CLINICAL TRIALS UPDATE

Solenno Therapeutics
Aardvark Therapeutics
Acadia Pharmaceuticals
Gedeon Richter
Neuren Pharmaceuticals

Prader-Willi Syndrome Association | USA  ●  www.pwsausa.org  ●  (941) 312-0400
Certain Notices and Disclaimers

Forward-Looking Statements

This presentation contains forward-looking statements that are subject to many risks and uncertainties. Forward-looking statements appear in a number of places throughout this presentation and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned product development and clinical trials; the timing of, and our ability to make, regulatory filings and obtain and maintain regulatory approvals for our product candidates; our intellectual property position; the degree of clinical utility of our products, particularly in specific patient populations; our ability to develop commercial functions; expectations regarding product launch and revenue; our results of operations, cash needs, and spending of the proceeds from this offering; financial condition, liquidity, prospects, growth and strategies; the industry in which we operate; and the trends that may affect the industry or us.

We may, in some cases, use terms such as “believes,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should,” “approximately” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this presentation.

You should also read carefully the factors described in the “Risk Factors” sections and other parts of our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q, available at www.sec.gov, in order to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this presentation will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all. Any forward-looking statements that we make in this presentation speak only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this presentation or to reflect the occurrence of unanticipated events.
DCCR Phase 3 Clinical Program Design

- C601 (DESTINY PWS): Multi-center, randomized, double-blind, placebo-controlled, parallel arm study in patients with PWS (Phase 3)
- C602: Open-label safety extension study

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment</th>
<th>Randomization</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-week Run-in</td>
<td>Screened N = 181</td>
<td>Enrolled N = 158</td>
<td>2:1 Randomization N = 127</td>
<td>DCCR N = 85</td>
<td>Completed n = 120 Early Termination n = 7</td>
</tr>
<tr>
<td>C601 13-Week Double-blind Treatment</td>
<td>Mean age = 13.5 years 44.4% M / 55.6% F 20.2% UK / 79.8% US 61.3% Deletion / 37.9% Non-deletion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C602 Open-label Extension</td>
<td>Enrolled N = 115</td>
<td>As of October 2022 N = 83</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
C601 Primary and Key Secondary Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>All Data</th>
<th>Data through March 1, 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCCR (N = 82)</td>
<td>Placebo (N = 42)</td>
</tr>
<tr>
<td>Mean (SE) Change from Baseline in Hyperphagia at Visit 7</td>
<td>-5.94 (0.88)</td>
<td>-4.27 (1.15)</td>
</tr>
<tr>
<td>LS Mean Difference [DCCR-Placebo] (SE)</td>
<td>-1.67 (1.29)</td>
<td>-3.13 (1.48)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.198</td>
<td>0.037</td>
</tr>
</tbody>
</table>

**Key Secondary Endpoints**

<table>
<thead>
<tr>
<th></th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Global Impression of Improvement at Visit 7 (CGI-I)</td>
<td>0.03</td>
<td>0.015</td>
</tr>
<tr>
<td>Mean Change From Baseline in Body Fat Mass (DXA) at Visit 7</td>
<td>0.023</td>
<td>0.003</td>
</tr>
<tr>
<td>Caregiver Global Impression of Change at Visit 7 (Caregiver GI-C)</td>
<td>0.41</td>
<td>0.031</td>
</tr>
</tbody>
</table>
DCCR Phase 3 Clinical Program Design

- C601 (DESTINY PWS): Multi-center, randomized, double-blind, placebo-controlled, parallel arm study in patients with PWS (Phase 3)
- C602: Open-label safety extension study

**2-week Run-in**
- Enrolled N = 158

**C601 13-Week Double-blind Treatment**
- 2:1 Randomization N = 127
- DCCR N = 85
- Placebo N = 42
- Completed n = 120
- Early Termination n = 7

**C602 Open-label Extension**
- Enrolled N = 115
- As of October 2022 N=83

Mean age = 13.5 years
44.4% M / 55.6% F
20.2% UK / 79.8% US
61.3% Deletion / 37.9% Non-deletion
C601/C602 Hyperphagia Change from Baseline

Weeks of Exposure to DCCR

LSMean (±SE) Change from Baseline in HQ-CT Score

* p < 0.0001
Change in Hyperphagia with DCCR Compared to PATH

<table>
<thead>
<tr>
<th></th>
<th>26 Weeks</th>
<th>52 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS Mean (± SE)</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td>PATH (N = 229)</td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td>DCCR (N = 108)</td>
<td>-2</td>
<td>-6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PATH (N = 138)</th>
<th>DCCR (N = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>-6</td>
</tr>
</tbody>
</table>
C601/C602 PWS Profile Behavioral Change Results after One Year of DCCR

