. The investigator must obtain Ferring Pharmaceutical's written permission before disposing of any records.

No trial site document may be destroyed without prior written agreement between the investigator and the sponsor. Should the investigator elect to assign the trial documents to another party or move them to another location, the sponsor must be notified.

16.2 Trial Master File

Ferring will archive the trial master file in accordance with ICH-GCP and applicable regulatory requirements.

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APPENDICES

Appendix I – Clinical Global Impressions Scales

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

Appendix II – Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness (HPWSQ-R) Scale – completed by the parent/caregiver

This survey will help keep track of how things have been with your child in the <u>past week.</u>

For each one of the survey items, please mark an ☒ in the one box that best describes your answer.

1. These questions are about how things have been with your child <u>during the past week?</u> For each question, please give the one answer that comes closest to the way to describe the situation-

	Not at all	A little bit	Moderate	Quite a bit	Extremely
	▼	▼	▼	▼	▼
a How upset did your child generally become when denied a desired food?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b How persistent was your child in asking or looking for food after being told "no" or "no more"?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c How distressed did your child become when stopped from talking about food or engaging in food-related behaviors?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d How "clever" or "fast" was your child in obtaining food?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e To what extent did food-related thoughts, talk, or behavior interfere with your child's normal daily routines, self-care, school, or work?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. How much of the time during the <u>past week did your child</u> …

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a Try to bargain or manipulate to get more food	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Forage through the trash for food	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Get up at night to food seek?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Talk about food or engaged in food-related behaviors, outside of normal meal times	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Try to steal food	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. During the past week, once your child had food on his/her mind, how <u>easy</u> was it for you or others to re-direct your child away from food to other things?

Extremely easy	Very easy	Somewhat hard	Very hard	Extremely hard
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix III – Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness (HPWSQ-R-C) Scale – administered by the clinician

This survey will help keep track of how things have been with the patient in the past week.

For each one of the survey items, please mark an ☒ in the one box that best describes your answer.

1. These questions are about how things have been with the patient during the past week? For each question, please give the one answer that comes closest to the way to describe the situation-

	Not at all	A little bit	Moderate	Quite a bit	Extremely
a How upset did the patient generally become when denied a desired food?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b How persistent was the patient in asking or looking for food after being told "no" or "no more"?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c How distressed did the patient become when stopped from talking about food or engaging in food-related behaviors?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d How "clever" or "fast" was the patient in obtaining food?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e To what extent did food-related thoughts, talk, or behavior interfere with the patient's normal daily routines, self-care, school, or work?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. How much of the time during the <u>past week did the patient</u> …

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
	▼	▼	▼	▼	▼
a Try to bargain or manipulate to get more food	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Forage through the trash for food	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Get up at night to food seek?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Talk about food or engaged in food-related behaviors, outside of normal meal times	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Try to steal food	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. During the past week, once the patient had food on his/her mind, how <u>easy</u> was it to re-direct the patient away from food to other things?

Extremely easy	Very easy	Somewhat hard	Very hard	Extremely hard
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix IV – Children's Yale-Brown Obsessive Compulsive Scale

CY-BOCS Symptom Checklist
Children's Yale-Brown Obsessive Compulsive Scale
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 (below), ascertain current and past symptoms.
3. Next, administer the 10 item severity ratings (other form) to assess the severity of the OCD during the last week.
4. Re-administer the CY-BOCS Severity Rating Scale to monitor progress.

Patient _____ Date _____

CY-BOCS Obsessions Checklist

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

Current	Past	Contamination Obsessions	Current	Past	Sexual Obsessions
□	□	Concern with dirt, germs, certain illnesses (e.g., AIDS)	□	□	Forbidden or perverse sexual thoughts, images, impulses
□	□	Concerns or disgust with bodily waste or secretions (e.g. urine, feces, saliva)	□	□	Content involves homosexuality
□	□	Excessive concern with environmental contaminants (e.g., asbestos, radiation, toxic waste)	□	□	Sexual behavior towards others (aggressive)
□	□	Excessive concern with household items (e.g., cleaners, solvents)	□	□	Other (describe) _____
□	□	Excessive concern about animals / insects			**Hoarding / Saving Obsessions**
□	□	Excessively bothered by sticky substances or residues	□	□	Fear of losing things
□	□	Concerned will get ill because of contaminant	□	□	Other (describe) _____
□	□	Concerned will get others ill by spreading contaminant (aggressive)	□	□	**Magical Thoughts / Superstitious Obsessions**
□	□	No concern with consequences of contamination other than how it might feel *	□	□	Lucky / unlucky numbers, colors, words
□	□	Other (describe) _____	□	□	Other (describe) _____
		Aggressive Obsessions			**Somatic Obsessions**
□	□	Fear might harm self	□	□	Excessive concern with illness or disease *
□	□	Fear might harm others	□	□	Excessive concern with body part or aspect of appearance (e.g. dismorphophobia)
□	□	Fear harm will come to self	□	□	Other (describe) _____
□	□	Fear harm will come to others (maybe because of something child did or did not do)			**Religious Obsessions**
□	□	Violent or horrific images	□	□	Excessive concern or fear of offending religious objects
□	□	Fear of blurting out obscenities or insults	□	□	Excessive concern with right / wrong morality
□	□	Fear of doing something embarrassing *	□	□	Other (describe) _____
□	□	Fear will act on unwanted impulses (e.g., to stab a family member)			**Miscellaneous Obsessions**
□	□	Fear will steal things	□	□	The need to know or remember
□	□	Fear will be responsible for something else terrible happening (e.g. ,fire, burglary, flood)	□	□	Fear of saying certain things

□	□	Other (describe) _____	□	□	Fear of not saying just the right thing
			□	□	Intrusive (non – violent) images
			□	□	Intrusive sounds, words, music, or numbers
			□	□	Other (describe) _____

Target Symptoms List for Obsessions

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

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

CY-BOCS Symptom Checklist
Children's Yale-Brown Obsessive Compulsive Scale

CY-BOCS Compulsions Checklist

Check all symptoms that apply (Items marked "*" may or may not be OCD phenomena)

