Intranasal Carbetocin for the Treatment of Prader-Willi Syndrome (PWS)

Psychopharmacologic Drugs Advisory Committee
Levo Therapeutics, Inc.
November 4, 2021
Introduction

Jay Cormier, JD, PhD
Senior Vice President
Levo Therapeutics, Inc.
Prader-Willi Syndrome

- Rare, life-threatening neurodevelopmental genetic disorder
- Uniquely complex phenotype
  - Intellectual disability, shortness of stature, hypogonadism
  - Hyperphagia, anxiousness and distress behaviors, and obsessive and compulsive symptoms
  - Does not fit neatly into standard psychiatric diagnoses
  - Heterogeneous manifestations that vary with age and overlap with autism
- High morbidity/mortality
  - Average life expectancy: ~30 years
  - Respiratory failure, CV events, GI events, obesity, diabetes, renal failure
Therapeutic Landscape

• No approved therapies for the most life-limiting symptoms
  – Growth hormone approved to normalize linear growth

• Psychiatric medications not studied in PWS
  – SSRIs, anti-psychotics, stimulants, etc.

• Vitamins and supplements
  – No evidence of efficacy in PWS
Patient and Caregiver Burden

- **Need to follow strict, daily routine**
  - Disruptions cause tantrums/meltdowns (into adulthood)

- **Rigid environmental controls**
  - Locking refrigerators, cabinets, and trash bins
  - Limiting type and amount of food consumed
  - Avoiding social situations that include food

- **Caregiver burden greater than Alzheimer’s disease**

Therapeutic and Mechanistic Rationale

- **Oxytocin involved in hunger/satiety pathways**
  - Released with meals in the paraventricular nucleus of the hypothalamus

- **Functional oxytocin deficiency in patients with PWS**
  - Demonstrated by human, animal, and in vitro data

- **Oxytocin hormone replacement therapy has had mixed results**
  - Likely due to off-target vasopressin effects

- **Carbetocin is an oxytocin receptor agonist**
  - Longer half-life and greater oxytocin receptor affinity than oxytocin
  - Lower activity at vasopressin receptors
Clinical Development Program

- Two adequate and well-controlled clinical trials
- Study 114
  - Phase 2, two-week study of 9.6 mg intranasal carbetocin
  - 37 PWS patients: 20 on placebo, 17 on 9.6 mg
- CARE-PWS
  - Phase 3, 8-week study of 3.2 mg and 9.6 mg intranasal carbetocin
  - 119 evaluable patients: 40 on placebo, 39 on 3.2 mg, 40 on 9.6 mg
    - Study truncated from originally planned 175 patients due to COVID-19
    - Includes 56-week LTFU and optional extension periods
Efficacy Results

- **Study 114: carbetocin 9.6 mg vs. placebo**
  - Statistically significant improvement in hyperphagia
  - Significant improvements also observed for obsessive/compulsive symptoms and clinical global impressions

- **CARE-PWS: carbetocin 3.2 mg and 9.6 mg vs. placebo**
  - Carbetocin 9.6 mg
    - Numeric improvements in hyperphagia, obsessive/compulsive symptoms, and clinical global impressions
  - Carbetocin 3.2 mg
    - Nominally significant improvements in hyperphagia, anxiousness and distress, and clinical global impressions
    - Numeric improvements in obsessive/compulsive symptoms
Interpretation of Efficacy Results

• Both studies demonstrate IN carbetocin provides clinically meaningful benefits to patients with PWS
  – Confirming therapeutic rationale based on functional oxytocin deficiency

• Carbetocin 3.2 mg is the lowest effective dose studied
  – Carbetocin 9.6 mg has no greater efficacy and had more discontinuations
  – Consistent benefit across multiple endpoints, over time, and using multiple sensitivity analyses
Intranasal Carbetocin Safety

- Generally safe and well tolerated
- Most common events transient and mild to moderate
  - Flushing
  - Events related to IN delivery
- No clinically relevant drug-drug reactions
- Clinical considerations
  - Warning and precaution regarding use during pregnancy
  - Use caution when taking with prostaglandins
LV-101 (carbetocin) nasal spray is indicated for the treatment of hyperphagia and anxiousness and distress associated with Prader-Willi syndrome.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
</table>
| Introduction              | **Jay Cormier, JD, PhD**  
Senior Vice President, Levo Therapeutics, Inc. |
| Unmet Medical Need        | **Shawn McCandless, MD**  
Professor of Pediatrics and Head, Section of Genetics and Metabolism,  
University of Colorado School of Medicine  
Department Chair for Clinical Genetics and Metabolism, Children's Hospital Colorado |
| Efficacy                  | **Jay Cormier, JD, PhD**  
Senior Vice President, Levo Therapeutics, Inc. |
| Safety                    | **Davis Ryman, MD, PhD**  
Vice President of Clinical Development, Levo Therapeutics, Inc. |
| Clinical Perspective      | **Cheri Deal, PhD, MD**  
Emeritus Professor, Université de Montréal  
Pediatric Endocrinologist and Clinical Investigator  
Research Center, CHU Ste-Justine |
Unmet Medical Need

Shawn McCandless, MD
Professor of Pediatrics and Head, Section of Genetics and Metabolism
University of Colorado School of Medicine
Department Chair for Clinical Genetics and Metabolism
Children's Hospital Colorado
Prader-Willi Syndrome

• Rare, life-threatening neurodevelopmental genetic disorder with a uniquely complex phenotype
• Orphan disease
  – Incidence: 1 in 10,000 - 30,000 births
  – Prevalence: 8,000 to 10,000 in United States\cite{1,2}

Prader-Willi Syndrome Genetics

15q11-13 Locus

- **Expressed from both**: (no known effect of missing one copy)
- **Expressed on maternal only**: absence of these genes causes Angelman syndrome
- **Expressed on paternal only**: (absence of these genes causes Angelman syndrome)