<table>
<thead>
<tr>
<th>Domain</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive Behaviors</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Compulsivity</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Depression</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disordered Thinking</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rigidity Irritability</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
C601/C602 Comparison to PATH – LS Mean Change in Behaviors from Baseline at Week 52

- Aggressive Behavior (p<0.001)
- Anxiety (p<0.001)
- Rigidity/ Irritability (p<0.001)
- Compulsivity (p<0.001)
- Depression (p=0.003)
- Disordered Thinking (p<0.001)

LS Mean Change from Baseline

<table>
<thead>
<tr>
<th>Behavior</th>
<th>PATH (n=101)</th>
<th>C601/C602 (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive Behavior</td>
<td>-2.0</td>
<td>-3.1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-3.1</td>
<td>-3.0</td>
</tr>
<tr>
<td>Rigidity/ Irritability</td>
<td>-3.0</td>
<td>-3.0</td>
</tr>
<tr>
<td>Compulsivity</td>
<td>-3.0</td>
<td>-3.0</td>
</tr>
<tr>
<td>Depression</td>
<td>-1.0</td>
<td>-1.4</td>
</tr>
<tr>
<td>Disordered Thinking</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

© 2023 Soleno Therapeutics
DCCR Safety Profile

• ~100 patients treated for more than one year
• Safety profile generally consistent with the known profile of diazoxide and prior experience with DCCR
• The most common adverse events reported were hypertrichosis, peripheral edema and hyperglycemia
• Most events were Grade 1 or 2 in severity, no Grade 4 or higher events
• Typically self limiting, some needing dose adjustment or treatment (e.g. with oral antidiabetics or short course diuretics)
• No DCCR-related serious unexpected adverse events (SUSARs)
C602 RANDOMIZED WITHDRAWAL PERIOD
DCCR Phase 3 Updated Clinical Program

- C601 (DESTINY PWS): Multi-center, randomized, double-blind, placebo-controlled, parallel arm study in patients with PWS (Phase 3)
- C602: Study with open-label extension (OLE) and randomized withdrawal (RW) periods
- C614: Open-label safety extension study
To the Participants of the DCCR Program and their families
ARD-101

A NOVEL ORAL DRUG FOR THE TREATMENT OF PWS

JUNE 2023
Summary

ARD-101: first-in-class oral drug targeting gut Bitter Taste Receptors (TAS2R) for the treatment of metabolic disorders, including Prader-Willi Syndrome

• Safe, gut-restricted drug, yet with potent systemic effects through gut-brain axis

• Regulates hunger, metabolism, and inflammation

• Suitable for chronic use as single agent or combination therapy

• Recent positive data from multiple Phase 2a trials
  • HQ-CT changes in Prader-Willi Syndrome
  • Weight loss and metabolic improvements in Obesity subjects
  • Decreased hunger in 3 different populations
Targeting Bitter taste receptors (TAS2Rs) has broad therapeutic potential

- TAS2Rs are found throughout the body (not just the mouth)
- Highly evolutionarily conserved to protect against toxins
- Activation of TAS2Rs elicit “anti-toxin” physiologic responses that can also convey therapeutic benefits

ARD-101 is the most potent TAS2R agonist known

- Stimulates intestinal enteroendocrine I-cells and L-cells to secrete multiple gut peptide hormones
- Induced secretion of gut peptides invokes gut-brain signaling which in turn impacts hunger, systemic metabolism and inflammation
Cholecystokinin (CCK) is a neuroincretin that is found in both the enteric and central nervous system\(^1,2\)

Gut-brain signaling: occurs via local secretion at intestine level inducing vagal nerve afferents

Previous attempts to target CCK through systemic drugs complicated by “off-target” side effects

Gastric emptying, food intake, and acid secretion
CCK is Safe and Effective When Secreted Locally in the Gut

ARD-101 stimulates CCK release locally in the gut act on vagal nerve, but not systemically (thus avoiding off-target toxicities)

GLP-1 primarily acts through systemic exposure
Distinct Neural Pathways of Hunger & Appetite

GLP-1

Bloodstream

Arcuate Nucleus of the Hypothalamus

POMC/CART Neurons

Release α-MSH

MC4R Neurons

PVN

Appetite = desire to eat, i.e. “Carrot”

CCK

Vagal Afferent Neurons

Nucleus Tractus Solitarius

Hunger = need to eat, i.e. “Stick”

CCK, cholecystokinin; GLP, glucagon-like peptide; POMC/CART, pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript; PVN, paraventricular nucleus
ARD-101 Suppresses Hunger Via Selective CCK Release in Gut

**ARD-101** → **Enteroendocrine cells locally release CCK** → **CCK activates to Vagal Nerve** → **Brain signals Satiety**

### PWS:
- CCK is not released normally from enteroendocrine cells with food stimulation.
- CCK receptor knock-out rats have hyperphagia, without the chromosome 15 deficiency.