Current	Past	Washing / Cleaning Compulsions	Current	Past	Hoarding / Saving Compulsions
□	□	Excessive or ritualized hand washing			Distinguish from hobbies and concern for objects of monetary or sentimental value
□	□	Excessive or ritualized showering, bathing, tooth brushing, grooming, toilet routine	□	□	Difficulty throwing things away, saving bits of paper, string, etc.
□	□	Excessive cleaning of items, such as personal clothes or important objects	□	□	Other (describe) _____
□	□	Other measures to prevent or remove contact with contaminants			**Excessive Games / Superstitious Behaviors**
□	□	Other (describe) _____	□	□	Distinguish from age appropriate magical games (e.g. array of behavior, such as sleeping over certain spots on a floor, touching an object / self a certain number of times to prevent something bad from happening)
		Checking Compulsions	□	□	Other (describe) _____
□	□	Checking locks, toys, school books / items, etc.	□	□	**Rituals Involving Other Persons**
□	□	Checking associated with getting washed, dressed, or undressed	□	□	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)
□	□	Checking that did not / will not harm others	□	□	Other (describe) _____
□	□	Checking that did not / will not harm self	□	□	**Miscellaneous Compulsions**
□	□	Checking that nothing terrible did / will happen	□	□	Mental rituals other than checking / counting
□	□	Checking that did not make mistake	□	□	Need to tell, ask, or confess
□	□	Checking tied to somatic obsessions	□	□	Measures, not checking, to prevent:
□	□	Other (describe) _____	□	□	harm to self
		Repeating Rituals	□	□	harm to others
□	□	Rereading, erasing, or rewriting	□	□	terrible consequences
□	□	Need to repeat activities (e.g. in / out of doorway, up / down from chair)	□	□	Ritualized eating behaviors*

□	□	Other (describe) _____	□	□	Excessive list making*
		Counting Compulsions	□	□	Need to touch, tap, rub*
□	□	Objects, certain numbers, words, etc.	□	□	Need to do things (e.g. touch or arrange until it feels just right)
□	□	Other (describe) _____	□	□	Rituals involving blinking or staring
		Ordering / Arranging	□	□	Trichotillomania (hair pulling)
□	□	Need for symmetry / evening up (e.g. lining items up in a certain way or arranging personal items in specific patterns)	□	□	Other self-damaging or self-mutilating behaviors
			□	□	Other (describe) _____

Target Symptoms List for Compulsions

COMPULSIONS (describe, listing by order of severity, with #1 being the most severe, #2 second most severe, etc.)

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

CY-BOCS Severity Ratings

Children's Yale-Brown Obsessive Compulsive Scale

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	Moderate	Severe	Extreme
		less than 1 hr/day or occasional intrusion	1 to 3 hrs/day or frequent intrusion	greater than 3 and up to 8 hrs/day or very frequent intrusion	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	Moderate	Severe	Extreme
		slight interference with social or school activities, but overall performance not impaired	definite interference with social or school performance, but still manageable	causes substantial impairment in social or school performance	incapacitating
Score	0	1	2	3	4

3. Distress Associated with Obsessive Thoughts

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

5. Degree of Control Over Obsessive Thoughts

	Complete Control	Much Control	Moderate Control	Little Control	No Control
		usually able to stop or divert obsessions with some effort and concentration	sometimes able to stop or divert obsessions	rarely successful in stopping obsessions, can only divert attention with difficulty	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**		

Appendix V – Food Domain of the Reiss Profile

REISS PROFILE OF FUNDAMENTAL GOALS
AND MOTIVATION SENSITIVITIES
FOR PERSONS WITH MENTAL RETARDATION
(*Food Domain Only)

Information on Person You are Rating

Be sure that you have known the person you are rating for at least four months

State of residence: _____

Age _____

Gender: ☐ Male ☐ Female

Racial Background: _____

Approximate IQ (check one):

☐ 50 and above

☐ 35 – 50

☐ less than 35

Does this person have psychiatric diagnosis or behavior problem? ☐ yes ☐ no

If yes, please indicate the diagnosis or the nature of the behavior problem as best you can.

_____

_____

_____

_____

_____

_____

_____

Instructions: Please indicate if you agree or disagree that each of the following phrases is true of the person you are rating. If the phrase is a valid description of the person, indicate if you agree or strongly agree. If the phrase is an invalid description of the person, indicate if you disagree or strongly disagree. Use the neutral rating if you have no opinion, do not know, or feel that the description is not applicable. Each rating should be made without consulting others. Thank you for your assistance.

SD	(Strongly Disagree):	this phrase is not at all characteristic of the person
D	(Disagree):	this phrase does not characterize the person well
N	(Neutral):	do not know, not applicable
A	(Agree):	this phrase somewhat characterizes the person
SA	(Strongly Agree):	this phrase is definitely characteristic of the person

1.	More than most people, enjoys eating…….SD	D	N	A	SA
2.	Always thinking about food…….. SD	D	N	A	SA
3.	Always eating…….. SD	D	N	A	SA
4.	Very hearty appetite…….. SD	D	N	A	SA
5.	Eating is more important than it is for most people…….. SD	D	N	A	SA
6.	More than most people, becomes upset if meals are delayed.... SD	D	N	A	SA
7.	Often asks about /plans next meal (*What's for lunch?*)…….. SD	D	N	A	SA

Appendix VI – Nutritional Phase Assessment

Phase 0 Decreased fetal movements and lower birth weight

Full-term birth weight and BMI are about 15–20% less than the siblings
Typically normal gestational age
85% have decreased fetal movements

Phase 1a Hypotonia with difficulty feeding (0–9 months)

Weak, uncoordinated suck. Usually cannot breastfeed
Needs assistance with feeding either through feeding tubes (nasal/oral gastric tube or gastrostomy tube) or orally with special, widened nipples. Many would die without assisted feeding
Oral feeds are very slow
Severely decreased appetite. Shows little or no evidence of being hungry
Does not cry for food or get excited at feeding time
If feeding just occurred when baby ‘‘acted hungry’’ then would have severe ‘‘failure-to-thrive’’
Weak cry

Phase 1b No difficulty feeding and growing appropriately on growth curve (9–25 months)

No longer needs assisted feeding
Growing steadily along growth curve with normal feeding
Normal appetite