Significant Unmet Need

• **Hyperphagia**  
  – Patients are subjected to a false state of starvation  
  – Uncontrollable appetite, lack of satiety, and low metabolic rate  
  – Permeates through all facets of the patients’ lives

• **Medical, behavioral, and developmental impact**  
  – Intellectual disability  
  – Behavioral challenges  
  – Broad endocrine abnormalities

• **Life-threatening and life-limiting**  
  – High risk of stomach rupture, choking, and food-seeking accidents  
  – Average age of death is approximately 30 years  
  – Unable to lead independent lives
### Natural History of Hyperphagia

#### Vanderbilt Longitudinal Data

- **4-62 years at baseline**
- Data collected typically every 2-3 years

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Change in HQ-CT Score from Baseline Mean (SD)</th>
<th>2-3 years (n=129)</th>
<th>0.99 (6.77)</th>
</tr>
</thead>
</table>

#### PATH for PWS Natural History Study

- Subset with 7-18 years at baseline
- Data collected roughly every 6 months

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Change in HQ-CT Score from Baseline Mean (SD)</th>
<th>26-34 weeks (n=176)</th>
<th>-0.33 (5.51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>43-64 weeks (n=104)</td>
<td></td>
<td>-0.74 (6.26)</td>
<td></td>
</tr>
</tbody>
</table>

Data obtained from Vanderbilt University and Foundation from Prader-Willi Research
Hyperphagia

• Pathological hunger drive
  – Constant and inexorable hunger

• Sense of urgency

• Desperation

• All-consuming and distracting

• Persistent and intractable

• Encompasses severely problematic behaviors
Behavioral and Psychological Impacts of Hyperphagia

- **Individuals experiencing hyperphagia are prone to**
  - Thinking constantly about food
  - Waking from sleep early thinking about food
  - Continuing to eat if portion size is not limited
  - Stealing food or money for food
  - Breaking into houses for food
  - Eating food from unsavory/inedible sources
  - Exhibiting “meltdowns” related to food

- **Morbidity related to food-seeking contributed to mortality in a third of PWS patients under 18 years of age**

There is No Treatment for Hyperphagia

- No effective pharmacologic options
- Environmental controls are used to reduce caloric intake and minimize excessive weight gain
  - Require 24-hour vigilance
  - Locking of refrigerators, pantries, trash cans, and bedrooms
- Environmental controls have no effect on hyperphagia
  - Can effectively manage weight
  - Do not affect patient experience of starvation
  - Only partially mitigate risks associated with food-seeking behaviors
Impact of Constant Supervision

- The need for constant supervision and enforcement of strict environmental controls upon PWS patients
  - High levels of caregiver burden (e.g., greater than Alzheimer’s)
  - Low levels of patient and caregiver quality of life
  - Significantly limits independence of patients

Effectively “institutionalizing” the home and isolating patients and families

High Burden of Psychiatric and Behavioral Issues

- High levels of anxiousness and distress
- Repetitive thinking and questioning
- Ritualistic and compulsive symptoms
- Maladaptive behaviors and cognitive rigidity
- Insistence upon routine
- Temper outbursts with mood lability

Psychiatric and behavioral issues cause very high burden for patients and families

Treating Behavioral Symptoms of PWS

- Often prescribed psychiatric medications
  - Selective serotonin reuptake inhibitors [SSRIs], anti-psychotics, stimulants, etc.
- Many take non-prescription interventions
  - Vitamins and nutritional supplements
- None have been shown in a clinical study to provide a benefit in PWS
  - Nor do they address an underlying deficiency related to the etiology of PWS and its pathophysiology
- Patients with PWS are exposed to the risks presented by multiple medications
  - Limited effects on PWS symptoms
  - None that improve PWS-specific hyperphagia, anxiousness, and distress
Hormone Replacement Therapy in PWS

• Broad endocrine disruption in PWS significantly contributes to phenotype
  – Functional deficiencies of multiple hormones
  – Impacts medical, psychiatric and behavioral symptoms

• Hormone replacement therapy highly effective in PWS
  – Human growth hormone (only approved therapy for PWS)
  – Many patients require thyroid replacement and sex hormone replacement

• Oxytocin deficiency remains untreated
Functional Oxytocin Deficiency in PWS

- **Multiple PWS brain autopsy studies reveal fewer oxytocin producing cells:**
  - 42% fewer oxytocin producing neurons in adult brains ($p=0.016$)\(^1\)
  - Fewer oxytocin mRNA-expressing cells in the paraventricular nucleus of the hypothalamus by FISH (photo on right)\(^2\)

- **Oxytocin replacement in a MAGEL2 mouse model of PWS rescues the 50% neonatal mortality**\(^2\)

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Functional Oxytocin Deficiency in PWS

- Oxytocin is involved in regulating social-emotional behaviors, bonding and anxiety
- Also a potent anorectic hormone\(^1\)
  - Pulsed with meals to enhance satiety
  - Low doses of oxytocin reduce food intake and the propensity to initiate feeding in wild-type rats in a dose-dependent manner\(^2\)
  - Mice that are null for either oxytocin or the oxytocin receptor (OXTR) develop adult-onset obesity\(^3\)
- Of great interest given overlap with important symptoms of PWS, namely the hyperphagia, anxiousness, and distress

Mixed Results for Oxytocin Replacement Therapy

- When dose is escalated, behavior worsens with increased temper outbursts observed (p=0.01)
- Off-target effects on vasopressin receptors may narrow therapeutic window
  - V1aR
    - Implicated in anxiety and depression
    - May exacerbate PWS behavioral symptoms and mute (or negate) any positive efficacy
  - V2R
    - Associated with increased risks of antidiuresis and hyponatremia
    - Can have significant adverse effects on hemodynamics

Unmet Need Conclusions

• PWS is a complex, rare, serious, life-altering, and life-threatening syndrome with significant unmet need

• Hyperphagia and behavioral issues prevent patients from leading independent lives
  – Need for constant supervision and management
  – Caregiver burden is extraordinarily high

