CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Carbetocin Nasal Spray for the Treatment of Hyperphagia in Prader-Willi Syndrome

Protocol Number: ACP-101-302
Amendment 2-GLOBAL

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SPONSOR SIGNATURE PAGE

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Carbetocin Nasal Spray for the Treatment of Hyperphagia in Prader-Willi Syndrome

Acadia PPD Clinical Development:
PPD MD
PPD Clinical Development
Acadia Pharmaceuticals Inc.
PPD
PPD
Phone: PPD

See appended electronic signature page

Signature Date

Acadia Study Lead:
PPD DO
Director of Clinical Research, Clinical Development
Acadia Pharmaceuticals Inc.
PPD
PPD
Phone: PPD

See appended electronic signature page

Signature Date

Acadia Biostatistics:
PPD Ph.D.
Executive Director, Biostatistics
Acadia Pharmaceuticals Inc.
PPD
USA
PPD
Phone: PPD

See appended electronic signature page

Signature Date

DECLARATION OF INVESTIGATOR

I confirm that I have read the above protocol. I understand it, and I will work according to the moral, ethical, and scientific principles governing clinical research as set out in the principles of Good Clinical Practice, as required by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E6 and as described in the applicable United States (US) Code of Federal Regulations (CFR) 21 CFR parts 50, 54, 56, 312, unless prohibited by other applicable local laws and regulations.

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Investigator

Signature	Date
Name (printed)	

PROTOCOL SYNOPSIS

Protocol number	ACP-101-302
IND number **EU CT number** **NCT number**	IND 138625 2023-506200-24-00 NCT06173531
Protocol title	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Carbetocin Nasal Spray for the Treatment of Hyperphagia in Prader-Willi Syndrome
Name of investigational product	Carbetocin nasal spray (ACP-101)
Indication	Hyperphagia in Prader-Willi syndrome
Phase of development	Phase 3
Sponsor	Acadia Pharmaceuticals Inc. 12830 El Camino Real, Suite 400 San Diego, CA 92130 USA
Study hypothesis	Carbetocin nasal spray (hereafter carbetocin) will be superior to placebo in the treatment of hyperphagia in Prader-Willi syndrome (PWS)
Primary objective To investigate the efficacy of treatment with carbetocin nasal spray versus placebo on hyperphagia in PWS	**Primary endpoint** • Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score – change from Baseline at Week 12
Secondary objectives To investigate the efficacy of treatment with carbetocin versus placebo on: • PWS • Hyperphagia in PWS	**Secondary endpoints** • Clinical Global Impression–Severity (CGI-S) for PWS score – change from Baseline at Week 12 • Clinical Global Impression–Change (CGI-C) for PWS score at Week 12 • Percentage of subjects with treatment response (defined as improvement from Baseline ≥8 points) based on the HQ-CT at Week 12 • CGI-S for hyperphagia in PWS score – change from Baseline at Week 12

Exploratory objectives To investigate the benefit of treatment with carbetocin versus placebo on • Anxiousness in PWS • Environmental controls • Caregiver burden • Healthcare utilization	**Exploratory endpoints** • PWS Anxiousness and Distress Behaviors Questionnaire (PADQ) score – change from Baseline at Week 12 • Food Safe Zone score – change from Baseline at Week 12 • Zarit Burden Interview (ZBI) score – change from Baseline at Week 12 • PWS-specific Healthcare Resource Use and Caregiver Burden Questionnaire (PWS-HRUQ) – change from Baseline at Week 12
Safety objective To investigate the safety and tolerability of treatment with carbetocin versus placebo	**Safety endpoints** • Treatment-emergent adverse events (TEAEs) • Serious adverse events (SAEs) • Withdrawals due to adverse events (AEs) • Potentially clinically important changes in other safety assessments • Device incidents, or device malfunctions
Pharmacokinetic objectives • To characterize the pharmacokinetics (PK) of carbetocin • To assess the exposure-response relationship	**Pharmacokinetic endpoints** • Plasma concentration of carbetocin • Carbetocin PK parameters using the population PK approach • Exposure-response (E-R) using appropriate E-R analysis methods

Number of study sites	Approximately 42 global sites will participate in this study.
Number of subjects planned	Approximately 170 subjects will be randomized.
Investigational product, dose, and administration	Carbetocin nasal spray 3.2 mg three times daily (TID) or placebo TID.
Study design	This is a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing carbetocin nasal spray 3.2 mg TID with placebo (matched placebo nasal spray TID) in subjects with PWS. Approximately 170 subjects will be randomized (85 subjects per treatment group). Randomization will occur at the

	Baseline visit. Subjects will be randomly assigned 1:1 to the active treatment group or placebo group in a blinded fashion, according to a computer-generated randomization schedule. The subject or legally acceptable representative (LAR) must provide written consent prior to the procedures being performed at the Screening visit. A caregiver must also provide written consent to participate as an informant in study assessments prior to the procedures being performed at the Screening visit. Randomization will be stratified by three age groupings: <12 years old, ≥12 to <17 years old, ≥17 years old; and by presence or absence of participation in a previous clinical study of carbetocin nasal spray. The Sponsor, subjects, caregivers, and Investigators and any other site or Sponsor personnel will be blinded to treatment assignment. **The study will have three periods:** • Screening period: up to 3 weeks • Double-blind treatment period: 12 weeks • Safety follow-up period: 30 (+4) days The study design schematic is provided in Figure S–1. The schedule of events and assessments is provided in Table S–1. An independent data and safety monitoring board (DSMB) will be convened for the study. **Screening Period (Up to 3 Weeks)** During the Screening period, subjects will be assessed for study eligibility. Only those subjects who meet all inclusion and no exclusion criteria will be eligible for the study. Investigators must not withdraw a subject's prohibited medication for the purpose of enrolling them into the study. Medications will be discontinued only if it is deemed clinically appropriate to do so and in consultation with the treating physician. **Double-blind Treatment Period (12 Weeks)** The Baseline visit will occur after screening procedures are completed and have not ruled the subject out of eligibility for the study. At Baseline, and upon confirmation of eligibility, subjects will be randomized in a 1:1 ratio to carbetocin or matching placebo. Baseline assessments (including a predose ECG) will be completed at the Baseline visit prior to administration of the first dose of study drug (Table S–1). A second (postdose) ECG

	will be completed 20 minutes (within a 10 to 40 minute window) after the first dose of study drug is administered. The first dose will be administered on the day of the Baseline assessments or on the following day. Subjects will be dosed with carbetocin 3.2 mg or placebo, administered TID at mealtimes, if possible. Study drug should be administered with a minimum of 2.5 hours between doses. All concomitant permitted medications should remain at a stable dose throughout the study, if possible. Study visits will be conducted at Baseline, Week 2, Week 4, Week 8, and Week 12 (end of treatment [EOT]), or upon early termination (ET) from the study. The Screening, Baseline, Week 2, Week 8, and Week 12 study visits will be conducted in person at the clinical research site. A remote visit will be conducted at Week 4. Subjects who complete the double-blind treatment may be eligible to participate in a separate open-label extension (OLE) study. An optional qualitative interview with caregivers of study subjects will be conducted only in the US remotely by web-based platform or telephone. The caregiver interview will be administered by 3rd party trained moderators within 2 weeks after an EOT or ET visit. **Safety Follow-up Period (30 Days)** Subjects who discontinue prematurely, or who complete but do not continue into the OLE study, will receive a follow-up telephone call (or video conference) to assess safety 30 (+4) days after the last dose of study drug. **End of Study Definition** A subject is considered to have completed the study if he/she has completed all phases of the study including the safety follow-up visit. For subjects enrolling in the open-label extension study a subject is considered to have completed the study if the subject has completed the EOT visit.

Study duration	The duration of participation for individual study subjects will be approximately 19 weeks, consisting of a screening period of up to 3 weeks, a 12-week double-blind treatment period, and a safety follow-up period of 30 (+4) days. The study start date is defined as the date the first subject is consented. The primary completion date is the last date that subject data are collected for the primary outcome measure. The study completion date is defined as the last date that subject data are collected, which includes the safety follow-up visit.
Criteria for inclusion and exclusion	To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion Criteria:** 1. Informed consent prior to the conduct of any study procedures is required as follows: a. For subjects who are minors: written informed consent will be obtained from the LAR (or LARs where local regulations require) or from the minor him/herself if deemed able by the Investigator per local regulations. When consent is obtained from the LAR, the subject should provide written or oral assent if deemed able by the Investigator, and according to local regulations. b. For subjects who are of legal age of consent: written informed consent will be obtained from the subject if the subject is not under guardianship and is deemed able by the Investigator. If the subject is under guardianship or deemed not able to provide consent, the subject should provide written or verbal assent if deemed able by the Investigator and a written informed consent will be obtained from the subject's LAR(s) according to local regulations. c. The subject's caregiver provides written consent to participate as an informant in study assessments. The caregiver may or may not be an LAR. 2. Is a male or female 5 to 30 years of age, inclusive, at Screening. 3. Has PWS with a documented disease-causing mutation.

	4. Has increased appetite with decreased satiety accompanied by food seeking (consistent with PWS Nutritional Phase 3). 5. Has an HQ-CT score of ≥13 at Screening and Baseline. 6. Has a CGI-S for hyperphagia in PWS score of ≥4 at Screening and Baseline. 7. Lives with a caregiver who understands and is willing and able to adhere to study-related procedures and is willing to participate in all study visits. a. The subject must be under the caregiver's consistent care and observation during the study when not attending school or day programs. b. The caregiver should be a family member of the subject or someone whose association with the subject is the equivalent of a family relation. OR The caregiver is not a family member but has cared for the subject for at least 6 months, plans to continue to care for the subject during this study, and spends time with the subject 5 days per week. c. The caregiver must have sufficient language skills to complete the assessments in the language of the assessments and be able to utilize electronic media for study visits and questionnaires. Caregivers will be trained to use the electronic media by which assessments are completed and respond in the local language. 8. Caregiver is able to receive study drug shipments, where permitted, and store study drug per instructions during the study. 9. Caregiver is able to snap the intranasal (IN) pump device onto the study drug vial. 10. Caregiver agrees to request and provide medical records to the investigative site. 11. Has been on a stable dose of any allowed chronic concomitant medications for at least 3 months prior to the Screening visit. Adjustments in growth hormone dose or medication changes that are not clinically significant in the judgment of the Investigator (i.e., having no reasonable possibility of causing changes in mood, behavior, or appetite, or otherwise affecting study endpoints) are allowed. If the medication was

	discontinued, the discontinuation occurred at least 2 weeks or 5 half-lives (whichever is greater) prior to Screening. 12. This criterion for female subjects varies depending on the location of the subject's clinical site due to local regulatory requirements (or requests). a. **In the EU:** If the subject is female, she must not be pregnant or breastfeeding. Subjects of childbearing potential should abstain from sexual activity for the duration of the study and for at least 30 days thereafter. If a subject is sexually active or becomes sexually active during the study, she must use a highly effective contraceptive method per Clinical Trials Facilitation and Coordination Group (CTFG) recommendations (16). The contraceptive method should be used for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter. b. **In the UK:** If the subject is female, she must not be pregnant or breastfeeding. Subjects of childbearing potential (including subjects who reach menarche during the study) should abstain from sexual activity for the duration of the study and for at least 30 days thereafter. If a subject is sexually active or becomes sexually active during the study, she must use an intrauterine device (IUD) plus barrier method (diaphragm, cap, or sponge with spermicide), OR she must use one of these acceptable methods of contraception and her partner must use a condom for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter. A female is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. c. **In North America:** If the subject is female, she must not be pregnant or breastfeeding. Subjects of childbearing potential should abstain from sexual activity for the duration of the study and for at least 30 days thereafter. If a subject is sexually active or

	becomes sexually active during the study, she must use a non-user-dependent method of contraception (e.g., IUD or implant) or a user-dependent hormonal method of contraception (e.g., injection, oral, transdermal, or intravaginal). The contraceptive method should be used for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter. 13. This criterion for male subjects varies depending on the location of the subject's clinical site due to local regulatory requirements (or requests). a. **In the EU:** If the subject is male and sexually active, he must use a condom (even if vasectomized) from the time of Screening until 90 days after the last dose of study drug. The male subject's female partner must use a highly effective contraceptive method per CTFG recommendations (16). The female partner's contraceptive method should be used for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter; OR the male subject must not have a female partner of childbearing potential. Subject must also agree not to donate sperm from the time of Screening until 90 days after the last dose of study drug. b. **In the UK:** If the subject is male and sexually active, he must use a condom (even if vasectomized) from the time of Screening until 90 days after the last dose of study drug. The male subject's female partner must use either an IUD or a barrier method (e.g., diaphragm, cap, or sponge with spermicide; a female condom in combination with a male condom is not acceptable); OR the male subject must not have a female partner of childbearing potential. Subjects must also agree not to donate sperm from the time of Screening until 90 days after the last dose of study drug. c. **In North America:** If the subject is male and sexually active, he must use a condom (even if vasectomized) from the time of Screening until 90 days after the last dose of study drug. The male subject's female partner must use either a non-user-dependent method of contraception (e.g., IUD or implant) or a user-dependent hormonal method of contraception (e.g., injection, oral,

	transdermal, or intravaginal). The female partner's contraceptive method should be used for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter; OR the male subject must not have a female partner of childbearing potential. Subject must also agree not to donate sperm from the time of Screening until 90 days after the last dose of study drug. **Exclusion Criteria:** 1. Is genetically diagnosed with Schaaf-Yang syndrome or another genetic, hormonal, or chromosomal cognitive impairment besides PWS. 2. Has an active upper respiratory infection at the Screening visit or the Baseline visit. 3. Has any clinically significant cardiovascular disorder, renal, hepatic, gastrointestinal, or respiratory disease, including severe asthma. 4. Has a history of, or current, cerebrovascular disease, brain trauma, epilepsy, or frequent migraines. A history of febrile seizures is not exclusionary. 5. Has significant, uncorrected visual or uncorrected hearing impairment. 6. Has had major surgery within 1 month of the Screening visit or planning to have surgery during the study. 7. Has had nasal surgery within 1 month of Screening visit or planning to have nasal surgery during the study. 8. Is unwilling to abstain from nasal saline, other nasal irrigation, and other IN medications (including IN vaccines) within two hours before or after administration of study drug during the Screening period and through the treatment period of the study. 9. Has had more than three episodes of sinusitis in the 12 months prior to the Baseline visit. 10. Has another nasal disorder that may affect deposition of IN medication. 11. Has known hypersensitivity to any component of study drug.

	12. Has been diagnosed with cancer (except managed basal cell carcinoma or squamous cell carcinoma of the skin). 13. Has had clinically significant irritability or agitation, requiring initiation of antipsychotic medication, within the 6 months prior to the Screening visit. 14. Has used prostaglandins, prostaglandin analogues, or prostaglandin agonists in the 3 months prior to the Baseline visit. Inhibitors of prostaglandin synthesis, such as nonsteroidal anti-inflammatory drugs, are not exclusionary. 15. Has started a glucagon-like peptide 1 (GLP-1) agonist within the 6 months prior to the Screening visit. Treatment with GLP-1 agonist is allowed if the subject has been taking it for more than 6 months prior to Screening. 16. Has used oxytocin, desmopressin (DDAVP), tesofensine, diazoxide choline, melanocortin-4 receptor (MC4R) agonists (e.g., setmelanotide), or any medication approved to treat hyperphagia within 6 months prior to the Baseline visit. 17. Has active psychotic symptoms, a history of psychotic symptoms, or a psychotic disorder. 18. Has a history of suicide attempt or inpatient psychiatric hospitalization. 19. Has new food-related interventions, including environment or dietary restrictions, within 1 month prior to the Screening visit or during the Screening period (i.e., before the Baseline visit). 20. Has participated in an interventional research study involving another investigational medication or device in the 6 months prior to the Screening visit. 21. Has a history of or current abuse of/dependence on alcohol or illicit drugs. 22. Has a clinically significant abnormal laboratory value at Screening. Laboratory testing may be repeated during the Screening period with agreement of the Medical Monitor. 23. Has serum potassium below the normal range (according to the central laboratory) at Screening. Serum potassium may be repeated during the

	Screening period with the agreement of the Medical Monitor. 24. Has a clinically significant thyroid function test result at Screening (as measured by thyroid stimulating hormone [TSH] and reflex free thyroxine [T4]). If TSH is abnormal and the reflex free T4 is normal, the subject may be randomized. 25. Has clinically significant abnormality in vital signs at Screening or Baseline. 26. Has any of the following: a. QTcF interval of >450 ms at Screening or Baseline (before dosing) b. History of a risk factor for torsades de pointes (e.g., heart failure or family history of long QT syndrome) c. History of clinically significant QT prolongation that is deemed to put the subject at increased risk of clinically significant QT prolongation d. Has any other clinically significant finding on ECG at Screening or Baseline (before dosing) 27. Has a positive pregnancy test at Screening. 28. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc. 29. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason. 30. **In France only:** Is under court protection, not affiliated to a social security system, or a protected adult under French law (Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1).
Pharmacokinetic assessments	Up to eight PK samples will be collected at the following visits: • Baseline: Two samples will be collected at the Baseline Visit. One sample will be collected before the first dose, and one sample will be collected 15 minutes to 1 hour postdose. The postdose sample should be collected as soon as possible after the postdose ECG is performed. The postdose ECG will be completed 20 minutes (within a 10 to 40 minute window) after the first dose of study drug is administered.