Phase 2a Weight increasing without an increase in appetite or excessive calories (2.1–4.5 years)

Infant starts crossing growth curve centile lines
No increase in appetite
Appetite appropriate for age
Will become obese if given the recommended daily allowance (RDA) for calories or if eating a ‘‘typical’’ toddler diet of 70% carbohydrates
Typically needs to be restricted to 60–80% of RDA to prevent obesity

Phase 2b Weight increasing with an increase in appetite (4.5–8 years)

Increased interest in food. Frequently asking ‘‘food related’’ questions
Preoccupied with food. Very concerned about the next meal/snack (e.g., ‘‘Did you remember to pack my lunch?’’)
Increased appetite
Will eat more food than a typical child if allowed
Will eat food within their line of sight if unattended
Will become obese if allowed to eat what they want
Can be fairly easily redirected about food
Can feel full
Will stop eating voluntarily

Phase 3 Hyperphagic, rarely feels full (8 years - adulthood)

Constantly thinking about food
While eating one meal they are already thinking about the next meal
Will awaken from sleep early thinking about food

Will continue eating if portion size is not limited
Rarely (truly) feels full
Will steal food or money to pay for food
Can eat food from garbage and other unsavory/inedible sources (e.g., dog food, frozen food, crayons, etc.)
Typically are not truthful about what they have eaten (i.e. amount and types of food)
Will gain considerable amount of weight over a short period of time if not supervised (e.g., some individuals are known to have gained up to 20 pounds in one weekend)
Food typically needs to be locked up. Frequently the child will ask the parent to lock the food if the parent has forgotten
Will break into neighbors' houses for food
Temper tantrums and ''meltdowns'' frequently related to food
Needs to be placed on a diet that is approximately 50–70% of the RDA to maintain a healthy weight

Phase 4 Appetite is no longer insatiable (adulthood)

Appetite may still be increased or may be normal or less than normal
Previously in phase 3, but now a noticeable improvement in their appetite control
Can feel full
Appetite can fluctuate in this phase, but the key component is noticeable improvement in control of appetite compared to when they were younger
Not as preoccupied with food
Absence of major temper tantrums and ''meltdowns'' related to food
Onset in adulthood. Could be as early as 20s or as late as 40–50s
Most adults have not gone into this phase and maybe some (most?) never will

Miller et al 2011 **(**5**)**

Appendix VII – List of Drugs Containing Prostaglandins

1. Apo-Misoprostol
2. Arthotec
3. Arthotec Akut
4. Arthotec Forte
5. Arthrotec
6. Artotec
7. Artrenac Pro
8. Artrene SR
9. Corrigast
10. Cyprostol
11. Cytolog
12. Cytotec
13. Glefos
14. Gymiso
15. Menpros
16. Mirolut
17. Misodex
18. Misopess
19. Misoprost
20. Misoprostol
21. Misotrol
22. Mizoprostol
23. Novo-Misoprostol
24. PMS-Misoprostol
25. Symbol

FERRING
PHARMACEUTICALS

Statistical Analysis Plan

Title of trial: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Intranasal Carbetocin in Subjects with Prader-Willi Syndrome (PWS)
NCT number: NCT01968187
Sponsor trial code: 000114
Date: -

[Template[I] for]
STATISTICAL ANALYSIS PLAN

A Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Intranasal Carbetocin in Subjects with Prader-Willi Syndrome (PWS)

Trial Code 000114

Investigational Product:	Carbetocin (FE 992097)
Indication:	Treatment of hyperphagia behavioral symptoms in children and adults diagnosed with PWS
Phase:	2a
Author:	PPD Ph.D.
Date of issue:	24 July 2014
Version:	1.0

Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes

Signed[II] agreement on Statistical Analysis Plan

Author:

PPD Ph.D.
PPD Biostatistics
C

Date (dd/mm/yyyy)

Review:

PPD M.D.
PPD Gastroenterology
aScience Center U.S., Inc.

Date (dd/mm/yyyy)

PPD MD, MBA
PPD
Ferring International PhamaScience Center U.S., Inc.

Date (dd/mm/yyyy)

PPD
ance Marketed Products

Date (dd/mm/yyyy)

PPD
PPD Clinical Operations
nternational PhamaScience Center U.S., Inc.

Date (dd/mm/yyyy)

PPD MSc.
PPD Biostatistics / Project Statistician
rnational PhamaScience Center U.S., Inc.

Date (dd/mm/yyyy)

PPD
PPD Pharmacokineticist
Ferring International PhamaScience

Date (dd/mm/yyyy)

Approval:

PPD Ph.D.
Biometrics
A/S

Date (dd/mm/yyyy)

[II] Can be replaced by a list of reviewers/approvers if sign off can be performed in the REAL system

TABLE OF CONTENTS

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical analyses for Trial 000114 based on the protocol amendment (version 4, dated 10 February 2014) "A Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Effectiveness of Intranasal Carbetocin in Subjects with Prader Willi Syndrome (PWS)".

The SAP provides a more technical and detailed elaboration of the statistical analyses of efficacy and safety as outlined and/or specified in the protocol as well as data handling rules and exploratory analyses not mentioned in the protocol.

1.1 Definitions/ Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
Enrolled	When subject and Investigator signed the Informed Consent Form
Randomised	Subject randomised to trial treatment
Screened	Subject who enters the screening phase

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CRF	Clinical Report Form
CS	Clinical Significant
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
ECG	Electrocardiogram
FAS	Full Analysis Set
F/U	Follow-up
HPWSQ-R	Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness – completed by the parent/caregiver
HPWSQ-R-C	Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness-Clinician – administered by the clinician
IMP	Investigational Medicinal Product

Abbreviations	**Meaning of abbreviations in document**
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinical Significant
OCD	Obsessive-Compulsive Disorder
PK	Pharmacokinetic
PWS	Prader Willi Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHODrug	World Health Organisation Drug Dictionary

2 Trial Objectives and Endpoints

2.1 Objectives

Primary objective

- To assess the effect of intranasal carbetocin (FE 992097) on hyperphagia behavioral symptoms in subjects with PWS, measured by the Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness (HPWSQ-R) scale – completed by the subject's parent/caregiver