• Functional oxytocin deficiency believed to be involved in hyperphagia and behavioral issues
  – Oxytocin as hormone replacement has potential off-target effects

• Substantial need for better oxytocin receptor agonists to alleviate hyperphagia and behavioral issues with limited off-target effects
Efficacy of Intranasal Carbetocin

Jay Cormier, JD, PhD
Senior Vice President
Levo Therapeutics, Inc.
Carbetocin

- More selective agonist of the oxytocin receptor
- Used in reproductive health outside the US
  - IV carbetocin is currently approved in over 90 countries
  - For prevention of excessive postpartum bleeding due to uterine atony
  - Administered in over 11 million women worldwide
  - IV dose results in similar total exposure to proposed 3.2 mg IN dose
- Developed as an intranasal form for PWS
- Orphan, rare pediatric disease, and fast track designation for the LV-101 PWS program
Comparison of Hormone Replacement Candidates

Oxytocin
- Natural hormone
- Short half-life (1-6 minutes)
- Non-selective receptor activity
  - OXTR: 2.3 nM EC\(_{50}\)
  - V1αR: 10 nM EC\(_{50}\)
  - V2R: 7 nM EC\(_{50}\)
- Limited therapeutic window
  - Dose-related antidiuresis/↑BP/↓HR
    • Mediated via V2R agonism
  - Negative behaviors observed at high doses
    • Hypothesized via V1αR agonism\(^1\)

Carbetocin
- Analogue of oxytocin
- Extended half-life (40-60 minutes)
- Selective for the OXT receptor
  - OXTR: 0.7 nM EC\(_{50}\)
  - V1αR: 41 nM EC\(_{50}\)
  - V2R: 172 nM EC\(_{50}\)
- Wider therapeutic window
  - No clinical antidiuresis/BP/HR effects
  - Negative behaviors less likely at equivalent doses

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Intranasal (IN) Carbetocin for Prader-Willi Syndrome

• Delivered intranasally three times per day with meals
  – One dose consists of two sprays in each nostril (total of four sprays) which deliver a total of 3.2 mg carbetocin
  – Dosing with meals mimics the body’s normal release of oxytocin with meals
Assessments for Prader-Willi Syndrome

- Only caregiver and clinician questionnaires are appropriate
  - Patients have intellectual disability and developmental delays
  - Limited insights into their symptoms
  - Unreliable reporters

- Questionnaires specifically designed for PWS measure its unique constellation of observable behavioral manifestations
  - Traditional psychiatric instruments do not capture PWS symptoms

- PWS instruments developed and validated for patient population
  - Align with FDA guidance on clinical outcome assessments
Measurements of Hyperphagia

- **HPWSQ-R**
  - PWS-specific instrument
  - Developed by Vanderbilt University
  - 11 questions completed by caregiver

- **HQ-CT**
  - PWS-specific instrument
  - Validated by Zafgen and RTI Health Solutions with FDA input
    - Evolution of HPWSQ-R
    - 9 questions completed by caregiver
      - Eliminated two questions from HPWSQ-R
      - Changed specific wording and scale of instrument
CY-BOCS
Children’s Yale-Brown Obsessive-Compulsive Scale

• Not a PWS-specific instrument
• Clinician-administered 81-item checklist with additional 10 scored questions
  – Lengthy administration
  – Relies heavily on experience of rater
• Secondary endpoint in Phase 2
• One of two primary endpoints in Phase 3
  – FDA advised against using as primary endpoint
PADQ
PWS Anxiousness and Distress Behaviors Questionnaire

• **PWS-specific instrument**
  – PADQ captures the observable behavioral distress symptoms that are common among patients with PWS
  – Designed to assess behaviors that are specific to PWS

• Designed in collaboration with FPWR, RTI Health Solutions, and PWS CTC Behavioral Outcome Measures Group

• Validated in accordance with FDA guidance

• 15 items completed by caregiver
Other Instruments

• **Clinical Global Impressions (CGIs) of PWS**
  – Single question assessment, 7-point scale
  – CGI-S (severity at the time of the visit)
  – CGI-C (change from Baseline)

• **Food Safe Zone (FSZ)**
  – PWS-specific instrument
  – Developed by Vanderbilt University
  – 31 questions assessing extent to which caregivers impose environmental controls to manage hyperphagia
  – Reductions over time likely reflect improvements in hyperphagia
Clinical Trials for Prader-Willi Syndrome Efficacy

Phase 2 Study 114 and Phase 3 Study LV-101-3-01 (CARE-PWS)
Shared Design Elements
Study 114 and CARE-PWS

• Randomized, double-blinded, placebo-controlled, multicenter studies
• 9.6 mg dose of carbetocin three times daily with meals vs. placebo
• Evaluate effect on behavioral symptoms in PWS
  – Hyperphagia and obsessive-compulsive symptoms
• Male and female hyperphagic subjects with genetically confirmed PWS
## Design Differences
### Study 114 and CARE-PWS

<table>
<thead>
<tr>
<th></th>
<th>Study 114</th>
<th>CARE-PWS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>37</td>
<td>119 for efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130 for safety</td>
</tr>
<tr>
<td><strong>Carbetocin dose</strong></td>
<td>9.6 mg</td>
<td>3.2 and 9.6 mg</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2 Weeks</td>
<td>8 Weeks (PBO-controlled)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56 Weeks (long-term follow up)</td>
</tr>
<tr>
<td><strong>Age range</strong></td>
<td>10 to 18 years</td>
<td>7 to 19 years</td>
</tr>
<tr>
<td><strong>Number of sites</strong></td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td><strong>CY-BOCS entry criteria</strong></td>
<td>No minimum score</td>
<td>Minimum of 9 points</td>
</tr>
<tr>
<td><strong>Hyperphagia instrument</strong></td>
<td>HPWSQ-R</td>
<td>HQ-CT</td>
</tr>
</tbody>
</table>
Carbetocin Phase 2 Study Design
Study 114