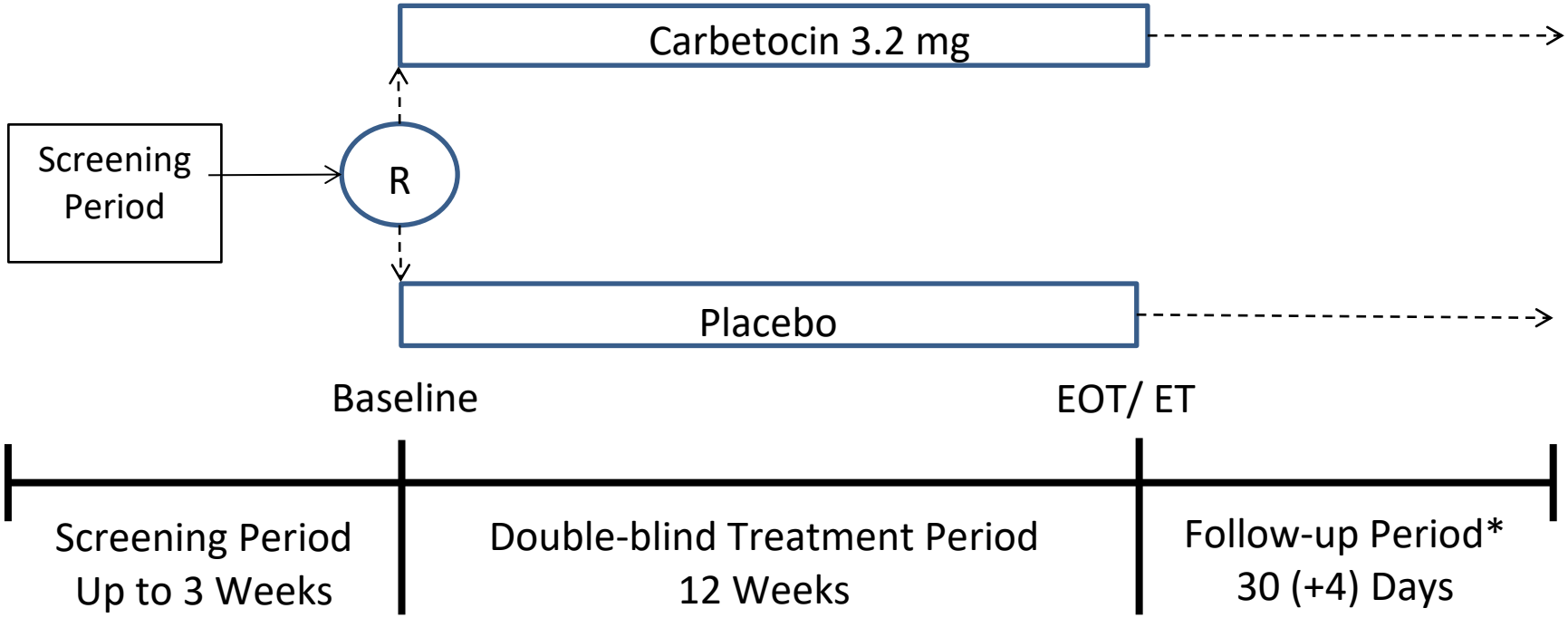
	• Week 2, Week 8, and Week 12 within one of two windows: o Window 1: 1.25 to 3 hours postdose – one sample (a second sample [at least 15 minutes later] should be collected, if possible) o Window 2: 3.25 to 4.5 hours postdose – one sample (a second sample [at least 15 minutes later] should be collected, if possible) Samples should be collected within different windows at Week 2 and Week 8. The Week 12 samples can be collected within either window. For subjects continuing into the OLE study, the Week 12 samples will be taken prior to the first dose of open-label study drug. Pharmacokinetic samples will also be collected, if possible, at any ET visit and immediately following any SAE or any adverse event (AE) leading to discontinuation. For all PK samples (scheduled and unscheduled), the dates and times of administration of the last three doses of study drug should be recorded, as well as the date and time of the sample draw.
Sample size calculations	The planned sample size is approximately 170 subjects randomized in a 1:1 ratio to the carbetocin group and placebo group (85 subjects per treatment group). Assuming the common standard deviation of change from Baseline at Week 12 in HQ-CT is 7 points, 80 subjects who complete the study per treatment group will provide 88% power to detect a difference in the mean change from Baseline at Week 12 in HQ-CT of 3.5 points between the carbetocin group and the placebo group at a significance level of 0.05 (two-sided *t*-test). Adjusting for a potential discontinuation rate of up to 5%, approximately 170 subjects need to be randomized.
Statistical hypothesis	Let Δ ($\mu_{CARB}-\mu_{PBO}$) be the difference in the mean change from Baseline at Week 12 in the HQ-CT score between the active treatment (μ_{CARB}) and the placebo (μ_{PBO}) groups. The null hypothesis is: $\Delta=0$. The alternative hypothesis is: $\Delta\neq0$.
Statistical methods	**Analysis Sets** <u>Randomized Analysis Set</u> The Randomized Analysis Set consists of all subjects who were randomized. Subjects will be classified according to the randomized treatment assignment.

	Safety Analysis Set The Safety Analysis Set (SAS) includes all randomized subjects who received at least one dose of study drug. The SAS will be used for the analyses of all safety endpoints based on the actual treatment received. Full Analysis Set The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of study drug and who have a baseline value for the HQ-CT score. The FAS will be used for the analyses of all efficacy endpoints based on the randomized treatment assignment. Pharmacokinetic Analysis Set The PK Analysis Set includes all subjects in the SAS with at least one measurable carbetocin plasma concentration. **Descriptive Statistics** All continuous outcomes will be summarized using the number of subjects with data values, mean, standard error of the mean, standard deviation, minimum, maximum, and median. All categorical outcomes will be summarized by the number and percentage of subjects in each category.
	Missing Data Handling of missing data will be described in detail in the statistical analysis plan (SAP). Sensitivity analyses assuming different missing mechanisms will be performed to assess the impact of missing data. **Efficacy Analyses** The estimand used for the primary endpoint analysis is described in Section 9.7.1. Primary Endpoint Analysis The primary endpoint is the change from Baseline in HQ-CT score at Week 12. The primary analysis will evaluate treatment effect of carbetocin 3.2 mg TID compared to placebo TID based on the FAS using mixed-effects model for repeated measures (MMRM). The model will include effects for treatment group, sex, randomization stratification factors (age grouping, and presence or absence of participation in a previous clinical study of carbetocin nasal spray), visit, treatment-by-visit interaction, baseline HQ-CT score, and baseline HQ-CT score-by-visit interaction. An unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The treatment effect will be estimated by the difference in least squares

	means (LSMs) of the change from Baseline in HQ-CT score at Week 12 and will be tested at the two-sided significance level of 0.05. The difference in LSMs, standard error, corresponding 95% confidence interval (CI), p-value, and Cohen's *d* effect size will be reported. <u>Secondary Endpoint Analyses</u> Percentage of subjects with treatment response (defined as improvement ≥8 points from Baseline) based on the HQ-CT at Week 12 will be summarized, and the proportion of responders at Week 12 will be analyzed using logistic regression adjusted by baseline HQ-CT, treatment group, sex, and randomization stratification factors (age grouping, and presence or absence of participation in a previous clinical study of carbetocin nasal spray).
	The following endpoints will be analyzed using MMRM similar to the primary endpoint analysis: • CGI-S for PWS score – change from Baseline at Week 12 • CGI-C for PWS score at Week 12 • CGI-S for hyperphagia in PWS score – change from Baseline at Week 12 <u>Exploratory Endpoint Analysis</u> The following exploratory endpoints will be analyzed similarly to the primary endpoint analysis: • PADQ score – change from Baseline at Week 12 • Food Safe Zone score – change from Baseline at Week 12 • Zarit Burden Interview (ZBI) score – change from Baseline at Week 12 Analysis of the following endpoint will be outlined in a separate health economics analysis plan. • PWS-specific Healthcare Resource Use and Caregiver Burden Questionnaire (PWS-HRUQ) – change from Baseline at Week 12 **<u>Safety Analyses</u>** Safety results will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-

	emergent adverse events (TEAEs) and device incidents, or device malfunctions, TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, nonserious TEAEs, treatment-emergent SAEs, and treatment-emergent SAEs related to study drug will all be summarized. Descriptive statistics for ECG, vital signs, clinical laboratory parameters, and physical examination results, including changes from Baseline, will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with International Council for Harmonisation (ICH) guidelines. Additional safety analysis details will be specified in the SAP. **Pharmacokinetic Analyses** Up to eight PK samples will be collected from all subjects, including samples at the Baseline (Week 0) visit before dosing, at the Baseline (Week 0) visit after dosing, and after dosing at the Week 2, Week 8, and Week12/EOT visits within the specified time windows. Plasma concentration data for carbetocin will be listed and summarized using descriptive statistics. Population PK analyses will be performed to further characterize the PK profile and exposure-response relationship of carbetocin using measures of safety and efficacy parameters. Carbetocin plasma concentration data will remain blinded until the unblinding of the clinical database at the end of the study. The details of the PK and exposure-response relationship analyses will be presented in a separate report in accordance with a separate data analysis plan.
Date	24 February 2025

Figure S–1 Schematic of Study Design for ACP-101-302



Abbreviations: EOT=end of treatment; ET=early termination; R=randomization
* If subjects continue into the open-label extension (OLE) from the current study, they will not complete the follow-up period and will roll over into the OLE.

Table S–1 Schedule of Events and Assessments for Study ACP-101-302

Study period	**Screening**	**Double-blind treatment**					**Safety follow-up**
Visit Week	**Week -3 to 0**	**0 Baseline**	**2**	**4**	**8**	**12 (EOT/ET)**	**30 Day follow-up[c]**
Visit	**1**	**2[a]**	**3[b]**	**4[b]**	**5[b]**	**6[b]**	
Visit windows		**N/A**	**±3 days**	**±3 days**	**±4 days**	**+4 days**	**+4 days**
Visit type	Clinic	Clinic	Clinic	Remote	Clinic	Clinic	Telephone or video conference
Informed consent (ICF)/assent	X						
Caregiver consent	X						
Inclusion and exclusion criteria	X	X					
Medical history and demographics	X						
Prader-Willi syndrome history	X						
Confirm documentation of mutation causing PWS[d]	X						
Physical examination including nasal assessment	X	X	X		X	X	
12-lead electrocardiogram[e]	X	X	X		X	X	
Clinical laboratory assessments (chemistry, hematology, urinalysis)	X	X	X		X	X	
TSH (and free T4, if necessary)	X						
Vital signs	X	X	X		X	X	
Height		X				X	
Weight	X	X	X		X	X	
Pregnancy test[f]	X	X	X		X	X	
Randomization		X					
Blood sample for pharmacokinetics		X	X		X	X	

Table S–1 Schedule of Events and Assessments for Study ACP-101-302 (Continued)

Study period	**Screening**	**Double-blind treatment**					**Safety follow-up**
Visit Week	**Week -3 to 0**	**0 Baseline**	**2**	**4**	**8**	**12 (EOT/ET)**	**30 Day follow-up[c]**
Visit	**1**	**2[a]**	**3[b]**	**4[b]**	**5[b]**	**6[b]**	
Visit windows		**N/A**	**±3 days**	**±3 days**	**±4 days**	**+4 days**	**+4 days**
Visit type	Clinic	Clinic	Clinic	Remote	Clinic	Clinic	Telephone or video conference
Hyperphagia Questionnaire for Clinical Trials (HQ-CT)[g]	X	X	X	X	X	X	
Clinical Global Impression–Severity (CGI-S) for PWS	X	X	X		X	X	
Clinical Global Impression–Change (CGI-C) for PWS			X		X	X	
Clinical Global Impression–Severity (CGI-S) for hyperphagia in PWS	X	X	X		X	X	
PWS Anxiousness and Distress Behaviors Questionnaire (PADQ)	X	X	X	X	X	X	
Food Safe Zone[g]	X	X	X	X	X	X	
Zarit Burden Interview (ZBI)		X	X	X	X	X	
PWS-specific Healthcare Resource Use and Caregiver Burden Questionnaire (PWS-HRUQ)		X				X	
Adverse event review	X	X	X	X	X	X	X
Device incident review		X	X	X	X	X	
Concomitant medications review	X	X	X	X	X	X	X
Study drug dispensed[h]		X					
Study drug return[h]			X		X	X	

Table S–1 Schedule of Events and Assessments for Study ACP-101-302 (Continued)

Study period	**Screening**	**Double-blind treatment**					**Safety follow-up**
Visit Week	**Week -3 to 0**	**0 Baseline**	**2**	**4**	**8**	**12 (EOT/ET)**	**30 Day follow-up[c]**
Visit	**1**	**2[a]**	**3[b]**	**4[b]**	**5[b]**	**6[b]**	
Visit windows		**N/A**	**±3 days**	**±3 days**	**±4 days**	**+4 days**	**+4 days**
Visit type	Clinic	Clinic	Clinic	Remote	Clinic	Clinic	Telephone or video conference
Study drug compliance diary			X		X	X	
Study drug accountability[h]			X		X	X	
Optional caregiver interview[i] (US only)						X	

Abbreviations: EOT=end of treatment; ET=early termination; ICF=informed consent form; PWS=Prader-Willi syndrome; TSH=thyroid stimulating hormone

[a] The Baseline visit assessments must occur prior to first dose of the double-blind study drug. Administration of the first dose and postdose ECG, and PK samples collection may be done on the same day or on the following day.

[b] Timing of postbaseline visits will be calculated from the first day of dosing (Day 1) (e.g., the Week 2 visit will occur 2 weeks [±3 days] after the first day of dosing).

[c] The Safety Follow-up visit will assess adverse events and concomitant medications and occur 30 (+ 4) days after the last dose of study drug. Subjects who roll over into the OLE study will not have the safety follow-up visit.

[d] If documentation of mutation is not complete, genomic testing for the mutation causing PWS should be conducted per the Investigator's standard practice.

[e] The (predose) ECG at the Baseline visit will be completed prior to administration of the first dose of study drug. The postdose ECG will be completed 20 minutes (within a 10 to 40 minute window) after the first dose of study drug is administered.

[f] A serum pregnancy test should be performed at Screening for women of childbearing potential. A urine pregnancy test should be performed at all designated visits after Screening for women of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.

[g] The primary assessment, the HQ-CT, will be administered to the caregiver by a rater using standardized prompts. Caregiver scales should be rated at the clinic whenever possible, however they may be done remotely if the primary caregiver is unable to attend the clinic visit. The Food Safe Zone should be administered immediately before administration of the HQ-CT.

[h] Study drug will be dispensed at the site during the Baseline visit. Thereafter study drug may be shipped to the subject (where permitted). Study drug shipment, return, and accountability will be performed in accordance with the Pharmacy Drug Distribution Manual.