Secondary objectives

- To assess the effect of intranasal carbetocin (FE 992097) on hyperphagia behavioral symptoms in subjects with PWS, measured by the Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness-Clinician (HPWSQ-R-C) scale – administered by the clinician
- To assess improvement of PWS symptoms, assessed by the Clinical Global Impression (CGI) scale
- To assess safety and tolerability of intranasal carbetocin
- To assess a population pharmacokinetic model for the patient population utilizing sparse data sampling
- To assess the effects of intranasal carbetocin on PWS maladaptive behaviors, assessed by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
- To assess the sensitivity of Food Domain of the Reiss Profile

2.2 Endpoints

Primary endpoint

- Change in HPWSQ-R total score from Visit 2/Baseline to Visit 4

Secondary endpoints

1. Clinical Global Impression-Improvement after treatment (CGI-I) score at Day 8 and Visit 4
2. Change from Visit 2/Baseline to Day 8 and Visit 4 for the following measurements:
   - HPWSQ-R hyperphagia behavior, drive, and severity domain scores
   - HPWSQ-R-C total score
   - HPWSQ-R-C hyperphagia behavior, drive, and severity domain scores
3. Change from Visit 1/Baseline to Day 8 and Visit 4 for the following measurements:

- CY-BOCS score
- Food Domain of the Reiss Profile

4. Population PK/PD relationships for carbetocin

Safety endpoints

- Frequency, severity and seriousness of adverse events
- Clinically significant changes in vital signs
- Clinically significant findings during physical and laboratory assessments
- Physical examinations, including focused nasal examinations and nasal irritation, graded 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

3 Trial design

3.1 General Design Considerations

This is a prospective, randomized, double-blind, placebo-controlled, multi-center, parallel trial in subjects with PWS between 10 and 18 years of age with genetically confirmed diagnosis of PWS and a documented nutritional phase 3 based on the criteria defined by Miller et al 2011. The trial includes a Screening Period, a 14-day Treatment Period, and a Follow-Up Period. Subjects, along with their parent or caregiver, will be required to visit the investigational site 4 times over the course of the trial, and participate in 2 phone call assessments.

- Visit 1: Screening Period (Day -7 to Day 0)
- Visit 2: Baseline 1st day dosing on site (Day 1)
- Visit 3: 2nd day dosing on site (Day 2)
- Phone call assessment (Day 8)
- Visit 4: End-of-Treatment Visit (Day 15)
- Follow-up phone call (Day 19±3)

Following appropriate informed consent procedures, subjects will undergo screening evaluations to determine eligibility before randomization. Screening evaluations include a physical examination, vital signs, height, weight, 12-lead electrocardiogram (ECG), nasal examination, and laboratory assessments - hematology, clinical chemistry, hemostasis, and urinalysis. Approximately 38 eligible male or female subjects will be randomized at Visit 2 to 1 of 2 treatment groups for 14 days:

- Carbetocin: each spray pump actuation will deliver a 50 µL volume of solution containing 1.6 mg carbetocin; each dose will consist of 3 spray pump actuations in each nostril to deliver a total of 9.6 mg carbetocin
- Placebo: each spray pump actuation will deliver a 50 µL volume of sterile sodium chloride solution 0.9%; each dose will consist of 3 spray pump actuations in each nostril

After randomization, efficacy measures and other assessments, including physical examination, vital signs, nasal examination, and collection of blood samples for clinical laboratory and pharmacokinetic (PK) evaluation, will be performed at selected visits according to Schedule of Activities in the Protocol. Subjects will be closely monitored for adverse events throughout the trial following informed consent.

Prior to first dosing at the investigational site, parents/caregivers will be trained on the proper use of the nasal spray device and procedures for Investigational Medicinal Product (IMP) home delivery. Parents/caregivers will be instructed to administer 3 intranasal spray pumps of blinded IMP per nostril 3 times daily before meals within the following intervals:

Morning dose: 06:00 a.m. – 09:00 a.m.

Midday dose: 11:00 a.m. – 1:00 p.m.

Evening dose: 4:30 p.m. – 6:00 p.m.

Initial IMP dosing at Visit 2 (Day 1) and Visit 3 (Day 2) will take place under observation of the site staff at the investigational site. Subject vital signs will be monitored prior to and after IMP dosing at 30-minute intervals for 2 hours after each dose. IMP will be shipped by central pharmacy directly to the subject's residence on regular intervals as needed for the duration of the Treatment Period. IMP will be administered by parents/caregivers 3 times per day before meals within the above specified dosing intervals. The IMP will require refrigeration during shipment to and during storage at the investigational site or subject's residence until administered.

3.2 Determination of Sample Size

Based on available literature (Dykens et al 2007), the HPWSQ-R total score at baseline (Visit 2) is assumed to be normally distributed with a standard deviation of 6.12, and the standard deviation of the change between baseline (Visit 2) and Visit 4 is estimated to be between 5 and 6. With 30 subjects eligible for the primary efficacy assessment, the trial has at least 80% power to detect a borderline statistically significant difference (1-sided 10% significance) between 2 groups when the true treatment group difference is -5 under the standard deviation of 5 to 6. Subjects are randomized in a 1:1 ratio to either placebo or carbetocin.

The efficacy of carbetocin will be assessed by change in HPWSQ-R total score from Visit 2/Baseline to Visit 4. Assuming a dropout rate of approximately 20%, at least 19 subjects per treatment arm will need to be randomized to have a total of 30 subjects eligible for the primary efficacy assessment.

4 Subject Disposition

The number of subjects who enrolled and/or randomized into the trial will be summarized overall. Subjects who discontinue IMP or are removed from the trial permanently will also be reported by the treatment received immediately prior to discontinuation. Reasons for trial discontinuation will be summarized by treatment as well as randomization errors and time of withdrawal from the trial, if appropriate. No formal statistical analysis will be performed.

The number of subjects screened but not randomized/allocated to treatment will be presented with the reason(s) for screen failure in a data listing.

5 Protocol Deviations

Rating of protocol deviations as 'minor' and 'major' will be decided by the Ferring clinical team on the basis of a blinded review of data before declaration of clean file and lock of database. Major protocol deviations will lead to exclusion of data from the Per Protocol analyses. Minor protocol deviations will not lead to exclusion of data from any analyses.