**Treatment Period**

Carbetocin 9.6 mg intranasally three times a day before meals

Conducted at Vanderbilt, University of Florida, and Winthrop University (PWS centers of excellence)
## Baseline Demographics

### Study 114

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo N=20</th>
<th>Carbetocin 9.6 mg N=17</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (40.0)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (60.0)</td>
<td>11 (64.7)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>13.6 (2.5)</td>
<td>13.9 (2.5)</td>
</tr>
<tr>
<td>Range</td>
<td>10.0-18.0</td>
<td>10.0-18.0</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
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<tr>
<td>Black/African American</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>19 (95.0)</td>
<td>17 (100.0)</td>
</tr>
<tr>
<td><strong>BMI (kg/m/m), Mean (SD)</strong></td>
<td>25.7 (7.5)</td>
<td>25.7 (5.9)</td>
</tr>
<tr>
<td><strong>HPWSQ-R Total Score, Mean (SD)</strong></td>
<td>39.7 (7.6)</td>
<td>35.6 (7.2)</td>
</tr>
</tbody>
</table>
Primary Endpoint: HPWSQ-R at Day 15
Study 114

Day 15

Placebo  Carbetocin 9.6 mg

Percent (%)

-25
-20
-15
-10
-5

-15.7
-15.7

p=0.0244 (1-sided)

-8.8

### Efficacy Results: Day 15

#### Study 114

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>LS Mean Difference (Upper Limit of 90% 1-sided CI)</th>
<th>P-value (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPWSQ-R Total score</td>
<td><img src="#" alt="Graph" /></td>
<td>0.024</td>
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<tr>
<td>Behavior domain</td>
<td><img src="#" alt="Graph" /></td>
<td>0.092</td>
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<tr>
<td>Drive domain</td>
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<tr>
<td>Severity domain</td>
<td><img src="#" alt="Graph" /></td>
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<tr>
<td>HPWSQ-R-C Total score</td>
<td><img src="#" alt="Graph" /></td>
<td>0.001</td>
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<tr>
<td>Behavior domain</td>
<td><img src="#" alt="Graph" /></td>
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<tr>
<td>Drive domain</td>
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<tr>
<td>Severity domain</td>
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<td>CGI-I</td>
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<tr>
<td>CY-BOCS</td>
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<tr>
<td>Reiss Profile Food Domain</td>
<td><img src="#" alt="Graph" /></td>
<td>0.013</td>
</tr>
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</table>

-12 -10 -8 -6 -4 -2 0 2
Efficacy Summary
Study 114

- Clinically meaningful reductions in hyperphagia
  - Significant difference favoring carbetocin
- Consistent benefit observed across all endpoints
  - Including clinical global impressions and obsessive-compulsive symptoms
- Demonstrated that carbetocin addresses functional oxytocin deficiency in PWS

Dykens EM, et. al. JCI Insight 2018; 3(12) pii: 98333. pmid:29925684
Opened enrollment Nov 2018
First patient dosed Dec 2018
COVID begins, enrollment paused Mar 2020
Discussion with FDA about trial status April 2020
Formal decision not to resume enrollment, last patient Week 8 visit May 2020
Database lock/unblinding July 2020
Patients begin transition to 3.2 dose Oct 2020
Last patient Week 64 visit May 2021

COVID begins, enrollment paused Mar 2020
Discussion with FDA about trial status April 2020
Formal decision not to resume enrollment, last patient Week 8 visit May 2020
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Patients begin transition to 3.2 dose Oct 2020
Last patient Week 64 visit May 2021

COVID-19
Targeted Enrollment
N=175

Actual Enrollment
N=130

Full Analysis Set
(patients randomized and dosed)
N=130

Primary Analysis Set
(patients from FAS with at least one post-Baseline visit completed prior to March 1, 2020)
N=119
CARE-PWS Study Design

Participants completing long-term follow-up may enter an optional extension period to continue to receive carbetocin.
Patient Disposition
CARE-PWS (Primary Analysis Set)

Baseline Visit
Initiation of Dosing

- Carbetocin 3.2 mg (n=43)
  - Included in PAS (n=39)
  - Discontinuation (n=9*)

- Placebo (n=43)
  - Included in PAS (n=40)

- Carbetocin 9.6 mg (n=44)
  - Included in PAS (n=40)
  - Discontinuation (n=2)

Week 8 Visit
Initiation of Follow-up Period

- Carbetocin 3.2 mg (n=59 PAS) (n=64 FAS)
- Carbetocin 9.6 mg (n=58 PAS) (n=64 FAS)

*Prior to switch to open-label 3.2 mg (Oct 2020), which occurred during either the long-term follow-up or extension periods

Randomized, Not Dosed (n=8)

Randomized (n=138)
## Baseline Demographics
### CARE-PWS (Primary Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>Placebo  N=40</th>
<th>Carbetocin 3.2 mg  N=39</th>
<th>Carbetocin 9.6 mg  N=40</th>
</tr>
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<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (42.5)</td>
<td>15 (38.5)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (57.5)</td>
<td>24 (61.5)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>11.8 (3.5)</td>
<td>12.3 (3.1)</td>
<td>11.7 (3.5)</td>
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<tr>
<td><strong>Weight, mean (SD), kg</strong></td>
<td>53.6 (25.5)</td>
<td>59.0 (24.5)</td>
<td>61.4 (32.5)</td>
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<tr>
<td><strong>BMI, mean (SD), kg/m²</strong></td>
<td>24.4 (8.8)</td>
<td>26.4 (8.3)</td>
<td>26.3 (9.3)</td>
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<tr>
<td><strong>Genetic Subtype, n (%)</strong></td>
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<tr>
<td>Deletion</td>
<td>22 (55.0)</td>
<td>23 (58.9)</td>
<td>26 (65.0)</td>
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<tr>
<td>UPD</td>
<td>9 (22.5)</td>
<td>9 (23.1)</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>ID</td>
<td>3 (7.5)</td>
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<td>1 (2.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (15.0)</td>
<td>6 (15.4)</td>
<td>5 (12.5)</td>
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<tr>
<td><strong>Baseline Scores, mean (SD)</strong></td>
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<td></td>
</tr>
<tr>
<td>HQ-CT</td>
<td>22.4 (4.7)</td>
<td>22.1 (5.1)</td>
<td>23.4 (5.7)</td>
</tr>
<tr>
<td>CY-BOCS</td>
<td>27.8 (6.0)</td>
<td>25.5 (4.1)</td>
<td>28.4 (4.0)</td>
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<tr>
<td>PADQ</td>
<td>43.9 (6.7)</td>
<td>43.1 (6.9)</td>
<td>42.6 (7.2)</td>
</tr>
</tbody>
</table>
Primary Endpoint: HQ-CT at Week 8
CARE-PWS (Primary Analysis Set)