[i] The caregiver interview will be completed by 3rd-party trained moderators within 2 weeks after an EOT or ET visit.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
ACP-101 (LV-101)	carbetocin nasal spray
AE	adverse event
CARE-PWS	**CAR**betocin **E**fficacy and Safety Study in **PWS**; LV-101-3-01
CGI-C	Clinical Global Impression–Change
CGI-S	Clinical Global Impression–Severity
CI	confidence interval
CSR	clinical study report
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
DSMB	data and safety monitoring board
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ET	early termination
EU	European Union
EU GDPR	European Union General Data Protection Regulation
FAS	Full Analysis Set
GCP	Good Clinical Practice
HPWSQ-R	Hyperphagia in Prader-Willi Syndrome Questionnaire–Responsiveness
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
ICF	informed consent form
ICH	International Council for Harmonisation
IN	intranasal(ly)
IRB	institutional review board
IV	intravenous
LAR	legally acceptable representative

LSM	least squares mean
LTFU	long-term follow-up
OLE	open-label extension
PADQ	PWS Anxiousness and Distress Behaviors Questionnaire
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PR	PR interval on ECG
PWS	Prader-Willi syndrome
PWS-HRUQ	PWS-specific Healthcare Resource Use and Caregiver Burden (HRU) questionnaire
QRS	QRS interval on ECG
QT interval	QT interval on ECG
QTc	corrected QT interval on ECG
QTcB	corrected QT interval using Bazett's correction method
QTcF	corrected QT interval using Fridericia's correction method
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
TEAE	treatment-emergent adverse event
TID	three times daily
TSH	thyroid stimulating hormone
US	United States
ZBI	Zarit Burden Interview

1. INTRODUCTION

This document is a research protocol, and the described study will be conducted in compliance with the protocol, the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) Guideline, and applicable regulatory requirements.

1.1. Background Information

Prader-Willi syndrome (PWS) is a rare, serious, and life-threatening neurodevelopmental disorder that occurs in approximately one out of every 16,000 births (Burd et al. 1990). This genetic disorder is caused by a defect on chromosome 15 (Cassidy and Driscoll 2009; Jin 2011). In healthy individuals, several relevant genes in the 15q11-13 locus are expressed only from the paternal allele. The corresponding maternal allele is silenced (or "imprinted"), resulting in a complete reliance on the copy inherited from the father (Kalsner and Chamberlain 2015). When an individual lacks expression of these paternal genes, he/she develops PWS.

Following birth, neonates with PWS show profound hypotonia and failure to thrive, often requiring the use of feeding tubes during the first year when nursing fails (Butler et al. 2019). Developmental delays and mild to moderate intellectual disability become apparent in the early years. Following the failure-to-thrive period, young children with PWS show rising levels of interest in food and food-related items. By around 8 years of age, patients with PWS are typically fixated on food and become hyperphagic (suffering from an unrelenting hunger and excessive drive to eat) (Butler et al. 2019). Hyperphagia in PWS is associated with the lack of a normal satiety response, in addition to a low basal metabolic rate (Lloret-Linares et al. 2013). Despite adequate energy reserves, these patients are subjected to a false state of starvation. If left unsupervised, patients with hyperphagia are known to eat to the point of gastric rupture. Due to irregular swallowing and rapid food consumption, patients with PWS also have a greater propensity to choke while eating (Stevenson et al. 2007). Thus, hyperphagic patients require constant supervision. Patients with PWS also show high levels of anxiety, repetitive thinking/questioning, and obsessive and compulsive symptoms; these symptoms can be food-related as well as non-food related (Irizarry et al. 2016).

Today, the only therapy currently approved by the US Food and Drug Administration (FDA) and in Europe to treat PWS is human growth hormone, which is used to increase linear growth (Pfizer Inc. 2019). Currently, there are no therapies approved to treat the hallmark features of PWS, including hyperphagia. Prader-Willi syndrome is a uniquely complex, serious, and life-threatening syndrome with significant unmet medical need.

While better known for its role in reproductive health and social-emotional behaviors, oxytocin is a potent anorectic hormone. Low doses of oxytocin injected intraperitoneally or intracerebroventricularly reduce food intake and the propensity to initiate feeding in wild-type rats in a dose-dependent manner (Arletti et al. 1989). Mice that are null for either oxytocin or the oxytocin receptor develop adult-onset obesity (Sabatier et al. 2013). Additionally, clinicians have identified an instructive group of patients that display a PWS-like phenotype and are deficient in oxytocin. These individuals have mutations in single-minded homolog 1 (*SIM1*), a gene expressing a transcription factor important for development of oxytocin-producing neurons (Holder et al. 2000). In the corresponding *SIM1*-deficiency animal models, replacement of

oxytocin rescues the hyperphagic phenotype. Postmortem studies in individuals with PWS have revealed significantly decreased numbers of oxytocin-secreting neurons in the paraventricular nucleus of the hypothalamus, suggesting that defects in the normal function of oxytocin may contribute to the severe hyperphagia and other behavioral symptoms characteristic of PWS (Swaab et al. 1995). In the aggregate, these data demonstrate the anorexigenic properties of oxytocin and point to the potential utility of oxytocin and similar compounds in the treatment of PWS.

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

1.2. Investigational Product

Carbetocin is a synthetic eight amino acid analogue of the endogenous neuroendocrine nonapeptide hormone oxytocin. It is an oxytocin receptor agonist with similar potency to native oxytocin, but with greater oxytocin receptor selectivity and a longer duration of action (i.e., longer half-life) relative to oxytocin (Engstrøm et al. 1998). Thus, carbetocin may avoid the potential side effects of oxytocin related to off-target excessive activation of vasopressin receptors. Carbetocin is approved in over 90 countries outside the United States (US) 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 (IV) injection. Since its initial approval in 1997, over 11 million patients have been treated with carbetocin without known significant safety concerns.

While the currently approved route of administration of carbetocin outside the US is delivery by IV injection, this route of delivery would be challenging when dosing chronically for the treatment of hyperphagia in PWS. Carbetocin is therefore being developed for IN administration, to enable chronic dosing. Carbetocin nasal spray (also known as ACP-101 and LV-101) is supplied as a solution to be delivered three times daily (TID). A dose consists of two 70 µL sprays in each nostril (total of four sprays).

1.3. Nonclinical Findings

The efficacy, high potency, and selectivity of carbetocin have been demonstrated in multiple in vitro and in vivo pharmacodynamic models. The efficacy and potency of carbetocin have been established in vitro in cells expressing cloned human, monkey, or rat oxytocin receptors, and selectivity has been established using assays of cloned vasopressin V2, V1a, and V1b receptors of these same species.

In addition, carbetocin produced behavioral changes that are presumed to be mediated via activation of central nervous system pathways. For example, carbetocin showed positive effects in a rodent model of depression.

For a more in-depth review of nonclinical carbetocin data, see the carbetocin Investigator's brochure (IB).

1.4. Previous Clinical Experience

Always refer to the latest version of the carbetocin nasal spray IB for the overall benefit/risk assessment and the most accurate and current information regarding nonclinical data, drug metabolism, pharmacokinetics (PK), efficacy, and safety.

1.4.1. Pharmacokinetics

Carbetocin is administered intranasally in order to reach the central nervous system directly. In healthy subjects (Study LV-101-1-02), carbetocin absorption following IN administration is rapid, with time to maximum plasma drug concentration (T_{max}) occurring in 15 to 25 minutes. Carbetocin elimination is also rapid, with the plasma half-life generally being approximately an hour or less. Carbetocin shows dose-proportional plasma PK following IN administration over the dosing range of at least 0.2 to 9.6 mg. Systemic bioavailability of the IN formulation of carbetocin is approximately 2.5%. Within-subject variability for the IN formulation is comparable in magnitude to the between-subject variability.

In healthy subjects, carbetocin plasma concentrations do not show accumulation or progressive decreases with repeated dosing with dosing as frequent as TID. Carbetocin plasma PK is not affected by variation in the spray delivery volume over the range of 50 to100 µL when holding the dose delivered constant.

Nasal tissues do not appear to act as a carbetocin reservoir by either delaying or sustaining the release of carbetocin to the systemic circulation. The systemic population PK of carbetocin following IN administration in a Phase 2 study in subjects with PWS (Study 000114) was described by a linear one-compartment model. There was some variability in systemic drug exposure between subjects, as well as in the rate and extent of absorption within subjects from one dosing occasion to another. Body weight, age, or sex did not appear to influence the systemic disposition of carbetocin in the studied population.

1.4.2. Efficacy

1.4.2.1. Study LV-101-3-01 (CARE-PWS)

A Phase 3, randomized, double-blind, placebo-controlled study (LV-101-3-01 [CARE-PWS]) was conducted to assess the efficacy and safety of carbetocin nasal spray (LV-101) through 8 weeks of double-blind treatment compared to placebo, and to further assess efficacy, safety, and tolerability during longer-term treatment with LV-101 for 56 weeks. A total of 130 subjects, between the ages of 7 to 19 years, were randomized and dosed (1:1:1) with 3.2 mg/dose LV-101, 9.6 mg/dose LV-101, or placebo, administered TID with meals. No new food-related interventions or restrictions were to be initiated from 1 month before screening until the end of the study. The 8-week placebo-controlled period was followed by a 56-week long-term follow-up (LTFU) period, during which all subjects received active treatment with LV-101. At the end of the LTFU period subjects had the opportunity to continue receiving LV-101 (extension period) until such time that it was available in an expanded access or market access

program, commercially available, or the extension period was terminated by the sponsor. Data presented for the LTFU and extension periods are still preliminary.

Results for the LV-101 9.6 mg/dose compared with placebo did not reach statistical significance, as defined by the Hochberg procedure, for either primary endpoint (Hyperphagia Questionnaire for Clinical Trials [HQ-CT] total score: least squares mean [LSM] difference [95% confidence interval {CI}]: -1.202 [-3.729, 1.324]; p = 0.3493 or Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS] total score: -0.608 [-2.890, 1.674], p = 0.6001). Thus, the study did not meet its primary objective by statistical criterion. Since all alpha was spent on these primary comparisons, all p-values presented below are nominal p-values and any results with a p-value <0.05 are nominally statistically significant. Of note, the minimal importance difference (MID), defined as one-half of the standard deviation of baseline scores on the outcome measures, was 2.6 points in HQ-CT.

When assessing these same primary endpoints for the 3.2 mg/dose (as the first secondary endpoint), LV-101 showed significant improvements compared with placebo in the HQ-CT total score (LSM difference [95% CI]: -3.136 [-5.685, -0.586]; p=0.0162; notably below the 0.025 threshold that would have been applied using the Hochberg procedure) and across multiple secondary endpoints (PWS Anxiousness and Distress Behaviors Questionnaire [PADQ]: -3.812 [-7.177, -0.466]; p=0.0266, CGI-C: -0.498 [-0.937, -0.059]; p=0.0266], and the HQ-CT Subset that was less susceptible to environment controls: -2.412 [-4.276, -0.548]; p=0.0114), with results repeatedly favoring the 3.2 mg/dose arm over placebo. Results for the other endpoint of CGI-S (-0.442 [-0.817, -0.068]; p=0.0209) supported these findings, and were consistent with CGI-C. While numerical reductions in CY-BOCS total score were observed in both dose arms, the results were not statistically significant.

Efficacy in the long-term follow-up:

Following the Week 8 visit in the placebo-controlled period, all subjects received active drug in the 56-week LTFU period. Subjects who received active drug during the placebo-controlled period maintained their originally assigned dose during the LTFU period, while those on placebo transitioned to either LV-101 3.2 mg/dose or 9.6 mg/dose (1:1). A total of 128 subjects entered the LTFU period.

Both treatment groups showed further improvements in HQ-CT total score following the placebo-controlled period that were sustained throughout the LTFU period. Specifically, mean scores among both treatment groups were reduced after the Week 8 visit and remained lower than the Week 8 visit (i.e., further improved) throughout the entire LTFU period.

1.4.2.2. Study 000114

A prospective, randomized, double-blind, placebo-controlled, multicenter, Phase 2 study (Study 000114) of 14 days of treatment with 9.6 mg/dose of carbetocin TID with meals was conducted in 37 subjects with genetically confirmed PWS, between the ages of 10 to 18 years, and with documented Nutritional Phase 3 criteria (see carbetocin nasal spray IB). Carbetocin nasal spray was well-tolerated and improved hyperphagia and behavioral symptoms of PWS in this study (Dykens et al. 2018). The primary efficacy endpoint was the change in Hyperphagia in Prader-Willi Syndrome Questionnaire–Responsiveness (HPWSQ-R) total score from Baseline to

Day 15. The HPWSQ-R was completed by the caregiver. A decrease in the HPWSQ-R total score indicates improvement in hyperphagia.

A statistically significantly greater decrease in the HPWSQ-R total score from Baseline to Day 15 was observed for carbetocin compared to placebo. The LSM change from Baseline to Day 15 for the carbetocin and placebo arms was -15.6 and -8.9, respectively (one-sided p=0.029).

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

1.4.3. Safety and Tolerability

1.4.3.1. Study LV-101-3-01 (CARE-PWS)

In the Phase 3 study of LV-101, LV-101 at the 3.2 mg/dose and 9.6 mg/dose, preliminary data show that carbetocin was well-tolerated compared to placebo during the 8-week, placebo-controlled period, and with continued exposure during the 56-week LTFU and extension periods, when administered IN TID in subjects with PWS.

The overall incidence of TEAEs during the placebo-controlled period was similar between the LV-101 all active (63.2%) and placebo (55.8%) arms; by dose, 60.5% in the 3.2 mg/dose group and 65.9% of subjects in the 9.6 mg/dose group reported TEAEs. The incidence increased with extended LV-101 exposure during the LTFU and extension periods (88.3% in the pooled LV-101 all active arm, including 49 subjects [76.6%] receiving a 9.6 mg dose and 93 subjects [86.1%] receiving a 3.2 mg dose).

In the placebo-controlled period, the most common TEAEs in the 9.6 mg dose group were flushing (9 subjects [20.5%]) and epistaxis (6 subjects [13.6%]) and in the 3.2 mg dose group were headache (7 subjects [16.3%]) and flushing (6 subjects [14.0%]). During the LTFU and extension periods, the most common TEAEs in the 9.6 mg dose group were nasopharyngitis (10 subjects [15.6%]), epistaxis (7 subjects [10.9%]), and headache (6 subjects [9.4%]), and in the 3.2 mg dose group were nasopharyngitis (21 subjects [19.4%]), anxiety (19 subjects [17.6%]), and headache (16 subjects [14.8%]). Most TEAEs were mild or moderate in intensity in all treatments at all time points. No deaths were reported during the study.

No TEAEs leading to study drug discontinuation were reported during the placebo-controlled period by subjects in the placebo or 3.2 mg/dose arm. A total of 3 subjects (6.8%) in the 9.6 mg/dose arm reported TEAEs during the placebo-controlled period that led to study discontinuation.

There was no consistent pattern in TEAEs leading to study drug discontinuation across LV-101 doses or time, and most TEAEs leading to study drug discontinuation were reported by one subject each. Most TEAEs assessed for suicidality during the placebo-controlled and LTFU and extension periods were reported by one subject each, with the exceptions of affect lability

emotional disorder, irritability, and suicidal ideation. No events of completed suicide occurred. Of all the TEAEs evaluated, a total of two events (one event of suicidal behavior and one event of suicidal ideation) were assessed by Investigators to be consistent with a suicide-related event, and all other events were assessed as not consistent with a suicide-related event.

Most nasal examinations at Baseline and throughout the course of the study were Grade 0 (no abnormal findings) or Grade 1A (focal nasal mucosal inflammation, erythema, or hyperemia). There were no clinically relevant changes in laboratory values, vital signs, electrocardiograms (ECGs), or physical findings, including Tanner Stage, during the placebo-controlled period and the LTFU period.

No deaths or SAEs in any dose group were reported during the placebo-controlled period. The incidence of SAEs was generally low following extended exposure in the LTFU period (15.6% in the pooled LV-101 all active arm). The most common treatment-emergent SAEs during the LTFU and extension periods were scoliosis surgery (5 subjects in the 3.2 mg dose group and 1 subject in the 9.6 mg dose group), pneumonia (3.2 mg dose no subjects, 9.6 mg dose 2 subjects), and bezoar (1 subject in each dose group).

