Development of Intranasal Carbetocin (LV-101) for the Treatment of Hyperphagia and Behavioral Symptoms in Prader-Willi Syndrome

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#839

Background

Prader-Willi syndrome (PWS) is a rare, life-limiting neurodevelopmental genetic disorder. There is evidence of a specific behavioral phenotype known as hyperphagia, which is associated with significant morbidity, mortality, and costs. There is currently no approved treatment for hyperphagia or behavioral symptoms in PWS.

Carbetocin

Carbetocin is a synthetic analogue of oxytocin that was specifically designed to increase selectivity for the oxytocin receptor. Intranasal administration of carbetocin has been shown to affect several mechanisms relevant for PWS, including appetite control and insulin sensitivity, and it has been used to treat other conditions such as postpartum uterine atony and excessive bleeding during cesarean section. More than 10 million doses of carbetocin have been administered to nearly 100,000 women in approved clinical trials. In 2019, Pharming Pharmaceuticals licensed intranasal carbetocin to Levo Therapeutics.

Objective

To assess the effect of intranasal carbetocin on hyperphagia and other behavioral symptoms in subjects with PWS.

Study Design

Prospective, double-blinded, placebo-controlled, Phase 2a study

Primary endpoint Change from baseline to Day 15

Hyperphagia

HPWSQ-R Questionnaire-Repeated measures (HPWSQ-R) was compiled by subject and caregiver

Baseline demographics

- Gender
- PWS Genetic Subtype
- BMI (kg/m2)
- HPWSQ-R Score, Baseline
- CGI-I, Baseline
- HPWSQ-R Score (change from baseline)
- LS Mean Difference (upper limit of 90% 1-sided C.I.)
- Treatment

Study treatment

Subjects received intranasal carbetocin or placebo 3 times per day before meals.

Conclusions

Intranasal carbetocin treatment was associated with significant reductions in HPWSQ-R score versus placebo. 3.5 mean change versus 0.0 mean change from baseline to Day 15 (p=0.005). Significant reductions in HPWSQ-R score were observed in patients with PWS and intranasal carbetocin was generally safe and well tolerated.

Acknowledgments

The authors acknowledge and thank the patients and families who participated in this clinical research study. The authors also thank the investigators and study teams for their support in conducting this study.

References


Conflicts of Interest

Dykens reports grant from NIH and the Foundation for Prader-Willi Research outside of the submitted work. Miller has no relevant disclosures. Angulo reports grant from NIH and the Foundation for Prader-Willi Research outside of the submitted work. Roof has no relevant disclosures. King reports grant from NIH and the Foundation for Prader-Willi Research outside of the submitted work. Cotter reports grant from NIH and the Foundation for Prader-Willi Research outside of the submitted work.

Study treatment

Primary endpoint: Change from baseline to Day 15

- HPWSQ-R Questionnaire-Repeated measures (HPWSQ-R) was compiled by subject and caregiver

Secondary endpoint efficacy results: Day 15

- HPWSQ-R Score (change from baseline)
- LS Mean Difference (upper limit of 90% 1-sided C.I.)

Safety measures

- No notable mean changes from baseline in chemistry, hematology or hemostasis values.
- No apparent differences in vital signs values across the treatment and placebo groups.
- No discontinuations

Effectiveness of intranasal carbetocin on hyperphagia and HPWSQ-R scores

HSWSQ-R Score (change from baseline)

-18
-16
-12
-10
-8
-6
-4
-2
0
2
4
6
8
10
Day 0
Day 15

Achieved pre-specified primary endpoint: HPWSQ-R at Day 15

Measurement 1: Total HPWSQ-R Score

Measurement 2: Changes from baseline to Day 15

Efficacy Outcomes

- Effective Carbetocin (n=17) Placebo (n=20)
- PWS Nutritional phase 3 (based on Miller, 2011)
- Genetically confirmed diagnosis of PWS
- Informed consent/pediatric assent, if applicable

Exclusion criteria:

- Mental incapacity or language barrier of the primary parent/caregiver precluding adequate understanding or cooperation
- Intake of an investigational medicinal product in the 12 weeks preceding screening or longer, if judged by the investigator
- History within the last 2 years or current abuse of drugs or alcohol
- Intranasal therapy, including nasal saline
- Known genetic, hormonal, or chromosomal cause of cognitive impairment other than PWS
- Negative pregnancy test for females of child bearing potential
- Patients with other serious conditions that may affect the interpretation of study outcomes
- Patients on medications known to affect appetite
- Patients with active upper respiratory tract infection
- Patients who are currently being investigated for abuse
- Patients who are randomized in error
- Patients who present signed informed consent form or assent form 1 week prior to first dose of study drug

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Study population

- Inclusion criteria: Presence of hyperphagia and behavioral symptoms of Prader-Willi syndrome (PWS) as measured by the HPWSQ-R, as well as willingness to participate in the study and comply with the study protocol
- Exclusion criteria: Mental incapacity or language barrier of the primary parent/caregiver precluding adequate understanding or cooperation
- Patients on medications known to affect appetite
- Patients with active upper respiratory tract infection
- Patients who are randomized in error
- Patients who present signed informed consent form or assent form 1 week prior to first dose of study drug

Results

Table 1: Baseline demographic characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Carbetocin (n=17)</th>
<th>Placebo (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male (7)</td>
<td>Male (8)</td>
<td>0.363</td>
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<tr>
<td>Age</td>
<td>10 (6-23)</td>
<td>10 (6-23)</td>
<td>0.716</td>
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<tr>
<td>BMI (kg/m2)</td>
<td>25.7 (15.8-35.3)</td>
<td>25.6 (15.8-35.3)</td>
<td>0.912</td>
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<tr>
<td>PWS Genetic Subtype</td>
<td>MPS I (10)</td>
<td>MPS I (12)</td>
<td>0.239</td>
</tr>
<tr>
<td>HPWSQ-R Score, Baseline</td>
<td>35.6 (26-49)</td>
<td>35.6 (26-49)</td>
<td>0.979</td>
</tr>
<tr>
<td>CGI-I, Baseline</td>
<td>13.6 (10-18)</td>
<td>13.6 (10-18)</td>
<td>0.979</td>
</tr>
<tr>
<td>HPWSQ-R Score (change from baseline)</td>
<td>-4 (0-10)</td>
<td>-4 (0-10)</td>
<td>0.611</td>
</tr>
</tbody>
</table>

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