Change in HQ-CT From Baseline to Week 8

- Placebo: N=40, Change = -2.2
- Carbetocin 3.2 mg: N=39, Change = -5.4, p=0.0162**
- Carbetocin 9.6 mg: N=40, Change = -3.4, p=0.3493*

* Two-sided p-value; primary analysis.
** Nominal two-sided p-value; first secondary analysis.
Primary and Secondary Endpoint Results
CARE-PWS (Primary Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HQ-CT</td>
<td>Improved p=0.016</td>
<td>Improved</td>
</tr>
<tr>
<td>CY-BOCS</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>PADQ</td>
<td>Improved p=0.027</td>
<td>No improvement</td>
</tr>
<tr>
<td>Clinical Global Impression of Change</td>
<td>Improved p=0.027</td>
<td>Improved</td>
</tr>
<tr>
<td>HQ-CT Subset</td>
<td>Improved p=0.011</td>
<td>Improved</td>
</tr>
<tr>
<td>HQ-CT Question 9</td>
<td>Improved</td>
<td>Improved</td>
</tr>
</tbody>
</table>

All tests are performed vs. placebo with two-sided p-values using the Primary Analysis Set (PAS).
Primary endpoints (HQ-CT and CY-BOCS) are tested for the 9.6 mg dose first, then repeated for the 3.2 mg dose as the first secondary endpoint. If no p-value is reported, the p-value was >0.05. All p-values presented are nominal p-values.
Consistency of Carbetocin 3.2 mg Benefit
CARE-PWS (Primary Analysis Set)

<table>
<thead>
<tr>
<th>Measure</th>
<th>95% CI of Placebo-adjusted Change (Baseline to Week 8)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HQ-CT</td>
<td></td>
<td>0.0162</td>
</tr>
<tr>
<td>CY-BOCS</td>
<td></td>
<td>0.5143</td>
</tr>
<tr>
<td>PADQ</td>
<td></td>
<td>0.0266</td>
</tr>
<tr>
<td>CGI-Change</td>
<td></td>
<td>0.0266</td>
</tr>
<tr>
<td>HQ-CT Subset</td>
<td></td>
<td>0.0114</td>
</tr>
<tr>
<td>HQ-CT Question 9</td>
<td></td>
<td>0.1137</td>
</tr>
</tbody>
</table>

*Nominal p-values
Patients with missing Week 8 data are included in the denominator but not the numerator (n=5 patients per arm)
HQ-CT Placebo Crossover Analysis
CARE-PWS (Primary Analysis Set)

<table>
<thead>
<tr>
<th>Placebo-Controlled Period</th>
<th>Long-Term Follow-Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 WEEKS</td>
<td>56 WEEKS</td>
</tr>
<tr>
<td>Carbetocin 3.2 mg/dose</td>
<td>Carbetocin 3.2 mg/dose</td>
</tr>
<tr>
<td>Carbetocin 9.6 mg/dose</td>
<td>Carbetocin 9.6 mg/dose</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Carbetocin 3.2 mg/dose</td>
<td>Carbetocin 3.2 mg/dose</td>
</tr>
<tr>
<td>Carbetocin 9.6 mg/dose</td>
<td>Carbetocin 9.6 mg/dose</td>
</tr>
</tbody>
</table>

**Baseline to Week 8**
(n = 20)

HQ-CT

- **LS mean (SE)**
  - Carbetocin 3.2 mg/dose: 0.2621 (1.374)
  - Placebo: -9.057 (1.637)
  - vs. first 8 weeks, LS mean (95% CI):
  - Carbetocin 3.2 mg/dose: -9.319 (-14.499, -4.139)

**Week 8 to Week 16**
(n = 18)

- Two-sided p-value: 0.0004*

*Nominal p-value
HQ-CT Total Score: Week 8 to Week 64
CARE-PWS, Long-Term Follow-Up Period (Full Analysis Set)

Data shown do not include patients originally assigned to placebo.
Data shown correspond to the original treatment assignment, including after all patients were switched to open label 3.2 mg/dose.

52% of subjects
≥8-point improvement at Week 64 vs. Baseline
(n=67/130)
PADQ Total Score: Week 8 to Week 64
CARE-PWS, Long-Term Follow-Up Period (Full Analysis Set)

Data shown do not include patients originally assigned to placebo
Data shown correspond to the original treatment assignment, including after all patients were switched to open label 3.2 mg/dose

53% of subjects ≥11-point improvement at Week 64 vs. Baseline (n=69/130)
Efficacy Summary
CARE-PWS

**Placebo-controlled period**
- Consistency of effect with 3.2 mg carbetocin
- Clinically meaningful reduction in hyperphagia
- Clinically meaningful reduction in anxiousness and distress behaviors

**Long-term follow-up**
- Additional improvements in hyperphagia and anxiousness and distress behaviors accrued through Week 16
- Benefits maintained through Week 64
Evidence Supporting Use of LV-101 in PWS