1.4.3.2. Study 000114

In the Phase 2 study (Study 000114) in subjects with PWS, there were no deaths, serious adverse events (SAEs), or severe TEAEs (see carbetocin nasal spray IB).

A similar percentage of subjects in the carbetocin and placebo arms experienced at least one treatment-related TEAE (35.3% and 30.0%, respectively).

Headache was the only TEAE reported for more than 2 subjects in the carbetocin arm (5 [29.4%] subjects). In the placebo arm, headache (6 [30.0%] subjects) and medication error (2 [10.0%] subjects) were reported for 2 or more subjects. There were no clinically important treatment arm differences (>1 subject) for any individual type of TEAE (preferred term).

In the six Phase 1 studies conducted in healthy subjects (exploring doses from 0.02 to 0.8 mg IV and intramuscular (IM) carbetocin, and 0.2 to 9.6 mg IN carbetocin), the most common adverse events (AEs) observed after dosing were facial warmth/facial flushing, headache, metallic taste, oropharyngeal pain, and breast tenderness. Mild tachycardia was observed in three studies of IV or IM administration of carbetocin (0.02 to 0.8 mg) and was accompanied by a decrease in diastolic blood pressure in one of these studies. No clinically relevant cardiovascular effects were observed with IN administration of carbetocin at 0.2 to 9.6 mg. No clinically concerning findings in laboratory values occurred after carbetocin administration in these studies.

1.5. Study Rationale

As described above, PWS is a devastating disorder for which there is as yet no treatment beyond symptomatic care resulting in a great unmet medical need. The CARE-PWS study included subjects between the ages of 7 to 19 years and provided evidence of the efficacy the carbetocin 3.2 mg TID in the treatment of hyperphagia in PWS based on the HQ-CT, the standard assessment in clinical studies. The study also provided placebo-controlled and long-term open-label data suggesting that carbetocin 3.2 mg TID is safe and well-tolerated in individuals with PWS. However, in CARE-PWS, assessment of efficacy of the 3.2 mg dose was not the primary outcome measure. The present study investigates the efficacy and safety carbetocin 3.2 mg TID

compared to placebo with the goal of seeking marketing authorization from regulatory authorities. The age range is expanded to include younger patients who develop hyperphagia early and patients above age 19 years into adulthood.

1.5.1. Rationale for Dose Selection and Comparator

Based on preclinical dose range finding studies, a clinical pharmacology study (Study 000040) was conducted in healthy subjects using a single IN ascending dose ranging from 0.2 mg to 9.6 mg and a multiple IN dose with cohorts receiving 0.8 mg TID, 3.2 mg TID, and 9.6 mg TID of carbetocin or placebo. A subsequent PK study (Study LV-101-1-02) in healthy subjects examined results at a single dose of 3.2 mg and 9.6 mg. Both Phase 1 studies did not identify any safety concerns and the doses were well-tolerated. These doses were later used in the CARE-PWS study where the strongest evidence was in support of the 3.2 mg TID IN carbetocin dose for the treatment of hyperphagia in PWS, where a signal for improvement was observed at this dose on the HQ-CT primary endpoint as well as secondary endpoints.

In this study, a placebo treatment group is used as a comparator given there are no approved medications for the treatment of hyperphagia in patients with PWS. In this case, there is clinical equipoise about the preferred treatment. The use of a comparator placebo group allows for a controlled study environment to establish efficacy and safety of an investigational product.

1.6. Benefit: Risk Assessment

1.6.1. Therapeutic Context

Prader-Willi syndrome is a rare, life-threatening neurodevelopmental genetic disorder with a complex psychiatric phenotype. Of the many features of PWS, hyperphagia and the unique anxiousness and distress associated with this syndrome are among the most challenging. The hallmark symptom of hyperphagia, or unrelenting hunger, is accompanied by a lack of normal satiety response and low basal metabolic rate. Despite adequate energy reserves, these patients are fundamentally subjected to a false state of starvation. Both food and non-food related, the anxiousness and distress unique to patients with PWS can be severe and, together with hyperphagia, limit patients' ability to engage in normal daily activities and lead independent lives. Parents and caregivers resort to rigidly structuring their families' lives around controlling access to food to manage the potentially life-threatening hyperphagia and associated challenging behaviors.

No therapy is currently approved to treat hyperphagia in PWS. Patients with PWS are often prescribed psychiatric medications (selective serotonin reuptake inhibitors, antipsychotics, stimulants, etc.) and take nonprescription interventions (e.g., vitamins and nutritional supplements) in an effort to reduce the most problematic symptoms of PWS. Accordingly, patients with PWS are often exposed to the risks presented by multiple drug interventions, and with limited effects on symptoms.

1.6.2. Potential Benefits

Carbetocin nasal spray has demonstrated reductions in hyperphagia in two clinical studies, consistent with the hypothesis that addressing the observed functional oxytocin deficiency in patients with PWS would be beneficial.

The Phase 2 study (Study 000114) was the first clinical study to show that pharmacological intervention could improve hyperphagia in PWS. Building on the Phase 2 data, the Phase 3 CARE-PWS study (Study LV-101-3-01) showed that a 3.2 mg dose of carbetocin provided nominally statistically significant improvements in hyperphagia (p=0.0162) in subjects with PWS.

Notably, in responder analyses, the 3.2 mg dose conferred clinically meaningful improvements in hyperphagia (50% vs. 14% of placebo subjects experiencing a 7-point reduction in HQ-CT scores). These benefits were sustained throughout the observed 56-week follow-up period in CARE-PWS and these reductions were similarly experienced by subjects who were on placebo and then transitioned to receive carbetocin 3.2 mg.

Taken together, and particularly in light of the minimal safety risks presented by chronic use of carbetocin 3.2 mg TID, the weight of evidence supports the further evaluation of carbetocin nasal spray 3.2 mg TID on hyperphagia in PWS, for which there is currently no treatment.

1.6.3. Potential Risks

Data from the clinical studies of carbetocin nasal spray show that carbetocin does not present significant risks to PWS patients. The AE profile observed in Phase 1, Phase 2, and Phase 3 studies demonstrate that carbetocin nasal spray is generally safe and well-tolerated. The clinical safety profile is consistent with nonclinical data that also showed no significant safety findings. Additionally, there were no AEs or complaints associated with the use of the nasal spray pump used to administer carbetocin in these studies.

Due to the known effects of oxytocin receptor agonism in women who are pregnant, use of carbetocin in patients who are pregnant would be contraindicated. Given the rarity of pregnancies among patients with PWS, this risk is expected to be adequately mitigated through the use of contraindication labeling.

Additionally, because prostaglandins potentiate the effect of oxytocin, it is expected that this may also occur with carbetocin. Therefore, it is recommended that systemic prostaglandins and carbetocin not be used together.

1.6.4. Overall Benefit-Risk Conclusion

The potential benefits on hyperphagia experienced by PWS patients receiving 3.2 mg carbetocin nasal spray TID substantially outweigh the risks identified.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of this study is to investigate the efficacy of treatment with carbetocin nasal spray versus placebo on hyperphagia in PWS.

2.1.1. Primary Endpoint

The primary endpoint is:

- Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score – change from Baseline at Week 12

2.2. Secondary Objectives

The secondary objectives are to investigate the efficacy of treatment with carbetocin versus placebo on:

- PWS
- Hyperphagia in PWS

2.2.1. Secondary Endpoints

The secondary endpoints for this study are:

- Clinical Global Impression–Severity (CGI-S) for PWS score – change from Baseline at Week 12
- Clinical Global Impression–Change (CGI-C) for PWS score at Week 12
- Percentage of subjects with treatment response (defined as improvement from Baseline ≥8 points) based on the HQ-CT at Week 12
- CGI-S for hyperphagia in PWS score – change from Baseline at Week 12

2.3. Exploratory Objectives

The exploratory objectives for this study are to investigate the benefit of treatment with carbetocin versus placebo on:

- Anxiousness in PWS
- Environmental controls
- Caregiver burden
- Healthcare utilization

2.3.1. Exploratory Endpoints

The exploratory endpoints for this study are:

- PWS Anxiousness and Distress Behaviors Questionnaire (PADQ) score – change from Baseline at Week 12

- Food Safe Zone score – change from Baseline at Week 12
- Zarit Burden Interview (ZBI) score – change from Baseline at Week 12
- PWS-specific Healthcare Resource Use and Caregiver Burden Questionnaire (PWS-HRUQ) – change from Baseline at Week 12

2.4. Safety Objectives

The safety objective of this study is to investigate the safety and tolerability of treatment with carbetocin versus placebo.

2.4.1. Safety Endpoints

The safety endpoints of this study are:

- Treatment-emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Withdrawals due to adverse events (AEs)
- Potentially clinically important changes in other safety assessments
- Device incidents, or device malfunctions

2.5. Pharmacokinetic Objectives

The PK objectives of this study are:

- To characterize the PK of carbetocin
- To assess the exposure-response relationship

2.5.1. Pharmacokinetic Endpoints

The PK endpoints of this study are:

- Plasma concentration of carbetocin
- Carbetocin PK parameters using the population PK approach
- Exposure-Response (E-R) analysis methods

3. STUDY DESCRIPTION

3.1. Overview of Study Design

This is a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing carbetocin nasal spray 3.2 mg TID with placebo (matched placebo nasal spray TID) in subjects with PWS.

Approximately 42 global sites will participate in this study. Approximately 170 subjects will be randomized (85 subjects per treatment group). Randomization will occur at the Baseline visit. Subjects will be randomly assigned 1:1 to the active treatment group or placebo group in a blinded fashion, according to a computer-generated randomization schedule. The subject or legally acceptable representative (LAR) must provide written consent prior to the procedures being performed at the Screening visit. A caregiver must also provide written consent to participate as an informant in study assessments prior to the procedures being performed at the Screening visit.

Randomization will be stratified by three age groupings: <12 years old, ≥12 to <17 years old, ≥17 years old; and by presence or absence of participation in a previous clinical study of carbetocin nasal spray.

The Sponsor, subjects, caregivers, and Investigators and any other site or Sponsor personnel will be blinded to treatment assignment.

The study will have three periods:

- Screening period: up to 3 weeks
- Double-blind treatment period: 12 weeks
- Safety follow-up period: 30 (+4) days

The study design schematic is provided in Figure S–1. The schedule of events and assessments is provided in Table S–1.

The study start date is defined as the date the first subject is consented.

The primary completion date is the last date that subject data are collected for the primary outcome measure.

The study completion date is defined as the last date that subject data are collected, which includes the safety follow-up visit.

The duration of participation for individual study subjects will be approximately 19 weeks, consisting of a screening period of up to 3 weeks, a 12-week double-blind treatment period, and a safety follow-up period of 30 (+4) days.

3.1.1. Screening Period (Up to 3 Weeks)

During the Screening period, subjects will be assessed for study eligibility. Only those subjects who meet all inclusion and no exclusion criteria will be eligible for the study.

Individuals who do not meet the criteria for participation in this study (screen failure; Section 4.3) may be rescreened with Medical Monitor agreement. Rescreened subjects should be assigned a new subject number for every screening/rescreening event.

Investigators must not withdraw a subject's prohibited medication for the purpose of enrolling them into the study. Medications will be discontinued only if it is deemed clinically appropriate to do so and in consultation with the treating physician.

3.1.2. Double-blind Treatment Period (12 Weeks)

The Baseline visit will occur after screening procedures are completed and have not ruled the subject out of eligibility for the study. At Baseline, and upon confirmation of eligibility, subjects will be randomized in a 1:1 ratio to carbetocin or matching placebo.

Baseline assessments (including a predose ECG) will be completed at the Baseline visit prior to administration of the first dose of study drug. A second (postdose) ECG will be completed 20 minutes (within a 10 to 40 minute window) after the first dose of study drug is administered (Table S–1). The first dose will be administered on the day of the Baseline assessments or on the following day.

Subjects will be dosed with carbetocin 3.2 mg or placebo, administered TID at mealtimes, if possible. Study drug should be administered with a minimum of 2.5 hours between doses.

All concomitant, permitted medications should remain at a stable dose throughout the study, if possible.

Study visits will be conducted at Baseline, Week 2, Week 4, Week 8, and Week 12 (end of treatment [EOT]), or upon early termination (ET) from the study. The Screening, Baseline, Week 2, Week 8, and Week 12 study visits will be conducted in person at the clinical research site. A remote visit will be conducted at Week 4.

Subjects who complete the double-blind treatment may be eligible to participate in a separate OLE study.

An optional qualitative interview with caregivers of study subjects will be conducted in the US only and remotely by web-based platform or telephone. The caregiver interview will be administered by 3rd party trained moderators within 2 weeks after an EOT or ET visit.

3.1.3. Safety Follow-up Period (30 Days)

Subjects who discontinue prematurely, or who complete the study but do not continue into the OLE study, will receive a follow-up telephone call (or video conference) to assess safety 30 (+4) days after the last dose of study drug. The follow-up telephone call will include assessment of concomitant medications and assessment of AEs.

3.1.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the safety follow-up visit. Subjects who enroll in the OLE study do not complete the safety follow-up visit and are considered to have completed the study if the EOT visit was completed. Procedures for when a subject is lost to follow-up are provided in Section 4.6.

The primary completion date is the last date that subject data are collected for the primary outcome measure.

The study completion date is defined as the last date that subject data are collected, which includes the safety follow-up visit.

4. SUBJECT ELIGIBILITY, DISCONTINUATION, AND WITHDRAWAL CRITERIA

To be eligible for this study, subjects must meet all of the inclusion criteria and none of the exclusion criteria.

4.1. Inclusion Criteria

A subject must meet all of the following inclusion criteria to be eligible for participation in the study:

1. Informed consent prior to the conduct of any study procedures is required as follows:
    a. For subjects who are minors: written informed consent will be obtained from the LAR (or LARs where local regulations require) or from the minor him/herself if deemed able by the Investigator per local regulations. When consent is obtained from the LAR, the subject should provide written or oral assent if deemed able by the Investigator, and according to local regulations.
    b. For subjects who are of legal age of consent: written informed consent will be obtained from the subject if the subject is not under guardianship and is deemed able by the Investigator. If the subject is under guardianship or deemed not able to provide consent, the subject should provide written or verbal assent if deemed able by the Investigator, and a written informed consent will be obtained from the subject's LAR(s) according to local regulations.
    c. The subject's caregiver provides written consent to participate as an informant in study assessments. The caregiver may or may not be an LAR.
2. Is a male or female 5 to 30 years of age, inclusive, at Screening.
3. Has PWS with a documented disease-causing mutation.
4. Has increased appetite with decreased satiety accompanied by food seeking (consistent with PWS Nutritional Phase 3).
5. Has an HQ-CT score of ≥13 at Screening and Baseline.
6. Has a CGI-S for hyperphagia in PWS score of ≥4 at Screening and Baseline.
7. Lives with a caregiver who understands and is willing and able to adhere to study-related procedures and is willing to participate in all study visits.
    a. The subject must be under the caregiver's consistent care and observation during the study when not attending school or day programs.
    b. The caregiver should be a family member of the subject or someone whose association with the subject is the equivalent of a family relation.
    OR
    The caregiver is not a family member but has cared for the subject for at least 6 months and plans to continue to care for the subject during this study, and spends time with the subject at least 5 days per week.
    c. The caregiver must have sufficient language skills to complete the assessments in the language of the assessments and be able to utilize electronic media for study visits and questionnaires. Caregivers will be trained to use the electronic media by which assessments are completed and respond in the local language.