The full list of major protocol deviations will be detailed and documented in the clean file document prior to treatment unblinding.

Major protocol deviations include, but are not restricted to, the following:

- Violation of inclusion or exclusion criteria that may affect the efficacy analysis such as:
    - Inclusion criterion 4, genetically confirmed diagnosis of PWS
    - Inclusion criterion 5, Nutritional phase 3 PWS criteria based on Miller et al, 2011;
    - Inclusion criterion 6, HPWSQ-R score greater than 13 at screening, Visit 1
    - Exclusion criterion 5, Prior or concomitant use of a selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI), antipsychotic medication, wakefulness-promoting drug, or thyroid hormone that does not comply with the criteria in Section 4.3.1 of the Protocol;
    - Exclusion criterion 6, Use of any of the prohibited medications or therapies listed in Section 4.3.2 of Protocol
- Actual treatment not in accordance with randomized treatment.
- Less 80% compliance with treatment and/or missing more than 4 consecutive doses
- HPWSQ-R assessment not completed on Day 15

6 Analysis sets

6.1 Intention-To-Treat Analysis Set

The intention-to-treat (ITT) analysis set comprises of all randomized (as planned) subjects.

6.2 Full-Analysis Set

The full analysis set (FAS) population will include all subjects in the safety population who have the primary efficacy endpoint measured (Baseline and Day 8±1 or Day 15). Analyses for the FAS will be conducted according to the randomized treatment. The primary endpoint will be analyzed in the FAS population.

6.3 Per Protocol Analysis Set

Subjects in the FAS population with major protocol deviations will be excluded from the PP (per-protocol) analysis set. These subjects will be identified prior to breaking the study blind. Analyses for the PP will be conducted according to the randomized treatment.

6.4 Safety Analysis Set

All subjects who received any amount of IMP will be included in the safety population. Analyses for the safety population will be conducted according to the actual treatment received.

6.5 Pharmacokinetic Analysis Set

The pharmacokinetic (PK) population will include all subjects in the safety population who have sufficient plasma carbetocin concentrations for inclusion in population PK modeling. *PK analysis will be addressed in a separate document.*

7 Trial population

7.1 Demographics and Other Baseline Characteristics

Categorical data will be summarized using numbers and percentages. The percentages are based on the total number of subjects with a corresponding assessment. Continuous data will be presented, for example, using the number of subjects (n), mean and standard deviation, median, minimum and maximum. Summary will be conducted for the safety population or FAS population if specified. All baseline characteristics will be listed.

Missing values concerning demographics and baseline characteristics will not be imputed.

7.1.1 Demographics

Baseline demographics variables include age, sex, race and ethnicity, height, weight and Body Mass Index (BMI). Age will be calculated as (Date of Informed Consent – Date of Birth)/365.25, rounded down to the nearest integer. BMI will be calculated as body weight (kg)/(height (m))^2, rounded to one decimal place.

Descriptive statistics of the demographics variables will be summarized based on FAS population by treatment randomized as well as based on safety population by actual treatment. No formal statistical analysis will be performed.

7.1.2 Vital Signs at Baseline

Baseline vital signs (blood pressure, pulse, body temperature, and respiration rate) will be summarized by treatment.

7.1.3 Trial-specific Baseline Variables or History of Disease

Descriptive statistics will be summarized by treatment for urine drug screen and alcohol test, and nutritional phase assessment.

Other baseline assessments will be presented and summarized in by-visit tables or in listings.

7.1.4 Laboratory Efficacy/Pharmacodynamic Parameters at Baseline

PK analysis will be addressed in a separate document.

7.2 Medical History

Medical and surgical history recorded at screening visit will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Medical and surgical history will be listed by treatment and subject as well as summarized by system organ class (SOC) and preferred term (PT).

7.3 Prior and Concomitant Medication

Prior and concomitant medications will be coded using World Health Organisation Drug (WHODrug) Dictionary version 01SEP2013. Medications will be listed by treatment and subject as well as summarized by Anatomical Therapeutic Chemical (ATC) classification 1st level (alphabetically), ATC classification 2nd level (in decreasing order of frequency) and treatment group. These medications will be tabulated separately for:

1) Prior medication; i.e. medication taken exclusively prior to first IMP administration
2) Concomitant medication, i.e. medication taken after IMP administration

If the timing of the dose of a concomitant medication cannot be established in relation to the administration of IMP, it will be considered as concomitant medication.

7.4 Physical Examination

Physical examination results will be listed by treatment and subject. Subjects with abnormalities at any screening, baseline, or post-baseline visit will be listed with all physical examination evaluations by body system for the Safety analysis set.

8 Exposure and Treatment Compliance

8.1.1 Extent of Exposure

The total trial treatment exposure will be summarized by treatment group for the safety population. Summary statistics are provided for the duration of exposure (number of days) of study medication (last known date patient took study medication - first dose date + 1).

8.1.2 Treatment Compliance

Treatment administration collected in the clinical report form (CRF) will be listed by treatment and subject. Treatment compliance will be calculated as (the number of actual doses intake / the number of planned doses)*100% where an actual dose consists of a total of six sprays between the two nostrils. The number of planned doses is 42 (=14*3) per study design.

The number of subjects who had at least 80% treatment compliance and missed no more than 4 consecutive dosing time-points will be summarized. The calculated treatment compliance will be listed as well.

9 Efficacy

9.1 General Considerations

Efficacy analysis will be conducted for the FAS population unless otherwise specified. All statistical tests will be performed using a one-sided test at a 10% significance level. No adjustments will be made for multiple tests. Baseline for all efficacy analyses will be the values obtained at the last assessment prior to the first dose of IMP.

Handling of missing scores of questionnaire

A subscore or domain score of the HPWSQ-R questionnaire is defined as the sum of all items scores in the domain. The average value of completed items in a domain will be used an estimate of missing items. If more than 50 percent of the items from a domain are missing, the corresponding domain score will be set to missing. Total score is the sum of these three subscores. Total score will be missing if any subscore is missing.