- **Phase 3 study identified a safe and effective dose**
  - Consistent benefit across multiple endpoints with 3.2 mg dose
- **Phase 2 study showed pharmacologic activity of IN carbetocin**
  - Confirms therapeutic rationale
- **Placebo-controlled data further supported by:**
  - Mechanistic data demonstrating functional oxytocin deficiency in PWS
  - Analyses of long-term efficacy data
- **Benefits are clinically meaningful and durable**
  - Inconsistent with natural history of PWS
  - Responder analyses favor carbetocin
Safety of Intranasal Carbetocin

Davis Ryman, MD, PhD
Vice President, Clinical Development
Levo Therapeutics, Inc.
Summary of Safety Data

• Safety is based primarily on placebo-controlled period of CARE-PWS
• Additional data from Study 114 and LTFU and extension periods of CARE-PWS
• Most common events transient and mild to moderate
  – Flushing
  – Events related to IN delivery
• Substantial history of safe clinical use of IV carbetocin
  – Currently approved in over 90 countries (ex-US)
  – For prevention of uterine atony and excessive bleeding following birth
  – Administered in over 11 million women worldwide over last 24 years
  – IV dose results in similar total exposure to proposed 3.2 mg IN dose
Carbetocin Exposure by Mean Daily Dose and Duration
120-Day Safety Update (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Treatment Duration (Weeks)</th>
<th>Carbetocin Any Dose N</th>
<th>Carbetocin ≥3.2 mg N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose or ≤2 days</td>
<td>243</td>
<td>213</td>
</tr>
<tr>
<td>≤14 days</td>
<td>146</td>
<td>146</td>
</tr>
<tr>
<td>≥60 days</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>≥90 days</td>
<td>124</td>
<td>124</td>
</tr>
<tr>
<td>≥120 days</td>
<td>116</td>
<td>116</td>
</tr>
<tr>
<td>≥180 days</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>≥270 days</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>≥365 days</td>
<td>102</td>
<td>102</td>
</tr>
</tbody>
</table>

Over 188 Total Patient-years of Exposure
**Safety Overview**  
CARE-PWS, Placebo-Controlled Period, 120-Day Safety Update (Safety Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=43 n (%)</td>
<td>24 (55.8)</td>
<td>26 (60.5)</td>
<td>29 (65.9)</td>
</tr>
</tbody>
</table>

**TEAEs by maximum severity**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Placebo</th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>19 (44.2)</td>
<td>21 (48.8)</td>
<td>24 (54.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (11.6)</td>
<td>5 (11.6)</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
</tbody>
</table>

**Treatment-emergent SAEs**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**TEAEs leading to study drug discontinuation**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>3 (6.8)</td>
</tr>
</tbody>
</table>

**Deaths**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: A TEAE is defined as an AE occurring after the initial dose of investigational product.

a. Each subject with a TEAE is counted only once by the TEAE of greatest severity. Adverse events with missing severity are counted as “severe.”
### Most Common (≥5%) TEAEs
CARE-PWS, Placebo-Controlled Period, 120-Day Safety Update (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo N=43 n (%)</th>
<th>Carbetocin 3.2 mg N=43 n (%)</th>
<th>Carbetocin 9.6 mg N=44 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Any TEAE</td>
<td>24 (55.8)</td>
<td>26 (60.5)</td>
<td>29 (65.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (7.0)</td>
<td>7 (16.3)</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>Flushing</td>
<td>0</td>
<td>6 (14.0)</td>
<td>9 (20.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.3)</td>
<td>4 (9.3)</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (4.7)</td>
<td>3 (7.0)</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>1 (2.3)</td>
<td>3 (7.0)</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>3 (7.0)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>3 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (2.3)</td>
<td>1 (2.3)</td>
<td>6 (13.6)</td>
</tr>
</tbody>
</table>
# TEAEs Leading to Discontinuation

**CARE-PWS, Placebo-Controlled Period, 120-Day Safety Update (Safety Analysis Set)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo N=43 n (%)</th>
<th>Carbetocin 3.2 mg N=43 n (%)</th>
<th>Carbetocin 9.6 mg N=44 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 TEAE leading to study drug discontinuation</td>
<td>0</td>
<td>0</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>0</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Impulsive behavior</td>
<td>0</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>0</td>
<td>1 (2.3)</td>
</tr>
</tbody>
</table>
CARE-PWS Long-Term Follow-Up and Extension Periods
## Safety Overview
CARE-PWS, LTFU and Extension Period, 120-Day Safety Update (Safety Analysis Set)

<table>
<thead>
<tr>
<th></th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=108 n (%)</td>
<td>N=64 n (%)</td>
</tr>
<tr>
<td>At least 1 TEAE</td>
<td>78 (72.2)</td>
<td>49 (76.6)</td>
</tr>
</tbody>
</table>

### TEAEs by maximum severity<sup>a</sup>

<table>
<thead>
<tr>
<th>Severity</th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>53 (49.1)</td>
<td>27 (42.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>19 (17.6)</td>
<td>19 (29.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (5.6)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>8 (7.4)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>TEAEs leading to study drug discontinuation</td>
<td>3 (2.8)</td>
<td>5 (7.8)</td>
</tr>
<tr>
<td>TEAEs leading to death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: A TEAE is defined as an AE occurring after the initial dose of investigational product.
<sup>a</sup> Each subject with a TEAE is counted only once by the TEAE of greatest severity. Adverse events with missing severity are counted as “severe.”
## Most Common (≥5%) TEAEs
CARE-PWS, LTFU and Extension Period, 120-Day Safety Update (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Carbetocin 3.2 mg (N=108) n (%)</th>
<th>Carbetocin 9.6 mg (N=64) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any TEAE</td>
<td>78 (72.2)</td>
<td>49 (76.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (13.0)</td>
<td>5 (7.8)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>9 (8.3)</td>
<td>7 (10.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (8.3)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8 (7.4)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (7.4)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (5.6)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (5.6)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>
### Treatment-Emergent SAEs
**CARE-PWS, LTFU and Extension Period, 120-Day Safety Update (Safety Analysis Set)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=108 n (%)</td>
<td>N=64 n (%)</td>
</tr>
<tr>
<td>Patients with any treatment-emergent SAE</td>
<td>8 (7.4)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Number of treatment-emergent SAEs</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Scoliosis surgery</td>
<td>3 (2.8)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Femoral derotation osteotomy</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Obstruction gastric</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Tonsillar hypertrophy</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Umbilical hernia repair</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Bezoar</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Hallucination, auditory</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Major depression</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>
# TEAEs Leading to Discontinuation
CARE-PWS, LTFU and Extension Period, 120-Day Safety Update (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=108 n (%)</td>
<td>N=64 n (%)</td>
</tr>
<tr>
<td>Patients with any TEAE leading to study discontinuation</td>
<td>3 (2.8)</td>
<td>5 (7.8)</td>
</tr>
<tr>
<td>Agitation</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Behavior disorder</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Emotional disorder</td>
<td>0</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Aggression</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Obsessive thoughts</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Separation anxiety disorder</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