8. Caregiver is able to receive study drug shipments, where permitted, and store study drug per instructions during the study.
9. Caregiver is able to snap the IN pump device onto the study drug vial.
10. Caregiver agrees to request and provide medical records to the investigative site.
11. Has been on a stable dose of any allowed chronic concomitant medications for at least 3 months prior to the Screening visit. Adjustments in growth hormone dose or medication changes that are not clinically significant in the judgment of the Investigator (i.e., having no reasonable possibility of causing changes in mood, behavior, or appetite, or otherwise affecting study endpoints) are allowed. If the medication was discontinued, the discontinuation occurred at least 2 weeks or 5 half-lives (whichever is greater) prior to Screening.
12. This criterion for female subjects varies depending on the location of the subject's clinical site due to local regulatory requirements (or requests).
    a. **In the EU:** If the subject is female, she must not be pregnant or breastfeeding. Subjects of childbearing potential should abstain from sexual activity for the duration of the study and for at least 30 days thereafter. If a subject is sexually active or becomes sexually active during the study, she must use a highly effective contraceptive method per Clinical Trials Facilitation and Coordination Group (CTFG) recommendations (16). The contraceptive method should be used for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter.
    b. **In the UK:** If the subject is female, she must not be pregnant or breastfeeding. Subjects of childbearing potential (including subjects who reach menarche during the study) should abstain from sexual activity for the duration of the study and for at least 30 days thereafter. If a subject is sexually active or becomes sexually active during the study, she must use an intrauterine device (IUD) plus barrier method (diaphragm, cap, or sponge with spermicide), OR she must use one of these acceptable methods of contraception and her partner must use a condom for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter.
    A female is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    c. **In North America:** If the subject is female, she must not be pregnant or breastfeeding. Subjects of childbearing potential should abstain from sexual activity for the duration of the study and for at least 30 days thereafter. If a subject is sexually active or becomes sexually active during the study, she must use a non-user-dependent method of contraception (e.g., intrauterine device [IUD] or implant) or a user-dependent hormonal method of contraception (e.g., injection, oral, transdermal, or intravaginal). The contraceptive method should be used for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter.

13. This criterion for male subjects varies depending on the location of the subject's clinical site due to local regulatory requirements (or requests).
    a. **In the EU:** If the subject is male and sexually active, he must use a condom (even if vasectomized) from the time of Screening until 90 days after the last dose of study drug. The male subject's female partner must use a highly effective contraceptive method per CTFG recommendations (16). The female partner's contraceptive method should be used for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter; OR the male subject must not have a female partner of childbearing potential. Subject must also agree not to donate sperm from the time of Screening until 90 days after the last dose of study drug.
    b. **In the UK:** If the subject is male and sexually active, he must use a condom (even if vasectomized) from the time of Screening until 90 days after the last dose of study drug. The male subject's female partner must use either an IUD or a barrier method (e.g., diaphragm, cap, or sponge with spermicide; a female condom in combination with a male condom is not acceptable); OR the male subject must not have a female partner of childbearing potential. Subjects must also agree not to donate sperm from the time of Screening until 90 days after the last dose of study drug.
    c. **In North America:** If the subject is male and sexually active, he must use a condom (even if vasectomized) from the time of Screening until 90 days after the last dose of study drug. The male subject's female partner must use either a non-user-dependent method of contraception (e.g., IUD or implant) or a user-dependent hormonal method of contraception (e.g., injection, oral, transdermal, or intravaginal). The female partner's contraceptive method should be used for at least 1 month prior to Baseline, throughout the study, and for at least 30 days thereafter; OR the male subject must not have a female partner of childbearing potential. Subject must also agree not to donate sperm from the time of Screening until 90 days after the last dose of study drug.

4.2. Exclusion Criteria

A subject must meet none of the following exclusion criteria to be eligible for the study:

1. Is genetically diagnosed with Schaaf-Yang syndrome or another genetic, hormonal, or chromosomal cognitive impairment besides PWS.
2. Has an active upper respiratory infection at the Screening visit or the Baseline visit.
3. Has any clinically significant cardiovascular disorder, renal, hepatic, gastrointestinal, or respiratory disease, including severe asthma.
4. Has a history of, or current, cerebrovascular disease, brain trauma, epilepsy, or frequent migraines. A history of febrile seizures is not exclusionary.
5. Has significant, uncorrected visual or uncorrected hearing impairment.
6. Has had major surgery within 1 month of the Screening visit or planning to have surgery during the study.
7. Has had nasal surgery within 1 month of Screening visit or planning to have nasal surgery during the study.
8. Is unwilling to abstain from nasal saline, other nasal irrigation, and other IN medications (including IN vaccines) within two hours before or after administration of study drug during the Screening period and through the treatment period of the study.

9. Has had more than three episodes of sinusitis in the 12 months prior to the Baseline visit.
10. Has another nasal disorder that may affect deposition of IN medication.
11. Has known hypersensitivity to any component of study drug.
12. Has been diagnosed with cancer (except managed basal cell carcinoma or squamous cell carcinoma of the skin).
13. Has had clinically significant irritability or agitation, requiring initiation of antipsychotic medication, within the 6 months prior to the Screening visit.
14. Has used systemic prostaglandins, prostaglandin analogues, or prostaglandin agonists in the 3 months prior to the Baseline visit. Inhibitors of prostaglandin synthesis, such as nonsteroidal anti-inflammatory drugs, are not exclusionary.
15. Has started a glucagon-like peptide 1 (GLP-1) agonist within the 6 months prior to the Screening visit. Treatment with GLP-1 agonist is allowed if the subject has been taking it for more than 6 months prior to Screening.
16. Has used oxytocin, desmopressin (DDAVP), tesofensine, diazoxide choline, melanocortin-4 receptor (MC4R) agonists (e.g., setmelanotide), or any medication approved to treat hyperphagia within 6 months prior to the Baseline visit.
17. Has active psychotic symptoms, a history of psychotic symptoms, or a psychotic disorder.
18. Has a history of suicide attempt or inpatient psychiatric hospitalization.
19. Has new food-related interventions, including environment or dietary restrictions, within 1 month prior to the Screening visit or during the Screening period (i.e., before the Baseline visit).
20. Has participated in an interventional research study involving another investigational medication or device in the 6 months prior to the Screening visit.
21. Has a history of or current abuse of/dependence on alcohol or illicit drugs.
22. Has a clinically significant abnormal laboratory value at Screening. Laboratory testing may be repeated during the Screening period with agreement of the Medical Monitor.
23. Has serum potassium below the normal range (according to the central laboratory) at Screening. Serum potassium may be repeated during the Screening period with the agreement of the Medical Monitor.
24. Has a clinically significant thyroid function test result at Screening (as measured by thyroid stimulating hormone [TSH] and reflex free thyroxine [T4]). If TSH is abnormal and the reflex free T4 is normal, the subject may be randomized.
25. Has clinically significant abnormality in vital signs at Screening or Baseline.
26. Has any of the following:
    a. QTcF interval of >450 ms at Screening or Baseline (before dosing)
    b. History of a risk factor for torsades de pointes (e.g., heart failure or family history of long QT syndrome)
    c. History of clinically significant QT prolongation that is deemed to put the subject at increased risk of clinically significant QT prolongation
    d. Has any other clinically significant finding on ECG at Screening or Baseline (before dosing)
27. Has a positive pregnancy test at Screening.

28. Is an employee or is a family member of an employee of Acadia Pharmaceuticals Inc.
29. Is judged by the Investigator or the Medical Monitor to be inappropriate for the study for any reason.
30. **In France only:** Is under court protection, not affiliated to a social security system, or a protected adult under French law (Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1).

4.3. Screen Failures

The Screening period is described in Section 3.1.1. The Investigator should maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Screen failures are defined as subjects for whom consent has been documented but are not subsequently randomized.

Subjects who fail Screening may be rescreened for study eligibility with Medical Monitor agreement.

4.4. Subject Withdrawal of Consent

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time, and for any reason, without prejudice to his or her future medical care. If the LAR or subject decides to withdraw consent from all components in the study, this must be documented and no additional assessments may be performed; in addition, no further contact with the subject will be made, including access to or review of the subject's medical records. The Sponsor may retain and continue to use any data collected before such a withdrawal of consent. The LAR or subject may request destruction of any samples taken and not tested, prior to their withdrawal of consent, and the Investigator must document this in the site study records.

4.5. Subject Discontinuation from Study Drug and Study

Subjects may be discontinued from the study drug and study for a number of reasons, including, but not limited to, those listed below.

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up (Section 4.6)
- Non-compliance with study drug (Section 5.1.6)
- Physician decision
- Pregnancy (Section 7.4.3)
- Protocol deviation
- Study terminated by Sponsor (Section 4.7)
- Use of prohibited medication (Section 4.8.2.1)

- Withdrawal of consent by LAR or subject
  - Note: if the LAR or subject decides to withdraw consent from all components in the study, this must be documented, and no additional assessments may be performed (Section 4.4)
- Other (e.g., LAR or subject wants to discontinue study drug but agrees to further evaluations, loss of LAR or caregiver without replacement, unacceptable lab results at Baseline, medical device incident, site terminated by Sponsor)
  - Note: the loss of LAR or caregiver will result in discontinuation only if the LAR or caregiver is not replaced. Any change of caregiver must be approved by the Medical Monitor and documented in the electronic case report form (eCRF). Any new caregiver must meet the relevant inclusion criteria.
  - Note: If the LAR or subject wants to discontinue treatment with the study drug and agrees to the evaluations specified at the EOT/ET visit and/or at safety follow-up (whichever is applicable), as outlined in Table S–1 agreed assessments should be conducted. This is not considered a withdrawal of informed consent. The LAR or subject's reason for wanting to discontinue treatment and the agreement to continue with the applicable assessments for study termination must be documented (in the source documentation).

4.5.1. Handling of Subject Discontinuation During the Treatment Period

Unless the LAR or subject has withdrawn consent from all components of the study (Section 4.4), every reasonable effort should be made to complete the Week 12 (EOT/ET) visit and the safety follow-up visit if applicable (as outlined in Table S–1) if a subject discontinues treatment prematurely during the treatment period of the study. All available information will be reported on the applicable pages of the eCRF.

If a subject is discontinued from treatment because of an AE, every reasonable attempt should be made to follow and appropriately treat (or refer for treatment) the subject until the AE resolves or until the Investigator deems the AE to be chronic or stable. For subjects who continue to be followed for safety, SAEs should continue to be reported as described in Section 7.4.2. All SAEs will continue to be followed and appropriately treated until such events have resolved or the Investigator deems them to be chronic or stable.

Pharmacokinetic samples will be collected, if possible, at the visit immediately following any SAE or AE leading to discontinuation, even if it is an unscheduled visit.

4.6. Subject Lost to Follow-up

A subject will be considered lost to follow-up if they fail to attend a scheduled visit (including the safety follow-up visit) and the study subject or caregiver is unable to be contacted by the study site after repeated documented attempts.

Every reasonable effort should be made to contact the subject and caregiver and will include a minimum of three documented phone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods. All contact attempts are to be documented in the source documents.

4.7. Study Discontinuation

The Sponsor reserves the right to discontinue the study at any time for any reason. Such reasons may be any of, but not limited to, the following:

- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known AEs
- Medical, ethical, or business reasons affecting the continued performance of the study

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organizations used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the LAR, subject, and caregiver, and should assure appropriate subject therapy and/or follow-up.

Regulatory authorities also have the right to terminate the conduct of the study in their region for any reason.

4.8. Prior and Concomitant Therapy

All medications used from 24 weeks prior to Baseline until completion of the safety follow-up visit are to be recorded.

4.8.1. Prior Medication

Prior medication is defined as any medication with a stop date prior to the date of the first dose of study drug. Medication history will be obtained at Screening.

4.8.2. Concomitant Medication

Concomitant medication is defined as any medication that is ongoing at the first dose of study drug or with a start date between the dates of the first dose and last dose of study drug, inclusive. Medication taken after the date of the last dose of study drug is considered post-treatment medication.

In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medication without prior consultation with the Investigator (unless the subject is receiving treatment for a medical emergency).

4.8.2.1. Permitted and Prohibited Medications

Prohibitions for concomitant medications should be followed between the initial Screening visit and Week 12/EOT/ET. Any questions regarding prohibited medications should be discussed with the Medical Monitor. The Investigator may prescribe appropriate medication to treat AEs.

Permitted concomitant medications should remain at a stable dose throughout the study, if possible.

The following concomitant therapies are permitted, but should not be used within two hours before or after administration of study drug:

- Nasal saline

- Other nasal irrigation
- IN medications (including IN vaccines)

Prohibited concomitant therapies include:

- Systemic prostaglandins, prostaglandin analogues, and prostaglandin agonists. Inhibitors of prostaglandin synthesis, such as nonsteroidal anti-inflammatory drugs, are allowed.
- Desmopressin (DDAVP)
- Tesofensine
- Oxytocin
- Diazoxide choline
- Melanocortin-4 receptor (MC4R) agonists (e.g., setmelanotide)
- Any medication approved to treat hyperphagia

Subjects who have taken a prohibited medication during the study will be discontinued from the study unless:

- the prohibited medication has been discontinued, AND
- discontinuation from the study presents an unacceptable medical risk to the subject

The justification to allow the subject who has taken a prohibited medication to continue in the study will be made by the Sponsor/Medical Monitor, with medical input from the Investigator, and will be documented. If a subject is allowed to remain in the study, this will be reported as a protocol deviation and not a waiver.

4.9. Lifestyle Considerations

Changes to food-related interventions, including environment or dietary restrictions, should be avoided during the study.

5. INVESTIGATIONAL PRODUCT

5.1. Investigational Product Description

5.1.1. Formulation, Appearance, Packaging, and Labeling

The drug product, carbetocin nasal spray (ACP-101), is a nonsterile solution of carbetocin. The Sponsor will supply carbetocin or matching placebo solution for IN administration. Inactive ingredients for the drug product are hypromellose, niacinamide, sorbitol, water, and pH modifiers (hydrochloric acid or sodium hydroxide). Carbetocin and placebo are provided in sealed, Type I glass vials along with separately packaged, commercially available nasal spray pumps (70 µL per spray). Carbetocin and placebo are identical in appearance.

5.1.2. Storage and Stability

At the clinical sites, study drug vials will be stored in a freezer at -10°C to -25°C. At the subject's home, study drug will be stored in a refrigerator, but may be kept frozen and transferred to a refrigerator for thawing before use.

5.1.3. Dosing and Administration

The study drug will only be dispensed to subjects who meet the eligibility criteria and are randomized. Study drug will be dispensed at the site during the Baseline visit. Thereafter, study drug may be shipped to the subject (where permitted). Study drug shipment, return, and accountability will be performed in accordance with the Pharmacy Drug Distribution Manual.

The first dose of study drug will be administered at the clinic.

Study drug will be supplied in frozen vials. Each vial will provide three doses of study drug. If stored frozen, study drug must be thawed before dosing. When thawed to a liquid state, the caregiver will manually attach a nasal spray pump to the vial. Supplies of study drug will be shipped frozen to the subject's home (where permitted) with a temperature monitor; supplies will be labeled as required per country requirement. Caregivers and sites will be provided instructions for the return of all used and unused vials of study drug.

To prepare each vial of study drug for use, the aluminum tear-off seal and stopper are removed from the vial and the nasal spray pump is manually snapped onto the open vial. The cap and lock ring on the spray pump are then removed and the pump is primed by actuating the pump 10times. Priming should be done using a priming bag and hands should be washed after each use.

For each dose, the caregiver (or the subject) holds the spray pump upright and administers four IN sprays (two sprays per nostril), alternating nostrils between each spray. After priming, each actuation of the pump delivers 70 µL of drug product for a total of 280 µL (0.28 mL) of delivered volume (3.2 mg of carbetocin or placebo). Between doses, the combined vial and pump assembly are to be stored in a refrigerator or in an insulated cooler bag.

5.1.4. Method of Assigning Subjects to Treatment Groups

All subjects will be centrally assigned to randomized study drug using an interactive response technology. Subjects will be randomized in a 1:1 ratio to carbetocin 3.2 mg dose or matching placebo during the placebo-controlled period. Study drug will be labeled with a kit number, such

that the study drug is blinded at the study level, preserving the blind for the Investigator, caregiver, and subject.

5.1.5. Blinding and Unblinding

Treatment assignments will be blinded to all study subjects, caregivers, Investigators, site personnel, and Sponsor personnel. Blinding will be assured by restricting access of Investigators and Sponsor personnel and/or designee to the treatment codes and providing identical packaging for the carbetocin and placebo treatments. Data will be unblinded after database lock, unless specified otherwise.

In the event of a medical emergency or pregnancy where breaking the blind is required so that appropriate medical care can be provided, treatment assignment for the affected subject may be unblinded to the Investigator through the interactive response technology system. The date and rationale for unblinding must be clearly explained in source documentation. The Investigator should contact the Sponsor Medical Monitor promptly regarding any emergency unblinding. Once a subject's treatment assignment is disclosed to the Investigator, the subject should have study drug discontinued.