The last observation carried forward (LOCF) method will be used to carry forward non-missing values of HPWSQ-R total score during the phone call assessment (Day 8±1) to impute missing values of HPWSQ-R total score at Visit 4 (i.e. exactly on Day 15). Any assessments not within the window Day 8±1 and prior to Day 15 will not be used for LOCF imputation. For subjects who discontinued IMP prior to Day 12, if they have HPWSQ-R assessments on Day 15, then the assessments are considered invalid for primary endpoint analysis. LOCF values at Day 15 will be populated with non-missing values of HPWSQ-R total score during the phone call assessment (Day 8±1).

Similarly, HPWSQ-R-C will be handled in the same way as HPWSQ-R. The analyses of HPWSQ-R and HPWSQ-R-C will be conducted based on LOCF values unless otherwise specified.

No imputation will be applied to the domain score of HPWSQ-R and HPWSQ-R-C, and other questionnaires (Clinical Global Impression, CY-BOCS and Food Domain of the Reiss Profile).

9.2 Primary Endpoint(s)

The Hyperphagia in Prader-Willi Syndrome questionnaire (HPWSQ-R) is an informant-based tool for examining the psychological, developmental, and neurobiological correlates of hyperphagia in PWS. The items measure hyperphagic symptoms are reported by caregivers and are rated on a five-point scale (1: not at all/none of the tim/extremely easy to 5: extremely/all of the time/extremely hard). HPWSQ-R Questionnaire is classified into 3 domains; behavior, drive, and severity.

Subdomain	Question
Hyperphagic Behavior	1d. How “clever” or “fast” was your child in obtaining food?
	2a. Try to bargain or manipulate to get more food
	2b. Forage through the trash for food

	2c. Get up at night to food seek 2e. Try to steal food
Hyperphagic Drive	1a. How upset did your child generally become when denied a desired food? 1b. How persistent was your child in asking or looking for food after being told "no" or "no more"? 1c. How distressed did your child become when stopped from talking about food or engaging in food-related behaviors? 3. Once food on mind, how easy to redirect away from food
Hyperphagic Severity	1e. To what extent did food-related thoughts, talk, or behaviour interfere with your child's normal daily routines, self-care, school, or work 2d. Talk about food or engaged in food-related behaviors, outside of normal meal times

The subscore for a domain is defined as the sum of all item scores in the domain. Total score is the sum of these three subscores. Total score will be missing if any subscore is missing. Missing item scores and total score will be handled as described in the section 9.1.

9.2.1 Primary Variable(s) Analysis

The primary variable is change in HPWSQ-R total score from baseline to Visit 4 (Day 15) and will be analyzed in the FAS population using an analysis of covariance (ANCOVA) model with treatment and site as fixed effects and HPWSQ-R total score at baseline as a covariate. The treatment group difference in total score between placebo and carbetocin will be calculated by subtracting the mean change from baseline in placebo from that in the carbetocin group. A borderline statistically significant difference at the 10% significant level will be achieved if the upper limit of the 90% 1-sided confidence interval (CI) for the treatment difference is less than zero. The corresponding p-value will be reported as well.

Summary of HPWSQ-R total score will be presented as well as a box-and-whisker plot of change in HPWSQ-R total score by visit.

9.2.2 Sensitivity Analyses

The analysis of the primary endpoint in the section 9.2.1 will be also conducted based on the subjects in the PP population and ITT population.

In addition, the primary endpoint will be analyzed using repeated measures analysis with treatment, site, visit and treatment-by-visit interaction as fixed effects and HPWSQ-R total score at baseline as a covariate. An unstructured working correlation matrix will be used for the analysis. LOCF will not be used to impute missing values because it would affect the correlation of observations between weeks. The two treatment groups will be compared at Visit 4 (Day 15). The LS means, the LS mean difference, and 90% 1-sided confidence interval (CI) for the treatment difference will be presented will be presented at each visit as well.

9.3 Secondary Endpoint(s)

Secondary endpoints include Clinical Global Impression-Improvement after treatment (CGI-I) score at Day 8 and Visit 4, change from Visit 2/Baseline to Day 8 and Visit 4 for the following measurements:

- HPWSQ-R hyperphagia behavior, drive, and severity domain scores
- HPWSQ-R-C total score
- HPWSQ-R-C hyperphagia behavior, drive, and severity domain scores

and change from Visit 1/Baseline to Day 8 and Visit 4 for the following measurements:

- CY-BOCS total score
- Food Domain of the Reiss Profile

The improvement of PWS symptoms will be assessed by the Clinical Global Impression (CGI). The CGI scale is a 7-point clinician rating of illness severity (1 = no illness, 7 = extremely ill), at the beginning of the trial and a 7-point clinician rating of improvement of patient condition (1 = very much improved, 7 = very much worse), during and at the end of the trial.

HPWSQ-R-C scale consists of the same 11 questions and has the same scoring as HPWSQ-R. HPWSQ-R-C is administered by the same clinician throughout the trial while the HPWSQ-R scale is administered by the parent or caregiver.

The CY-BOCS is a clinician rated, semi-structured inventory of specific symptoms and symptom severity (0 = none, 4 = extreme) in pediatric obsessive-compulsive disorder (OCD). It includes 2 primary components: the Symptom Checklists 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 food domain of the Reiss Profile consists of 7 questions that pertain to food seeking behaviour. For analysis purpose, the scales of Food Domain of the Reiss Profile will be scores as follows:

Scales of Food Domain of the Reiss Profile	Score
Strongly Disagree	-2
Disagree	-1
Neutral	0
Agree	1
Strongly Agree	2

Total score of Food Domain of the Reiss Profile is defined as the sum of all individual item scores.

The secondary endpoints will be analyzed in a similar fashion as the primary endpoint. All analysis of secondary endpoints will be conducted using ANCOVA model treatment and site as fixed effects

and baseline score as a covariate. Clinical Global Impression - Severity (CGI-S) will be used as baseline covariate for CGI-I analysis.

9.4 Exploratory Analyses

The relation between the primary endpoint and the secondary endpoints will be explored by visit for the FAS population using the Pearson correlation coefficients. An ad-hoc analysis might be performed to further explore the relation between the primary endpoint and the secondary endpoints.