Note: Patients may have more than one TEAE per PT. Patients who experienced one or more AE within the PT level are counted once for the PT level.
Phase 2 Study 114
# Safety Overview

## Study 114

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=20</td>
<td>N=17</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>All TEAEs</td>
<td>8 (40.0)</td>
<td>7 (41.2)</td>
</tr>
<tr>
<td>TEAEs by intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>7 (35.0)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (5.0)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-emergent SAEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs leading to withdrawal</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## Treatment-Emergent Adverse Events
### Study 114

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo N=20</th>
<th>Carbetocin 9.6 mg N=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6 (30.0)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Conjunctivitis infective</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Flushing</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Medication error</td>
<td>2 (10.0)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1 (5.0)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Aggression</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Agitation</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Ulna fracture</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Urine analysis abnormal</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
</tbody>
</table>
Safety Conclusions

• Generally safe and well tolerated

• Most common events transient and mild to moderate
  – Flushing
  – Events related to intranasal delivery

• Nature and severity of events were consistent across studies and in LTFU and extension periods of CARE-PWS
Clinical Perspective

Cheri Deal, PhD, MD
Emeritus Professor, Université de Montréal
Pediatric Endocrinologist and Clinical Investigator
Research Center, CHU Ste-Justine
The View of the Pediatric Endocrinologist
### PWS is a Challenging Condition to Study

- Patients already adhering to multiple treatments
- Heterogeneity of manifestations and response
- Lack of objective endpoints
- Difficult for patients/families to participate in studies
- Small population
- No investigational treatments for hyperphagia have gotten this far
Oxytocin Replacement Therapy is Challenging

- Oxytocin is homologous with vasopressin (two amino acids different)
  - They elicit opposing anxiolytic and anxiogenic effects and have significant cross-talk
  - Oxytocin can modulate the hemodynamic effects of vasopressin

- Attempts to achieve physiologic levels at the oxytocin receptor with exogenous replacement can result in off-target activity at the vasopressin receptor
  - Difficult hormone system to address with exogenous therapy
  - Narrow therapeutic window

- Carbetocin’s selectivity allows for expansion of the therapeutic window
  - Greater activity at the oxytocin receptor
  - Lower activity at the vasopressin V2 receptors (water reabsorption and cardiovascular effects); some residual activity at V1aR (anxiogenic effects)
Evidence Supporting IN Carbetocin

- Reassuring safety profile
- Two randomized placebo-controlled trials
- Benefits across multiple endpoints
- Clinically meaningful improvements
- Efficacy gains through Week 16 (long-term follow-up period)
- Persistence of benefit through Week 64
- Support of efficacy through participation in extension period
- Greatest efficacy observed for 3.2 mg dose
Consistency of Carbetocin 3.2 mg Benefit
CARE-PWS (Primary Analysis Set)

95% CI of Placebo-adjusted Change (Baseline to Week 8)

<table>
<thead>
<tr>
<th>Measure</th>
<th>95% CI of Change</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HQ-CT</td>
<td>-8.0 to 0.0</td>
<td>0.0162</td>
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<tr>
<td>CY-BOCS</td>
<td>-6.0 to 0.0</td>
<td>0.5143</td>
</tr>
<tr>
<td>PADQ</td>
<td>-4.0 to 0.0</td>
<td>0.0266</td>
</tr>
<tr>
<td>CGI-Change</td>
<td>-6.0 to 0.0</td>
<td>0.0266</td>
</tr>
<tr>
<td>CGI-Severity</td>
<td>-4.0 to 0.0</td>
<td>0.0209</td>
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</tbody>
</table>

*Nominal p-value
Improvements in HQ-CT at Week 8 and 16
CARE-PWS (Primary Analysis Set)

Placebo-Controlled Period (Week 8)

Long-Term Follow-Up Period (Week 16)

Change in HQ-CT from Baseline (SE)

-14 -12 -10 -8 -6 -4 -2 0

Placebo to Carbetocin 3.2 mg

Carbetocin 3.2 mg
Number Needed to Treat: HQ-CT $\geq$8-Point Improvement
CARE-PWS, Placebo-Controlled Period (Primary Analysis Set)

LV-101 3.2 mg  
33.3%

Placebo  
12.5%

NNT = 5
ARR = 0.875 – 0.667 = 0.208
NNT = 1/0.208 = 4.8
Long-Term Efficacy in All Subjects
HQ-CT Total Scores, Long-Term Follow-Up Period (Full Analysis Set)

Study Weeks: 8, 12, 16, 20, 24
N: 130, 128, 127, 120, 110, 105, 104, 103

HQ-CT Total Score (SE)

- All Carbetocin

Dotted line denotes multiple treatment arms through Week 8
Placebo-Controlled Period is Baseline to Week 8
Food Safe Zone Assessment: 64-Week Completers vs. Study Dropouts
CARE-PWS (Full Analysis Set)