In the event of a potential suspected unexpected serious adverse reaction (SUSAR), the safety management plan should be followed.

If pregnancy occurs during the study, the pregnant subject should be discontinued from the study after unblinding so that counseling or medical intervention, if necessary, may be offered based on whether the fetus was exposed to carbetocin or placebo.

5.1.6. Study Drug Compliance

Study drug supplies for each subject will be inventoried and accounted for throughout the study to verify the subject's compliance with the dosage regimen. Subjects and caregivers will be counseled regarding compliance at every visit.

If a subject misses a dose of study drug, he or she should not take an extra dose before the next scheduled dose.

If a subject shows significant undercompliance (<80%), the Medical Monitor should be notified to determine if the subject shall be discontinued.

5.1.7. Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. Overdoses must be reported using the Sponsor's Overdose Reporting form, regardless of outcome, even if toxic effects were not observed (Section 7.4.4). All events of overdose are to be captured as protocol deviations.

5.2. Investigational Product Accountability Procedures

The Investigator or designee will keep current and accurate records of the study drug dispensed, used, and returned to the study center for each subject to assure the regulatory authority and the Sponsor that the study drug is being handled appropriately. Caregivers will be provided

instructions for the return of all packaging and unused study drug. Any study drug supplied is for use in this study only and should not be used for any other purpose.

At appropriate intervals during the study, study drug reconciliation will be performed by the Sponsor (or designee) who may return appropriate unused study drug and used and unused packaging to the Sponsor's designee. Any remaining unused study drug and all used and unused packaging will be sent back to the Sponsor's designee for destruction or destroyed at the site, as allowed by country-specific regulations.

At the conclusion of the study, final study drug reconciliation will be conducted. Documentation of study drug destruction will be recorded and maintained by both the Sponsor and the Sponsor's designee.

6. STUDY ASSESSMENTS

Study assessments are detailed below. All assessments will be completed according to the schedule described in Table S–1. Every effort should be made to complete the required procedures and evaluations at the designated visits and times.

6.1. Screening Assessments

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The following assessments will be performed at Screening:

- Informed consent/assent of the LAR(s)/subject
- Informed consent of the caregiver
- Inclusion and exclusion criteria
- Medical history and demographics
- PWS history
- Confirmation of documentation of mutation causing PWS

Efficacy assessments performed at Screening are discussed in detail in Section 6.2 and include the HQ-CT, CGI-S for PWS, CGI-S for hyperphagia in PWS, PADQ, and Food Safe Zone. The following safety assessments are discussed in detail in Section 6.3 and will be performed at Screening:

- Physical examination including nasal assessment
- ECG
- Clinical laboratory assessments (chemistry, hematology, urinalysis, thyroid function tests)
- Vital signs, weight, pregnancy test
- Concomitant medication review

6.2. Efficacy Assessments

The following efficacy assessments will be used in this study:

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

The HQ-CT is a nine-item questionnaire designed to be completed by caregivers of subjects with PWS. It is a revision of the 11-item HPWSQ-R and has been further validated. The questionnaire uses a 5-point scale of 0 to 4 with the minimum score being 0 and the maximum score of 36. The Foundation for Prader-Willi Research has made the HQ-CT available for clinical studies in PWS, and it is the consensus instrument within the PWS research community for measuring observable behaviors that stem from subjects' excessive drive to eat.

The HQ-CT should be completed by the same caregiver throughout the study. The HQ-CT will be administered to the caregiver by a rater using standardized prompts. The Food Safe Zone should be administered immediately before administration of the HQ-CT.

A higher score on the HQ-CT indicates greater severity of hyperphagia. A 7.7-point improvement (decrease) on the HQ-CT has been identified as a threshold for a within-patient responder definition that can be used to assess for a clinically meaningful response (RTI Health Solutions 2016).

6.2.2. Clinical Global Impression–Severity (CGI-S) for PWS, Clinical Global Impression–Change (CGI-C) for PWS, and Clinical Global Impression–Severity (CGI-S) for Hyperphagia in PWS

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

The scales are to be administered by the Investigator or a designated rater (trained and qualified). For a given subject, the same person should perform this task throughout the study.

6.2.3. PWS Anxiousness and Distress Behaviors Questionnaire (PADQ)

The PADQ is a caregiver-reported instrument designed to capture the observable signs of anxiousness and distress that are common among subjects with PWS (Cotter et al. 2023). It was developed in collaboration with RTI-Health Solutions (RTI-HS), the Foundation for Prader-Willi Research, and a working group of three experienced researchers who are also parents of individuals with PWS. The PADQ score is computed based on responses to the first 14 items of the measure. Specifically, item responses are summed to yield scores ranging from 0 to 56, with higher scores indicating greater levels of anxiousness and psychological distress. Item 15 is included in the PADQ as an overall summary of caregivers' observations, but this item is not included in the score. The PADQ has also been known as the PWS Anxiety and Distress Behaviors Questionnaire and the PWS Anxiety and Distress Questionnaire.

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

6.2.4. Food Safe Zone

This caregiver rated questionnaire measures food-related restrictions or controls (e.g., where access to food has been limited by locking or other measures). There are 20 items, with each item rated as 1 (none of the time), 2 (some of the time), or 3 (most/all of the time). Higher scores indicate a greater degree of caregiver control/oversight.

For a given subject, the same caregiver should perform this task throughout the study. The Food Safe Zone should be administered immediately before administration of the HQ-CT.

6.2.5. Zarit Burden Interview

The Zarit Burden Interview (ZBI) was designed to assess the stress experienced by caregivers of patients with dementia (Zarit et al. 1980). The ZBI will be administered as an interview. The

interview consists of 22 statements reflecting how people sometimes feel when taking care of another person. The statements are phrased as questions for the family member caregiver to indicate how often they feel the way described in the statement. Responses are Never, Rarely, Sometimes, Quite Frequently, and Nearly Always. When the caregiver is not a family member, this scale will not be completed.

The ZBI should be completed by the same caregiver throughout the study.

6.2.6. PWS-specific Healthcare Resource Use and Caregiver Burden Questionnaire (PWS-HRUQ)

A Prader-Willi Syndrome (PWS) specific caregiver reported questionnaire (PWS-specific Healthcare Resource Use and Caregiver Burden Questionnaire [PWS-HRUQ]) was developed to assess the amount and type of healthcare resources utilized by the subject such as outpatient hospitalization, emergency rooms visits, physician/general practitioner visits, and allied health professional visits (e.g., nutritionist visits). Additionally, the number of inpatient hospitalizations, if any, and associated length of stay will be assessed. Furthermore, the impact of PWS on subjects' classroom productivity will be assessed.

The PWS-HRUQ also includes questions related to the caregiver's employment status and their work productivity related to absenteeism (i.e., amount of time absent from work) and presenteeism (i.e., amount of unproductive time at work).

All items in the PWS-HRUQ have a 2-week recall period and will be assessed at Week 0 (Baseline) and Week 12 (study endpoint). Analysis of this questionnaire will be outlined in a separate health economics analysis plan.

6.3. Safety Assessments

6.3.1. Physical Examination

A general physical examination will be conducted at Baseline and at all other designated visits. The physical exam procedures will include the following organ systems:

- Neurological
- Head, ears, eyes, throat and nasal assessment
- Skin
- Cardiovascular
- Respiratory
- Abdomen
- Genitourinary (optional)
- Musculoskeletal

The nasal assessment will be 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

Note: Grades 3 and 4 will be documented as adverse events.

6.3.2. Vital Signs, Height, Weight, and Body Mass Index

Vital signs will include body temperature, resting respiration rate, sitting systolic and diastolic blood pressure, and pulse rate. The sitting blood pressure should be measured after the subject has been sitting for ≥3 minutes.

Height will be measured and reported.

Weight will be measured and reported.

Body mass index will be calculated using the following formula:
Weight (kg) / [height (m)]^2.

6.3.3. Electrocardiograms

All 12-lead ECGs will be complete, standardized recordings.

The subject should rest in a supine position for 5 minutes before the ECG is obtained. ECG tracings (paper or electronic) will be reviewed and interpreted by a qualified clinician. All ECGs will also be centrally read; the interpretation by the central cardiologist is considered the official interpretation. ECG tracings and results (ventricular rate, PR, QRS, QT, QTcF, and QTcB intervals) will be included in the subject's study records.

At Baseline, a subject may be enrolled based on the review and interpretation of results of the predose Baseline ECG by a qualified clinician at the research site. If the interpretation of the ECG by the central cardiologist indicates QTcF outside of the allowable range, the subject will be discontinued from the study, but enrollment of the subject will not be considered a protocol deviation.

The (predose) ECG at the Baseline visit will be completed prior to administration of the first dose of study drug. The postdose ECG will be completed 20 minutes (within a 10 to 40 minute window) after the first dose of study drug is administered. The postdose PK sample should be collected as soon as possible after the postdose ECG is performed (Section 6.5).

6.3.4. Laboratory Evaluations

Clinical laboratory sample collection is encouraged, but not required, to be completed under fasting conditions. The laboratory evaluations will include, but are not limited to, the following:

- Clinical chemistry serum tests (CHEM)
  - Sodium (Na), potassium (K), carbon dioxide (CO_2), chloride (Cl), calcium (Ca), blood urea nitrogen (BUN), creatinine (CR)
  - Glucose

- Albumin (ALB)
- Total protein
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
- Thyroid function tests
  - Thyroid stimulating hormone (TSH)
    - TSH should be performed only at Screening
    - Free T4 will be measured only if the TSH is abnormal

- Pregnancy tests
- A serum pregnancy test should be performed at Screening for women of childbearing potential
- A urine pregnancy test should be performed at all designated visits after Screening for women of childbearing potential
  - If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place

- Hematology tests
- Complete blood count (CBC) including:
  - White blood cell (WBC) count
  - Complete differential (relative and absolute)
  - Hematocrit (Hct), hemoglobin, red blood cells (RBC), platelets

- Urinalysis (UA)
- Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH

Laboratory evaluations will be completed according to the schedule presented in Table S–1 and procedures detailed in the study laboratory manual. Additional safety testing may be performed at the discretion of the Investigator or designee.

6.3.5. Adverse Event and Medical Device Incident Assessments

Adverse events and medical device incidents will be assessed as discussed in Table S–1 and in Section 7.

6.3.6. Monitoring of Adverse Events Associated with Suicidal Ideation or Behavior

The Investigator will assess the subject for suicidal ideation and behavior at every visit as part of the AE review. Any reported adverse events associated with suicidal ideation or behavior will be monitored, and action will be taken as deemed appropriate by the Investigator. The Medical Monitor will follow up with the Investigator regarding clinical management of the event.

In addition, AEs associated with suicidal ideation or behavior will be monitored by the Medical Monitor and followed when clinically appropriate. AEs under the following MedDRA high-level group terms consistent with potential concern for suicidal ideation or behavior will be monitored and queried:

- Adjustment disorders
- Depressed mood disorders and disturbances
- Manic and bipolar mood disorders and disturbances
- Mood disorder and disturbances NEC
- Suicidal and self-injurious behavior

All AEs will be assessed for severity in accordance with Section 7.2.1.

6.4. Caregiver Interview

An optional, qualitative interview with caregivers of study subjects will be conducted in the US only. Caregiver interviews will be conducted remotely by web-based platform or telephone. Only caregivers in the US of subjects for whom separate informed consent for the caregiver interview is completed will be interviewed. Interviews will be conducted by trained moderators from a 3rd party and are anticipated to be up to approximately 60 minutes in duration. The interviews are planned to elicit a better understanding of the observable signs as well as the impact of study drug and PWS, in particular hyperphagia, both on the study subject and on the caregiver. The interviews will document changes observed by the caregivers over the course of participation in the study. The interviews will also provide an opportunity to describe the meaningfulness of any improvements that may have occurred from the perspective of the caregiver. Interviews will be audio-recorded and transcribed for analysis. Any personally identifiable health information mentioned during the interview will be redacted from the transcripts. Furthermore, if any potential adverse events are revealed during the interview, the interviewer will inform the Investigator of the potential adverse event.

Following the analysis of the qualitative data, a summary report that describes the objectives, methods, participants, and results of the qualitative interviews will be prepared and reported separately from the clinical study report.

The caregiver interview will be administered within 2 weeks after an EOT or ET visit.

6.5. Blood Sampling

Up to eight PK samples will be collected at the following visits:

- Baseline: Two samples will be collected at the Baseline Visit. One sample will be collected before the first dose, and one sample will be collected 15 minutes to 1 hour postdose. The postdose sample should be collected as soon as possible after the postdose ECG is performed. The postdose ECG will be completed 20 minutes (within a 10- to 40-minute window) after the first dose of study drug is administered.
- Week 2 and Week 8, and Week 12 in one of two windows:

- Window 1: 1.25 to 3 hours postdose – one sample (a second sample [at least 15 minutes later] should be collected, if possible)
- Window 2: 3.25 to 4.5 hours postdose – one sample (a second sample [at least 15 minutes later] should be collected, if possible)

Samples should be taken at different windows at Week 2 and Week 8. The Week 12 can be collected within either window. For subjects continuing into the OLE study, the Week 12 samples will be taken prior to the first dose of open-label study drug.

Pharmacokinetic samples will also be collected, if possible, at any ET visit and immediately following any SAE or any AE leading to discontinuation.

For all PK samples (scheduled and unscheduled), the dates and times of administration of the last three doses of study drug should be recorded, as well as the date and time of the sample draw.

In addition to PK samples, blood will be taken for various safety assessments as applicable (Section 6.3.4). The blood volumes taken for these safety assessments and PK sampling are shown in Table 6-1 by visit.

Table 6-1: Blood Volumes Taken in Study ACP-101-302 by Visit

Sample	Visit 1 (Screening) (mL)	Visit 2 (Baseline) (mL)	Visit 3 (Week 2) (mL)	Visit 5 (Week 8) (mL)	Visit 6 (Week 12 [EOT/ET]) (mL)
PK samples	–	8.0	8.0	8.0	8.0
Chemistry[a]	5.0	5.0	5.0	5.0	5.0
Hematology	3.0	3.0	3.0	3.0	3.0
TSH[b]	2.5	–	–	–	–
Pregnancy test[c]	2.5	–	–	–	–
Total volume	13.0	16.0	16.0	16.0	16.0

Abbreviations: EOT=end of treatment; ET=early termination; PK=pharmacokinetic; TSH=thyroid stimulating hormone
[a] Exclusive of TSH, which is listed separately below.
[b] Reflex testing of T4 following abnormal TSH requires no additional blood.
[c] Only for women of childbearing potential.

6.6. Study Drug Compliance Diary

The study drug compliance diary will be completed on an ongoing basis throughout the study from Baseline to Week 12/EOT/ET.

6.7. Safety Follow-up

A 30-day safety follow-up telephone/video conference contact is to be completed for subjects who complete the treatment period of the study (unless the subject is enrolling in the OLE study) as well as those who discontinue prematurely from the study. Subjects should have the following completed at 30 (+4) days after last dose of study drug:

- Assessment of concomitant medications
- Assessment of AEs

6.8. Unscheduled Visits

Unscheduled visits may occur as determined by the Investigator. The following safety assessments generally should be recorded at each unscheduled visit: assessment of AEs, assessment of concomitant medications, and measurement of vital signs and weight. The Investigator may perform any additional safety evaluations or any other assessments deemed by the Investigator to be clinically indicated.

7. ADVERSE EVENTS

7.1. Specification of Safety Parameters

7.1.1. Definition of Adverse Event

An AE is defined as "any untoward medical occurrence in a patient or clinical study participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment".

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease in a patient or clinical study participant administered a pharmaceutical product, without any judgment about causality or seriousness. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE.

AEs do not include the following:

- Stable or intermittent chronic conditions (such as myopia requiring eyeglasses) that are present prior to Baseline and do not worsen during the study.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) or scheduled surgery/procedure. The condition that leads to the procedure is an AE if not present at time of consent.
- Overdose of concomitant medication without any signs or symptoms will not be considered an AE, but if a subject is hospitalized or has other serious criteria, the overdose will be considered an AE and shall be reported on the Sponsor's Overdose Reporting form.
- Hospitalization for elective surgery planned prior to study (situation where an untoward medical occurrence has not occurred).
- Pregnancy will not be considered an AE, but if it occurs, it will be reported on a pregnancy form.