10 Safety

10.1 General Considerations

Safety parameters will be evaluated for the safety analysis set. Complete listings and summary tables for all safety information, including adverse events, clinical laboratory safety data, physical examination, nasal examination, vital signs, and ECG will be presented. No formal statistical analysis will be performed.

Unscheduled assessments prior to the first IMP administration will be included to derive baseline while post-baseline unscheduled assessments will not be included in the data analysis unless specified.

10.2 Adverse Events

Adverse events (AEs) are classified according to the MedDRA version 16.1 give a system organ class and preferred term for each event.

A treatment-emergent adverse event (TEAE) is any adverse event that begins during the treatment period or worsening of a pre-existing medical condition. The Treatment Period is the period during which a subject receives IMP (including the residual time of drug effect). More specially, for subjects who completing all doses as planned on Day 14, the Treatment Period is Day 1 to Day 15. For subjects who discontinued IMP, the Treatment Period is Day 1 to the dose date + 1.

TEAEs will be listed by treatment and subject, and the incidence of TEAEs will be presented by treatment. In addition, TEAEs will be presented by causality (relationship to the trial medication) and intensity (severity) and seriousness. Serious adverse events (SAEs) and adverse events leading to discontinuation will be listed.

If a subject has an AE with unknown intensity, then the subject is counted in the category of "Severe". If an AE with unknown relationship to IMP, then the AE is considered to be related to IMP.

10.2.1 Overview of Treatment-Emergent Adverse Events

A TEAE overview summary table will be prepared including the number of subjects reporting a TEAE, the percentage of subjects (%) with a TEAE, and the number of events (E) reported, for the following categories:

- Treatment-emergent adverse events
- Treatment-emergent adverse events leading to Deaths
- Treatment-emergent adverse events by intensity
- Serious treatment-emergent adverse events

- Treatment-emergent adverse events leading to withdrawal
- Adverse drug reactions

10.2.2 Incidence of Adverse Events

TEAEs will be summarized in a table by treatment, system organ class (SOC) and preferred term (PT). The table will display the total number of subjects reporting a TEAE, the percentage of subjects (%) with a TEAE, and/or the number of events (E) reported. TEAEs will be presented by SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- All TEAEs
- TEAEs with an incidence [≥ 5%] of subjects in any treatment group
- TEAEs by causality (related/unrelated)
- TEAEs by intensity

Supporting data listings will be provided for:

- All adverse events
- Serious adverse events
- Adverse events leading to withdrawal.

10.3 Safety Laboratory Variables

Baseline for all laboratory analyses will be the values obtained at the last assessment prior to the first dose of IMP. End of trial will include the last post-baseline observation during the trial.

10.3.1 Summary Statistics

All chemistry, haematology, haemostasis, and urinalysis laboratory continuous data will be summarized for the baseline and post-baseline evaluations, as well as change from baseline, using descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum values.

10.3.2 Laboratory Variable Changes Relative to Normal Range

Changes relative to normal ranges are presented with shift tables with total number of subjects, and number and percent of subjects who experienced a shift.

The following categories for shift tables are defined:

- Low: Values which are below the lower reference range limit;
- Normal: Values which are within the lower and upper reference range;

- High: Values which are above the upper reference range limit.
- Absent: No value for measured variable (for urinalysis only)
- Present: Any value obtained for measured variable (for urinalysis only)

For all haematology, haemostasis and clinical chemistry laboratory variables, shift tables will be prepared to compare baseline values to the worst value at post-baseline (including unscheduled values). More specifically, for haematology, haemostasis and clinical chemistry, tables presenting the changes from *Low* or *Normal* to *High* and from *High* or *Normal* to *Low* will be provided. For urinalysis variables, shift tables will summarize the number (%) of subjects who had "absent" values at baseline and "present" values at post-baseline.

10.3.3 Markedly Abnormal Changes

A summary table will be prepared that displays for each laboratory variable the number and percentage of subjects in each treatment group with normal baseline values who had at least one pre-specified markedly abnormal value anytime during the treatment period. Pre-specified markedly abnormal criteria for laboratory tests are given in Appendix 1.

10.3.4 Data Listings

Clinical safety laboratory values will be listed by treatment, subject and test. All values outside the normal range will be identified.

Subjects with any markedly abnormal changes at any time-point will be also listed with all values of the corresponding laboratory tests. The laboratory values with markedly abnormal changes will be flagged out.

10.4 Vital Signs and ECG

10.4.1 Vital Signs

Baseline for all vital signs (blood pressure, pulse, body temperature, and respiration rate) analyses will be the values obtained at the last assessment prior to the first dose of IMP. End of trial will include the last post-baseline observation during the trial.

10.4.1.1 Summary Statistics

All vital signs data will be summarized for the baseline and post-baseline evaluations, as well as change from baseline, using descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum values.

10.4.1.2 Markedly Abnormal Changes

A summary table will be prepared that displays for each vital signs parameter the number and percentage of subjects in each treatment group with normal baseline values who had one or more

pre-specified markedly abnormal treatment-emergent values, according to the definition in Appendix 1. The markedly abnormal criteria will be used to define normal baseline as well.

10.4.1.3 Data Listings

Vital signs values will be listed by treatment and subject.

Subjects with any markedly abnormal changes at any time-point will be also listed with all values of the corresponding vital signs. The vital signs values with markedly abnormal changes will be flagged out.

10.4.2 ECGs

Baseline for all ECG analyses will be the values obtained at the last assessment prior to the first dose of IMP. End of trial will include the last post-baseline observation during the trial.

10.4.2.1 Summary Statistics

ECG qualitative data will be summarized in number (%) for "normal", "abnormal – not clinically significant (NCS)" and "abnormal –clinically significant (CS)" collected in CRF.

10.4.2.2 Markedly Abnormal Changes

Not applicable since no quantitative data will be collected for this study.

10.4.2.3 Data Listings

ECG data will be listed by treatment and subject.

10.5 Other Safety Variables

The remainder of the data collected in the CRF (e.g., pregnancy test, nasal examination) will be listed by treatment and subject. Nasal examination will be also summarized as described in the following section.