Changes in Food Safe Zone

<table>
<thead>
<tr>
<th>Follow-Up Visit</th>
<th>N</th>
<th>Change from Baseline to Follow-Up Mean (95% CI)</th>
<th>Study Completers vs. Early Discontinuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 64</td>
<td>100</td>
<td>-7.54 (-9.7, -5.3)</td>
<td>-10.5 (-15.8, -5.3) 0.0001</td>
</tr>
<tr>
<td>Early Termination</td>
<td>17</td>
<td>3.00 (-2.0, 7.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Nominal p-value
7-Year-Old Male Subject

PWS diagnosis: 1 month

PWS etiology: UPD

Baseline BMI (z-score): 1.1

Baseline CGI severity: 5 (markedly ill)

Concomitant Medications
- Growth hormone since before age 2y
- Vitamin D
- Vitamin B complex
- Aripiprazole

Related and Unrelated Medical History
- Autistic spectrum – severe intellectual disability
- Severe expressive dysphasia
“The associate director of [my 7 year-old son’s] school said…

‘...the place of [my child] was not in school but in a psychiatric institution. Because, according to her, he will never be able to learn academically. I was devastated but I did not believe her.’”

Received from the teacher several weeks after the following school year began:

“[Your son] is the model of the class. He is always on top of his work and we congratulate him so often that he is proud, calm and ready for learning!!”
Observed Efficacy Consistent with Expected Effects of Hormone Replacement in PWS

- **Benefits with hormone replacement well established in PWS**
  - Global disruption of endocrine signaling
  - Growth hormone, sex hormones, thyroid hormone, cortisol
  - Dose to achieve physiologic levels/effects

- **Compelling molecular and genetic data pointing to oxytocin deficiency**
  - Reduction in oxytocin producing neurons (cadaver studies)
  - Rescue of phenotype with oxytocin replacement in animal model of PWS
  - Prohormone convertase 1 deficiency

- **Carbetocin addresses functional oxytocin deficiency**
  - Fits into hormone replacement approach
Clinical Perspective Conclusions

• Hyperphagia and behavioral symptoms represent greatest unmet needs

• Intranasal carbetocin is safe, in both the short and long term

• Data demonstrate effectiveness as do clinical observations
  – Clinically meaningful improvements across multiple endpoints
  – Effects are dramatic and life-changing for patients and families

• Patients and families should have access to IN carbetocin
# Responders Available for Q&A

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Qualifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jay Cormier, JD, PhD</td>
<td>Senior Vice President, Levo Therapeutics, Inc.</td>
</tr>
<tr>
<td>Shawn McCandless, MD</td>
<td>Professor of Pediatrics and Head, Section of Genetics and Metabolism, University of Colorado School of Medicine Department Chair for Clinical Genetics and Metabolism, Children's Hospital Colorado</td>
</tr>
<tr>
<td>Davis Ryman, MD, PhD</td>
<td>Vice President, Clinical Development, Levo Therapeutics, Inc.</td>
</tr>
<tr>
<td>Cheri Deal, PhD, MD</td>
<td>Emeritus Professor, Université de Montréal, Pediatric Endocrinologist and Clinical Investigator Research Center, CHU Ste-Justine</td>
</tr>
<tr>
<td>Brent Blumenstein, PhD</td>
<td>Principal Consultant, Trial Architecture Consulting</td>
</tr>
<tr>
<td>Lisa Cole Burnett, PhD</td>
<td>Director, Early Research and Development, Levo Therapeutics, Inc.</td>
</tr>
<tr>
<td>Sheri Fehnel, PhD</td>
<td>Vice President, Patient-Centered Outcomes Assessment, RTI Health Solutions</td>
</tr>
<tr>
<td>Deepan Singh, MD</td>
<td>Vice-Chair, Ambulatory Services, Department of Psychiatry, Maimonides Medical Center</td>
</tr>
</tbody>
</table>
Backups Shown During Q&A
PADQ Question-Level Changes – Baseline to Week 8
CARE-PWS (Primary Analysis Set)

Q1: Asks excessive event details
Q2: Confirm information already known
Q3: Repeat same question
Q4: Move in agitated way
Q5: Engage in nervous habits
Q6: Concern when separating from caregiver
Q7: Repeatedly check possessions
Q8: Engage in self-soothing activity
Q9: Worry about possible change in plans
Q10: Upset when a change in plans happens
Q11: Hard time calming down
Q12: Emotional outburst when desire not followed
Q13: Anxious about food-related plans
Q14: Repeatedly ask about upcoming meals
Q15: Overall anxiety or distress

Placebo (n=35)  Carbetocin 3.2 mg (n=34)  Carbetocin 9.6 mg (n=34)

Change in PADQ Individual Question Score

-1.2 -1 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4 0.6

BU-627
Carbetocin Dosing in Perspective

<table>
<thead>
<tr>
<th></th>
<th>Carbetocin 3.2 mg</th>
<th>Carbetocin 9.6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalent oxytocin dose¹</td>
<td>160-320 IU</td>
<td>480-960 IU</td>
</tr>
<tr>
<td>Relative to Einfeld higher dose²</td>
<td>4-8x</td>
<td>12-24x</td>
</tr>
<tr>
<td>Estimated oxytocin receptor activation relative to Einfeld higher dose³</td>
<td>12-23x</td>
<td>35-69x</td>
</tr>
<tr>
<td>Estimated V1aR activation relative to Einfeld higher dose⁴</td>
<td>0.25-0.5x</td>
<td>0.75-1.5x</td>
</tr>
</tbody>
</table>

1. 1/40th of 3.2 mg IN dose is equivalent to 80% of 0.1 mg IV carbetocin, which is equivalent to 5-10 IU oxytocin
2. 40 IU oxytocin
3. Carbetocin exhibits 2.9x greater activation of oxytocin receptors at equivalent oxytocin dose
4. Carbetocin exhibits 16x less activation of V1aR at equivalent oxytocin dose
Baseline BMI Z-score vs. Baseline HQ-CT
CARE-PWS (Primary Analysis Set)

$R^2 = 0.002$
HQ-CT at Week 8
CARE-PWS (Primary Analysis Set)