For subjects who enroll into the OLE study, AEs for this study will be recorded from the time informed consent is obtained in the present study until the first dose of study drug in the OLE study.

For subjects who discontinue from this study or do not enroll into the OLE study, AEs will be recorded from the time informed consent is obtained until 30 (+4) days after the last dose of study drug.

7.1.2. Definition of Serious Adverse Event

In addition to the severity rating, each AE will be classified by the Investigator as "serious" or "not serious." The seriousness of an event will be defined according to the applicable regulations and generally refers to the outcome of an event. An SAE is one that meets one or more of the following:

- Is fatal
- Is life-threatening
- Results in disability or permanent damage
- Requires hospitalization (initial or prolonged)
- Results in congenital anomaly or birth defect
- Other serious event (medically significant/important medical event)

Definition of Life-threatening

A life-threatening event places the subject at immediate risk of death from the event as it occurred. This does not include an AE, which, had it occurred in a more severe form, might have caused death.

Definition of Hospitalization

Hospitalization is defined by the Sponsor as a full admission to the hospital for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization.

Examples of visits to a hospital facility that do not meet the serious criteria for hospitalization include:

- Emergency room visits (that do not result in a full hospital admission)
- Outpatient surgery
- Preplanned or elective procedures
- Protocol procedures
- Social hospitalization, defined as admission to the hospital as a result of inadequate family support or care at the subject's primary residence

Definition of Disability or Permanent Damage

Disability is defined as a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Definition of Medically Significant

Important medical events (medically significant events) that may not result in death, be life-threatening, or require hospitalization may be considered to be an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An SAE may also include any other event that the Investigator or Medical Monitor judges to be serious or that suggests a significant hazard, contraindication, side effect, or precaution.

7.1.3. Definition of Medical Device Incidents (Including Malfunctions)

A medical device incident is a malfunction or deterioration in the characteristics or performance of a device, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

A malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended.

A serious incident is any incident that directly or indirectly led, might have led, or might lead to the death or the temporary or permanent serious deterioration in the state of health of a patient, user or other person, or posed a serious public health threat. A serious public health threat is an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

Examples of medical device incidents include:

- A subject is injured as a result of a medical device failure or its misuse.
- A subject's study intervention is interrupted or compromised by a medical device failure.
- A subject's health deteriorates due to medical device failure.

Intranasal spray pumps are being provided for use in this study for administration of investigational product. The Investigator is responsible for the detection and documentation of events meeting the definitions of medical device incident or malfunction of spray pumps that occur during the study.

7.2. Classification of an Adverse Event

7.2.1. Severity of Event

The severity of each AE will be assessed as described below and reported in detail as indicated on the eCRF:

- **Mild**: awareness of sign or symptom but easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities
- **Moderate**: sufficiently discomforting to interfere with normal everyday activities
- **Severe**: incapacitating and/or preventing normal everyday activities

7.2.2. Relationship to Study Drug

The causality of each AE should be assessed and classified by the Investigator as "related" or "not related." An event is considered related if there is a reasonable possibility that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Consider the following when assessing causality:

- Temporal associations between the agent and the event

- Response to drug cessation (de-challenge) or re-challenge
- Compatibility with known class effect
- Known effects of concomitant medications
- Pre-existing risk factors
- A plausible mechanism
- Concurrent illnesses
- Past medical history

7.2.3. Duration

The start and stop dates for AEs will be recorded using the following criteria:

- **Start:** Date of the first episode of the AE or date of worsening in severity
- **Stop:** Date when AE recovered or resolved, recovered or resolved with sequelae, or worsened in severity

7.2.4. Frequency

The frequency of the AE should be indicated according to the following definitions:

- **Single:** Experienced once, without recurrence at same severity
- **Recurrent:** More than one discrete episode with the same severity

7.2.5. Action Taken with Study Drug

- **Dose not changed:** No change in study drug
- **Drug interrupted:** Study drug temporarily stopped
- **Drug withdrawn:** Study drug discontinued permanently
- **Not applicable**
- **Unknown**

7.2.6. Therapy

- **None:** No new treatment instituted
- **Medication:** New treatment initiated as a direct result of AE
- **Other:** Other action required

7.2.7. Outcome

- **Recovered/resolved:** Recovered or resolved
- **Recovered/resolved with sequelae:** Recovered or resolved with sequelae
- **Not recovered/not resolved:** Not recovered or not resolved

- **Fatal:** Death due to an AE
- **Unknown:** Unknown

7.2.8. Seriousness

- Not serious
- Serious (see Section 7.1.2)

7.2.9. Definition of Unexpectedness

An AE, the nature or severity of which is not consistent with the information provided in the Reference Safety Information section of the current ACP-101 Investigator's brochure.

7.3. Time Period and Frequency for Event Assessment and Follow-up

For subjects who enroll into the OLE study, AEs for this study will be recorded from the time informed consent is obtained in the present study until the first dose of study drug in the OLE study. For subjects who discontinue from this study or do not enroll into the OLE study, adverse events will be recorded from the time informed consent is obtained through the study safety follow-up period. If an AE is ongoing at the end of the study safety follow-up period, every reasonable attempt should be made to follow and appropriately treat the subject until the AE resolves or until the Investigator deems the AE to be chronic or stable.

In the event that a subject discontinues from the study and has an ongoing AE at the time of discontinuation (Section 4.5.1), the subject should be followed and appropriately treated until the AE resolves or until the Investigator deems the AE to be chronic or stable. If a subject or LAR withdraws consent from the study because of an AE, no additional assessments may be performed (Section 4.4).

7.4. Reporting Procedures

7.4.1. Adverse Event Reporting

The Investigator must record all observed AEs and all reported AEs. At each visit, the Investigator should ask the subject a nonspecific question (e.g., "Have you noticed anything different since your last visit?") to assess whether any AEs have been experienced since the last report or visit.

Note that any use of medication (and specifically any newly prescribed medication) during the course of a study may indicate the occurrence of an AE that may need to be recorded on both the AE and the concomitant medication page.

All AEs, serious and not serious, will be recorded on the AE eCRF page using appropriate medical terminology. Severity and relationship to study drug will be assessed by the Investigator.

When possible, clinical AEs should be described by diagnosis and not by symptoms (e.g., "cold" or "seasonal allergies" instead of "runny nose").

All AEs, *whether or not related to the study drug*, must be fully and completely documented on the AE eCRF and in the subject's notes.

7.4.2. Serious Adverse Event Reporting

The reporting of SAEs by the Sponsor or designee to the regulatory authorities is a regulatory requirement. Each regulatory authority has established a timetable for reporting SAEs based upon established criteria.

When an SAE occurs, Investigators will review all documentation related to the event and will complete the SAE-Device Incident Report Form with all required information (for initial and updated/follow-up information, including resolution of event, if applicable) and send (within 24 hours of discovery) as per the contact information provided on the SAE-Device Incident Report Form, as well as enter the SAE into the EDC system in a timely manner.

At a minimum, events identified by the Sponsor to require expedited reporting as serious, unexpected, and related to study drug must be brought to the attention of the responsible institutional review board/ethics committee (IRB/EC) and global regulatory authorities, as per applicable regulations. These will be provided by the Sponsor after their assessment.

For European Union (EU) member states, the Sponsor or its designee will provide reports of SUSARs directly to the ECs and the EudraVigilance database, as required by local legislation and regulations.

In all other countries, it is the Investigator's responsibility to provide these expedited reports to the responsible IRB/EC. It is also the Investigator's responsibility to notify the responsible IRB/EC regarding any new and significant safety information.

Unless they roll over into the OLE, subjects will be followed through the safety follow-up period (i.e., 30[+4] days after last dose of study drug) for any SAEs and/or other reportable information until such events have resolved or the Investigator deems them to be chronic or stable.

In the event of any SAE (other than death), the study subject will be instructed to contact the Investigator (or designee) using the telephone number provided in the informed consent form (ICF). All subjects experiencing an SAE will be seen by the Investigator or designee as soon as is feasible following the report of the SAE.

Serious AEs occurring after the safety follow-up period (i.e., 30[+4] days after last dose of study drug) should be reported if in the judgment of the Investigator there is "a reasonable possibility" that the event may have been caused by the study drug.

SAEs should also be reported to the IRB/EC according to local regulations.

7.4.3. Reporting of Pregnancy

Any female subject who becomes pregnant during the study (with or without AEs) must be discontinued from the study. If the pregnancy occurred after exposure to the study drug, it must be reported on the Pregnancy Form within 24 hours of discovery to the Sponsor or its designee. Any female subject who becomes pregnant during the study will be followed through the pregnancy outcome, unless the subject or LAR withdraws consent for any and all follow-ups.

If pregnancy occurs during the study, the pregnant subject should be unblinded so that counseling may be offered based on whether the fetus was exposed to the active study drug or placebo.

Any AEs that are the consequence of pregnancy and which meet the criteria for serious should also be reported via the SAE-Device Incident Report Form.

7.4.3.1. Reporting Paternal Study Drug Exposure

Paternal study drug exposure is defined as a father's exposure to a medicinal product before or during his partner's pregnancy. Any paternal study drug exposure cases must be reported to the Sponsor within 24 hours of discovery via the Pregnancy Form. Any AEs that are the consequence of paternal study drug exposure and which meet the criteria for serious must also be reported to the Sponsor within 24 hours of discovery via the SAE-Device Incident Report Form.

7.4.4. Reporting of Overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than the maximum recommended dose per protocol. It must be reported to the Sponsor or designee on the Sponsor Overdose Reporting Form within 24 hours of discovery. In addition, all events of overdose are to be captured as protocol deviations (see Section 5.1.7).

7.4.5. Reporting of Medical Device Incidents (Including Malfunctions)

The Investigator must report all incidents/malfunctions occurring with the medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical device being used in the clinical study.

When a medical device incident/malfunction occurs, Investigators will complete the SAE-Device Incident Report Form with all required information (for initial and follow-up information) and send (within 24 hours of discovery) as per the contact information provided on the SAE-Device Incident Report form, as well as enter the device incident/malfunction into the EDC system in a timely manner.

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

The Investigator must provide his/her assessment of causality (relationship to the medical device provided by the Sponsor) at the time of reporting and describe any corrective or remedial actions taken to prevent recurrence of the incident. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident/malfunction. This includes any amendment to the device design to prevent recurrence.

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

Any AEs that are a consequence of medical device incidents/malfunctions will be followed and reported in the same manner as other AEs (Section 7.4.1).

Any AEs that are the consequence of medical device incidents/malfunctions and which meet the criteria for an SAE must also be reported in the same manner as other SAEs via the paper SAE-Device Incident Report Form, and into the EDC system (Section 7.4.2).

The Investigator, or designee will comply with the applicable local regulatory requirements relating to the reporting of medical device incidents to the IRB/EC.

8. MONITORING

Routine monitoring of study sites is described in Section 10.9.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol and amendment(s) as applicable, with GCP, and with applicable regulatory requirements. Details of the study site monitoring process are described in a separate clinical monitoring plan document.

9. STATISTICAL METHODS AND DATA ANALYSIS

Statistical methods will be documented in detail in a statistical analysis plan (SAP) to be approved by the Sponsor prior to unblinding and database lock. Deviations from the approved SAP will be described and justified in the final clinical study report (CSR).

9.1. Statistical Hypothesis

The primary analysis will evaluate treatment effect of carbetocin nasal spray (3.2 mg) compared to placebo based on the primary endpoint at the significance level of 0.05 (two-sided). The null and alternative hypotheses for the primary endpoint are as follows:

Let Δ ($\mu_{CARB}-\mu_{PBO}$) be the difference in the mean change from Baseline at Week 12 in the HQ-CT score between the active treatment (μ_{CARB}) and the placebo (μ_{PBO}) groups.

The null hypothesis is: $\Delta=0$.

The alternative hypothesis is: $\Delta\neq0$.

9.2. Multiplicity Adjustment

Multiplicity adjustment is not applicable in this study.

9.3. Sample Size Determination

The planned sample size is approximately 170 subjects randomized in a 1:1 ratio to the carbetocin group and placebo group (85 subjects per treatment group).

Assuming the common standard deviation of change from Baseline at Week 12 in HQ-CT is 7 points, 80 subjects who complete the study per treatment group will provide 88% power to detect a difference in the mean change from Baseline at Week 12 in HQ-CT of 3.5 points between the carbetocin group and the placebo group at a significance level of 0.05 (two-sided *t*-test).

The difference of 3.5 points was selected based on findings from the previous Phase 3 study in IN carbetocin for hyperphagia in PWS (Study LV-101-3-01 [CARE-PWS]), where the MID, defined as one-half of the standard deviation of baseline scores on the outcome measures, was 2.6 points in HQ-CT. In this study, the observed between-group HQ-CT difference of -3.1 points for the 3.2 mg/dose group exceeded this threshold of clinical meaningfulness. For the current study, a difference of 3.5 points is selected to use as the basis on which to calculate sample size.

Adjusting for a potential discontinuation rate of up to 5%, approximately 170 subjects need to be randomized.

9.4. Descriptive Statistics

All continuous outcomes will be summarized using the number of subjects with data values, mean, standard error of the mean, standard deviation, minimum, maximum, and median. All categorical outcomes will be summarized by the number and percentage of subjects in each category.

9.5. Missing Data

Handling of missing data will be described in detail in the SAP. Sensitivity analyses assuming different missing mechanisms will be performed to assess the impact of missing data.

9.6. Analysis Sets

The **Randomized Analysis Set** consists of all subjects who were randomized. Subjects will be classified according to the randomized treatment assignment.

The **Safety Analysis Set** (SAS) includes all randomized subjects who received at least one dose of study drug. The SAS will be used for the analyses of all safety endpoints based on the actual treatment received.

The **Full Analysis Set** (FAS) includes all randomized subjects who received at least one dose of study drug and who have a baseline value for the HQ-CT score. The FAS will be used for the analyses of all efficacy endpoints based on the randomized treatment assignment.

The **Pharmacokinetic Analysis Set** includes all subjects in the SAS with at least one measurable carbetocin plasma concentration.

Any other analysis sets, if necessary, will be defined in the SAP.

9.7. Efficacy Analyses

All efficacy analyses will be based on the FAS and all statistical tests will be two-sided hypothesis tests performed at the 5% level of significance. In addition, all CIs will be two-sided 95% CIs, unless stated otherwise.

9.7.1. Estimand

The primary clinical question of interest for the primary objective is: what is the difference in the change from Baseline in HQ-CT score at Week 12 comparing carbetocin 3.2 mg TID versus placebo, in subjects with PWS, assuming all subjects complete 12 weeks of treatment.

The hypothetical estimand is described by the following attributes:

Population: Male or female subjects 5 to 30 years of age, inclusive, with PWS, as defined by the inclusion/exclusion criteria of the study.

Variable (primary endpoint): Change from Baseline in HQ-CT score at Week 12.

Treatment condition: carbetocin 3.2 mg TID and placebo.

Intercurrent events and strategies:

- The intercurrent event (ICE) “treatment discontinuation” will be addressed by the hypothetical strategy (i.e., assuming that subjects with this ICE evolve in the same way after ICE occurrence as the subjects in the same treatment group who complete the treatment). Efficacy data after such ICE will not be collected for the purpose of this estimand. Every effort will be made to minimize missing data during the trial.
- Alternative approaches to handling ICEs will be addressed in the sensitivity analyses. Details on the sensitivity analyses will be provided in the SAP.

Population-level summary: difference (carbetocin 3.2 mg TID versus placebo) in the change from Baseline in HQ-CT score at Week 12.

9.7.2. Primary Estimator

The primary endpoint is the change from Baseline in HQ-CT score at Week 12. The primary analysis will evaluate treatment effect of carbetocin 3.2 mg TID compared to placebo based on the FAS using mixed-effects model for repeated measures (MMRM). The model will include effects for treatment group, sex, randomization stratification factors (age grouping, and presence or absence of participation in a previous clinical study of carbetocin nasal spray), visit, treatment-by-visit interaction, baseline HQ-CT score, and baseline HQ-CT score-by-visit interaction. An unstructured covariance matrix will be used to model the within-subject errors, and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The treatment effect will be estimated by the difference in LSMs of the change from Baseline in HQ-CT score at Week 12 and will be tested at the two-sided significance level of 0.05. The difference in LSMs, standard error, corresponding 95% CI, p-value, and Cohen's *d* effect size will be reported.