10.5.1 Nasal examination

Baseline for nasal examination analyses will be the values obtained at the last assessment prior to the first dose of IMP. End of trial will include the last post-baseline observation during the trial.

Number (%) of subjects with each grade of nasal examination result will be summarized by treatment, visit and timepoint. In addition, the changes in nasal examination result by treatment, visit and timepoint are presented with shift tables with total number of subjects, and number and percent of subjects who experienced a shift.

11 Interim analyses

No interim analysis is planned.

12 Deviations from protocol analysis

There are no deviations from the analyses planned in the protocol.

13 References

[1] Dykens EM, Maxwell MA, Pantino E, Kossler R, Roof E. Assessment of hyperphagia in Prader-Willi syndrome. Obesity. 2007;15:1816-26.

[2] Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome. Am J Med Genet A. 2011;155:1040-9.

14 Tables, Listings and Figures

The document with tables, figures and listings (TLF) shells presented in a separate document.

Appendix 1 Markedly Abnormal Laboratory Safety Values, Vital Signs

Table 1: Markedly abnormal Criteria for Laboratory Tests

HAEMATOLOGY				
Variable	**Units**	**Age**	**Markedly Abnormal Criteria**	
			Low	**High**
Hemoglobin	g/dL	6 mo-18 yr	≤ 8	NA
RBC	$x10^6/mm^3$	6 mo-18 yr	≤ 3.5	NA
Hematocrit	%	6 mo-18 yr	≤ 30	≥ 50
Leukocytes	$x10^3/mm^3$	6 mo to 18 yr	≤ 2.8	≥ 20
Neutrophils	$x10^3/mm^3$	6 mo-18 yr	≤ 1	≥ 10
Lymphocytes	$x10^3/mm^3$	2-18 yr	< 1	≥ 10
Eosinophils	%*	All ages	NA	≥ 10
Monocytes	%*	6 mo-18 yr	NA	≥ 15
Basophils	%*	6 mo-18 yr	NA	≥ 5
Platelets	$x10^3/mm^3$	6 mo-18 yr	≤ 50	≥ 750

*The percentage indicates the *relative* number of each type of leucocytes in the blood. The *absolute* count is calculated by multiply the relative value (%) by the total leukocyte count/100.

HEMOSTASIS AND COAGULATION				
Variable	**Units**	**Age**	**Markedly Abnormal Criteria**	
			Low	**High**
Fibrinogen	g/L	All	NA	≥ 5
Prothrombin Time (PT)	seconds	All	NA	≥ 20
Partial Thromboplastin Time (APTT)	seconds	6 mo-18 yr	≤ 20	≥ 50

CHEMISTRY				
Variable	**Units**	**Age**	**Markedly Abnormal Criteria**	
			Low	**High**
ALT	U/L	1-19yr	Not applicable	≥ 3x ULN
AST	U/L	10-19yr	Not applicable	≥ 3x ULN
Total protein	g/L	> 1yr	≤ 40	≥ 90
Albumin	g/L	All	≤ 25	> 60
Alkaline phosphatase	U/L	All	Not applicable	≥ 3x ULN
Total bilirubin	µmol/L	10-18yr	Not applicable	≥ 1.5xULN
Creatinine	µmol/L	All	Not applicable	≥ 120
Glucose	mmol/L	24m-11yr 12-18yr	≤ 2.5 ≤ 2.8	> 8 > 10
GGT	U/L	All	Not applicable	≥ 3x ULN
Urea nitrogen	mmol/L	All	Not applicable	≥ 8.0
Potassium	mmol/L	> 2m	≤ 3	≥ 6
Sodium	mmol/L	All	≤ 130	≥ 150
Calcium total	mmol/L	All	≤ 1.8	≥ 3
Chloride	mmol/L	All	≤ 90	≥ 115

Table 2: Markedly abnormal Criteria for Vital Signs

Markedly abnormal Criteria for Pulse Rate

Age	Low	High
9 years ≤ x < 11 years	≤66	≥114
11 years ≤ x < 13 years girls	≤66	≥114
11 years ≤ x < 13 years boys	≤61	≥109
13 years ≤ x < 15 years girls	≤61	≥109
13 years ≤ x < 15 years boys	≤56	≥104
15 years ≤ x < 17 years girls	≤56	≥104
15 years ≤ x < 17 years boys	≤51	≥99
17 years ≤ x < 19 years girls	≤51	≥99
17 years ≤ x < 19 years boys	≤46	≥94

Markedly abnormal Respiratory rate (breaths/min)

Age	Low	High
5 years <= x < 12 years	≤10	≥40
12 years <= x < 16 years	≤7	≥40
16 years <= x	≤7	≥30

Markedly abnormal blood pressure levels for BOYS by age

Age (years)	Unit	SBP Lower limit (≤)	SBP Upper limit (≥)	DBP Lower limit (≤)	DBP Upper limit (≥)
10 years <= x < 11 years	mmHg	77	127	34	88
11 years <= x < 12 years	mmHg	79	129	35	89
12 years <= x < 13 years	mmHg	81	131	35	89
13 years <= x < 14 years	mmHg	84	134	36	90
14 years <= x < 15 years	mmHg	86	136	36	90
15 years <= x < 16 years	mmHg	89	139	37	91
16 years <= x < 17 years	mmHg	92	141	39	93
17 years <= x < 18 years	mmHg	94	144	41	95
18 years <= x < 19 years	mmHg	94	144	41	95

Markedly abnormal blood pressure levels for GIRLS by age

Age (years)	**Unit**	**SBP Lower limit (≤)**	**SBP Upper limit (≥)**	**DBP Lower limit (≤)**	**DBP Upper limit (≥)**
10 years <= x < 11 years	mmHg	78	126	35	86
11 years <= x < 12 years	mmHg	80	128	36	87
12 years <= x < 13 years	mmHg	81	130	37	88
13 years <= x < 14 years	mmHg	83	132	38	89
14 years <= x < 15 years	mmHg	85	134	39	90
15 years <= x < 16 years	mmHg	86	135	40	91
16 years <= x < 17 years	mmHg	87	136	41	92
17 years <= x < 18 years	mmHg	87	136	41	92
18 years <= x < 19 years	mmHg	87	136	41	92