9.7.3. Other Endpoint Analyses

9.7.3.1. Secondary Endpoints Analyses

Percentage of subjects with treatment response (defined as improvement ≥8 points from Baseline) based on the HQ-CT at Week 12 will be summarized, and the proportion of responders at Week 12 will be analyzed using logistic regression adjusted by baseline HQ-CT, treatment group, sex, and randomization stratification factors (age grouping, and presence or absence of participation in a previous clinical study of carbetocin nasal spray).

The following endpoints will be analyzed using MMRM similar to the primary endpoint analysis:

- CGI-S for PWS score – change from Baseline at Week 12
- CGI-C for PWS score at Week 12
- CGI-S for hyperphagia in PWS score – change from Baseline at Week 12

9.7.3.2. Exploratory Endpoint Analysis

The following exploratory endpoints will be analyzed similarly to the primary endpoint analysis:

- PWS Anxiousness and Distress Behaviors Questionnaire (PADQ) score – change from Baseline at Week 12
- Food Safe Zone score – change from Baseline at Week 12
- Zarit Burden Interview score – change from Baseline at Week 12

Statistical methods for the analysis of these exploratory endpoints will be provided in the SAP.

The analysis of PWS-specific Healthcare Resource Use and Caregiver Burden Questionnaire (PWS-HRUQ) – change from Baseline at Week 12 will be outlined in a separate health economics analysis plan.

9.8. Safety Analyses

Safety results will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints. Adverse events will be classified into standard terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) and device incidents, or device malfunctions, TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, nonserious TEAEs, treatment-emergent SAEs, and treatment-emergent SAEs related to study drug will all be summarized by treatment group.

Descriptive statistics for ECG, vital signs, physical examination results, and clinical laboratory parameters, including changes from Baseline, will be tabulated by timepoint. Additionally, categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines.

Additional safety analysis details will be specified in the SAP.

9.8.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Treatment-emergent adverse events (TEAEs) are:

- Any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug

All adverse events will be included in the listing, and TEAEs will be summarized by system organ class and preferred term. Treatment-emergent adverse events and device incidents, or device malfunctions, TEAEs leading to discontinuation, TEAEs related to study drug, TEAEs by maximum severity, fatal TEAEs, nonserious TEAEs, treatment-emergent SAEs, and treatment-emergent SAEs related to study drug will all be summarized by treatment group.

9.8.2. Clinical Laboratory Evaluations

The serum clinical chemistry, hematology, and urinalysis laboratory data will be summarized by study visit. Change from baseline values will also be summarized.

The number and percentage of subjects with potentially clinically important postbaseline laboratory values will be summarized for selected parameters. The criteria for potentially clinically important values will be specified in the SAP.

9.8.3. Vital Signs, Body Weight and BMI

Vital signs and body weight will be summarized by study visit. Change from baseline values will also be summarized as well as the number and percentage of subjects with potentially clinically important postbaseline values. The criteria for potentially clinically important values will be specified in the SAP.

9.8.4. Electrocardiogram

ECG parameters will be summarized by study visit. Change from baseline values will also be summarized as well as the number and percentage of subjects with potentially clinically

important postbaseline values. Categorical analyses will be conducted on the incidence of subjects with prolonged QTc intervals and changes in QTc intervals in accordance with ICH guidelines and based on the FDA E14 Guidance Document. The criteria for potentially clinically important values will be specified in the SAP.

9.8.5. Physical Examinations

The results of the physical examinations will be tabulated by study visit.

9.9. Pharmacokinetic Analyses

Plasma concentration data for carbetocin will be listed and summarized using descriptive statistics. Population PK analyses will be performed to further characterize the PK profile. The exposure-response relationship of carbetocin using measures of safety and efficacy parameters will be assessed. Carbetocin plasma concentration data will remain blinded until the unblinding of the clinical database at the end of the study.

The details of the PK and exposure-response relationship analyses will be presented in a separate report in accordance with a separate data analysis plan.

9.10. Interim Analyses

No interim analyses are planned for this study.

9.11. Data and Safety Monitoring Board

An external data and safety monitoring board (DSMB) will review ongoing safety data, including data on AEs, SAEs, and safety laboratory data. The DSMB will be independent of the Sponsor and the Investigators and will be empowered to recommend whether the study should be terminated due to safety concerns, continue as planned, or continue with modification.

The DSMB membership, activities, responsibilities, and frequency of meetings will be described separately in the DSMB charter.

While the DSMB will be making recommendations regarding future conduct of the study, the Sponsor retains final decision-making authority on all aspects of the study.

10. STUDY MANAGEMENT AND DATA COLLECTION

10.1. Data Collection and Management Responsibilities

All documents required for the conduct of the study as specified in the ICH E6 (GCP) guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor and regulatory authorities.

The Investigator and institution must permit authorized representatives of the Sponsor or designees (including monitors and auditors), regulatory authorities (including inspectors), and the IRB/EC direct access to source documents (such as original medical records, both in paper format and in electronic systems, where applicable) as allowed by local regulations. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are needed for the evaluation of the study, either in person or through remote video/electronic medium (such as email) if applicable. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

10.2. Source Documents

All study specific information obtained at each study visit must be recorded in the subject's record (source documentation), and then entered into a validated EDC database by trained site personnel and/or transferred electronically. The source documentation may consist of source notes captured by site personnel, as well as laboratory reports, ECG reports, electronic source data, electronic clinical outcomes assessments, and rating scales platforms.

10.3. Case Report Forms

Subject data required by this protocol are to be recorded in an EDC system on eCRFs and/or transferred electronically and securely for data review. The Investigator and his or her site personnel will be responsible for completing the eCRFs. The Investigator is responsible for the accuracy and reliability of all the information recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification data, visit date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documentation (unless eCRF is considered the source) at the site.

10.4. Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs, medical records, or other documents submitted to the Sponsor or designees, subjects must be identified by a subject identification number only. Subject identifiers uniquely identify subjects within the study and do not identify any person specifically. Documents that are not de-identified (e.g., signed ICFs) should be kept in strict confidence by the Investigator in compliance with Federal regulations or other applicable laws or ICH E6 (GCP) guidelines and as such, should not be submitted to the Sponsor or designees. These documents should remain accessible on site (Section 10.1). Data collection and handling should comply with the European Union General Data Protection Regulation (EU GDPR) and other relevant regulations

concerning data privacy, where applicable. Acadia has assigned a Data Protection Officer as per the EU GDPR.

10.5. Study Records Retention

Investigators are required to maintain all essential study documentation as per ICH E6 (GCP) guidelines. This includes, but is not limited to, copies of signed, dated, and completed eCRFs, documentation of eCRF corrections, signed ICFs, audio recordings, subject-related source documentation, and adequate records for the receipt and disposition of all study drug. Investigators should maintain all essential study documentation, for a period of at least 2 years following the last approval of marketing application in an ICH region (US, Europe, and Japan), or until at least 2 years after the study drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. Only the Sponsor can notify an Investigator or vendor when any records may be discarded. Investigators should contact the Sponsor before destroying any files.

10.6. Protocol Exceptions and Deviations

No prospective entry criteria protocol deviations are allowed; all subjects must meet all eligibility criteria in order to participate in the study.

Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If a subject is enrolled and later discovered not to meet all eligibility criteria, this will be reported as a major protocol deviation and not a waiver. In this situation, the subject will be discontinued, unless the discontinuation presents an unacceptable medical risk. The justification to allow the subject to continue in the study will be made by the Sponsor, with medical input from the Investigator, and will be documented. All follow-up safety assessments must be completed and documented as outlined in the protocol (Section 6.7). The Investigator must report any protocol deviation to the Sponsor and, if required, to the IRB/EC in accordance with local regulations, within reasonable time.

10.7. Protocol Amendments

Changes to the protocol may be made only by the Sponsor (with or without consultation with the Investigator). All protocol modifications must be submitted to the site IRB/EC in accordance with local requirements and, if required, to regulatory authorities, as either an amendment or a notification. Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the changes involve only logistical or administrative aspects of the study. No approval is required for notifications.

10.8. Serious Breach Reporting

A “serious breach’ is any deviation from the approved protocol version or the clinical trial regulation likely to affect to a **significant** degree the safety and/or rights of a subject or the reliability and robustness of the data generated in the clinical study.

The Investigator, site staff, and service providers delegated by the Investigator/institution must identify the occurrence of a (possible or suspected) serious breach and immediately report to the Sponsor at seriousbreachrandd@acadia-pharm.com or (+1) 858-558-2871, Press 2.

10.9. Urgent Safety Measure

Where an unexpected event is likely to seriously affect the benefit-risk balance for subjects (e.g., immediate hazard to a subject's health and/or safety), the Sponsor and the Investigator must take appropriate urgent safety measures (USM) to protect the subjects.

If the Investigator (and not the Sponsor) has instigated the USM, the Sponsor Study Lead must be notified immediately so that the Sponsor can assess and report the USM within the timelines required.

11. QUALITY MANAGEMENT

11.1. Quality Risk Management

The Sponsor utilizes the ICH E6 (GCP) quality risk management approach that includes methods to assure and control the quality of the study proportionate to the risks inherent in the study and the importance of the information collected. The intent is that all aspects of this study are operationally feasible and that any unnecessary complexity, procedures, and data collection are avoided. The Sponsor's risk management approach includes the following documented activities:

- Critical process and data identification: during protocol development, risks of processes and data that are critical to ensure human subject protection and the reliability of study results are identified and assessed and, where applicable, quality tolerance limits are defined.
- Risk identification: risks to critical trial processes, governing systems, study drug, study design, data collection, and recording are identified.
- Risk evaluation: identified risks are evaluated by considering the following factors: (a) likelihood of occurrence, (b) impact on human subject protection and data integrity, and (c) detectability of errors.
- Risk control: risks that can be avoided, reduced (i.e., mitigated), or accepted are differentiated. Risk mitigation activities are incorporated in protocol design and implementation, study plans, training, processes, and other documents governing the oversight and execution of study activities. Where possible, predefined quality tolerance limits are defined to identify systematic issues that can impact subject safety or data integrity and deviations from the predefined quality tolerance limits will trigger an evaluation and possibly an action. Contingency plans are developed for issues with a high risk factor that cannot be avoided.
- Periodic risk review, communication, and escalation of risk management activities during study execution and risk outcome reporting in the CSR.

11.2. Quality Control and Quality Assurance

The Sponsor or designees and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Sponsor's or designee's monitor is responsible for inspecting the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records (both in paper format and in electronic systems, where applicable) needed to verify the entries on the eCRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH E6 (GCP) guidelines and the Sponsor's audit plans, sites participating in this study may be audited. These audits may include a review of site facilities (e.g., pharmacy, drug storage areas, and laboratories) and review of study-related records may occur in order to evaluate the study conduct and compliance with the protocol, ICH E6 (GCP) guidelines, and applicable regulatory requirements.

The Sponsor's or designee's representatives, regulatory authority inspectors and IRB/EC representatives who obtain direct access to source documents should also respect subject confidentiality, taking all reasonable precautions in accordance with applicable regulatory requirements to maintain the confidentiality of subjects' identities.

12. ETHICAL CONSIDERATIONS

12.1. Ethical Standard

The study will be conducted in compliance with the protocol, the Declaration of Helsinki, applicable ICH E6 (GCP) guidelines, Regulation [EU] No. 536/2014 (Regulation [EU] No. 536/2014 Annex I, section D, no. 17, letter a), and other applicable regulatory requirements (e.g., serious breach reporting [Section 10.8], urgent safety measures, and EU GDPR).

Studies in the US (or with study sites in the US) will be performed in accordance with current US Health Insurance Portability and Accountability Act (HIPAA) regulations, applicable US FDA GCP Regulations, and ICH E6 (GCP) guidelines and clinical safety data management (E2A).

As per ICH E6 (GCP), whether the study is completed or prematurely terminated, a clinical study report will be prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The clinical study report, if part of a marketing applications, shall meet the standards of the ICH Guidance for Structure and Content of Clinical Study Reports (E3) and follow the process as outlined in Acadia's standard operating procedure.

The CSR will be signed by Acadia and the Coordinating (or Principal) Investigator, as per standard operating procedure, unless decided otherwise by Acadia.

12.2. Institutional Review Board/Ethics Committee

The Investigator or designee will provide the IRB/EC with all requisite material, including a copy of the protocol, informed consent, the IB for the drug studied, any subject information or advertising materials, and any other requested information. The study will not be initiated until the IRB/EC provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Investigator and copies received by the Sponsor. All amendments will be sent to the IRB/EC for information (minor amendment) or for submission (major amendment) before implementation. The Investigator will supply the IRB/EC and the Sponsor with appropriate reports on the progress of this study, including any necessary safety updates, in accordance with the applicable government regulations and in agreement with policy established by the Sponsor.

12.3. Informed Consent/Assent Process

Properly executed, written informed consent must be obtained from each subject or subject's LAR(s) prior to any screening procedures. When a subject lacks capacity to consent, and consent is being provided by an LAR, subject should provide written or oral assent if deemed able by the Investigator and according to local regulations. The subject's caregiver must also provide written consent to participate as an informant in study assessments prior to the procedures being performed at the Screening visit.

Local regulations may require that two LARs provide consent for subjects who are minors or adults under guardianship.

The informed consent must, at a minimum, include the elements of consent described in ICH E6 (GCP) and the US CFR 21 part 50.25. A copy of the ICF planned for use will be reviewed by the

Sponsor or designee for acceptability and must be submitted by the Investigator or designee together with the protocol, to the appropriate IRB/EC for review and approval prior to the start of the study at that investigational site. Consent forms must be in a language fully comprehensible to the prospective subject. The Investigator must provide the Sponsor or designee with a copy of the IRB/EC letter approving the protocol and the ICF before the study drug supplies will be shipped and the study can be initiated.

The consent form must be revised if new information becomes available during the study that may be relevant to the subject's willingness to continue participation. Any revision must be submitted to the appropriate IRB/EC for review and approval in advance of use.

12.3.1. Consent and Other Informational Documents Provided to Subjects

The subject or subject's LAR must be given a copy of the signed informed consent (and assent, if applicable) and the original maintained in the designated location at the site.

12.3.2. Consent Procedures and Documentation

It is the Investigator or designee's responsibility to obtain written informed consent from the subject or subject's LAR(s) after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The subject or subject's LAR(s) must be given ample time to decide about study participation and opportunity to inquire about details of the study. The IRB/EC-approved consent form must be personally signed and dated by the subject or subject's LAR(s) and by the person who conducted the informed-consent discussion. The Investigator or appropriate site personnel must document the details of obtaining informed consent in the subject's study documents.

The subject's caregiver must also indicate their understanding of the study and their role as a caregiver to the subject during the study. The subject's caregiver must provide written consent prior to any screening visit procedures being performed indicating their agreement to participate in the study in the caregiver role.

Records related to a study subject's participation will be maintained and processed according to local laws, and where applicable, the EU GDPR. The consent and study information documentation will include statements describing local and regional requirements concerning data privacy, and who to contact for questions.

13. PUBLICATION PLAN

All publication rights are delineated in the clinical study agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

14. CONFLICT OF INTEREST POLICY

14.1. Finance, Insurance, and Indemnity

Arrangements for finance, insurance, and indemnity are delineated in the clinical study agreement and/or other separate agreements with the Investigator and/or Institution, as applicable.

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16. APPENDICES

APPENDIX A. CTFG RECOMMENDATIONS ON HIGHLY EFFECTIVE CONTRACEPTION

The Clinical Trials Facilitation and Coordination Group (CTFG) has defined highly effective contraception in *Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials*, version 1.2, 07 March 2024.

4.1 Birth control methods which may be considered as highly effective

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - injectable
  - implantable 2
- intrauterine device (IUD) 2
- intrauterine hormone-releasing system (IUS) 2
- bilateral tubal occlusion 2
- vasectomised partner 2,3
- sexual abstinence 4

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1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see section 4.3)

2 Contraception methods that in the context of this guidance are considered to have low user dependency.

3 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

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