### Diet Induced Obesity:
- High calorie diets reduce CCK production.
- DIO mouse models demonstrated significant weight loss with CCK administration.

---

2. [PMCID: PMC1642702](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1642702/pdf/rstb20061857.pdf)
ARD-101 in PWS: Ongoing Pilot Phase 2 trial - Study Sites

Children’s Hospital Colorado
University of Colorado Anschutz Medical Campus School of Medicine Aurora, CO
Co-Principal Investigator
Shawn E. McCandless, MD
Professor of Pediatrics
Section head, Clinical Genetics and Metabolism

Stanford Medicine
Lucile Packard Children’s Hospital Palo Alto, California
Co-Principal Investigator
Diane Stafford, MD
Clinical Professor, Pediatrics
Endocrinology and Diabetes

Sponsor
Supported by

Proprietary
ARD-101 Reduced Hunger Score in PWS and Obesity Trials

**Study design:**
- Open label (n=12, ongoing)
- Oral ARD-101, 200mg BID for 28d
- PWS subjects, ages 17-65 years
- HQ-CT score > 10

**Efficacy signals:**
- Reduced hyperphagia in 11/12 subjects (HQ-CT scores)
- 4 subjects with near complete resolution of symptoms
- Reduced body fat
- Reduced hunger
- Marked reduction anxiety about food

**PWS Phase 2**

**Obesity Phase 2**

How upset did the person generally become when denied a desired food?

Post Bariatric Surgery
ARD-101 for the treatment of PWS – Next Steps

- Early findings of the ongoing trial using a low dose of oral ARD-101 in young adults with PWS confirm safety and show encouraging efficacy signal consistent with the proposed novel mechanisms of action.

- Based on these findings, FDA granted Orphan Drug Designation to ARD-101 in PWS.

- Clinical trials moving forward will include dose escalation study in preparation for registration-enabling larger trials.
Acadia Pharmaceuticals – Clinical Trial Program for Prader-Willi Syndrome

James M. Youakim, MD
Vice President, Clinical Development
Acadia Pharmaceuticals Inc.
Acadia Pharmaceuticals

Acadia is trailblazing breakthroughs in neuroscience to elevate life.

Our 500+ employees in San Diego, California, Princeton, New Jersey, and around the world fight diseases to help brighter moments shine through for patients and their loved ones.

OUR PURPOSE
We fight disease so more of you shines through

OUR MISSION
Elevating life through science

OUR VALUES

✔️ We fight for patients… to elevate life through science

✔️ We are driven by innovation… to forge a healthy future

✔️ We are family… united through collaboration and diverse perspectives

✔️ We are determined… we break through barriers… we persevere

✔️ We take our work seriously… but not ourselves
We focus on disorders for which no approved therapies currently exist.

In 2016, our trailblazing research led to the first and only FDA-approved treatment for hallucinations and delusions associated with Parkinson’s disease psychosis.

On March 10, 2023, Acadia received FDA approval for the first and only treatment of Rett syndrome for adults and children with Rett syndrome aged 2 years and older.

Rett syndrome is a rare, genetic neurodevelopmental disorder. Symptoms include loss of speech and motor skills, respiratory dysfunction, and seizures.

FDA, US Food and Drug Administration.
Carbetocin will be evaluated in patients with Prader-Willi syndrome

**Oxytocin** is a natural hormone that regulates several functions in the body, including hunger, anxiety, social behavior, and bonding.\(^1\)\(^2\)

Oxytocin deficiency is associated with hyperphagia and behavioral issues in patients with **Prader-Willi syndrome (PWS)**.\(^3\)

In PWS, there are fewer neurons that produce oxytocin in the brain.\(^3\)

**Carbetocin** binds to oxytocin receptors with greater sensitivity than oxytocin, meaning potentially fewer side effects.\(^4\)

Intravenous carbetocin, which is used widely outside of the US in 90 countries to prevent postpartum hemorrhaging, has a well-established safety profile.\(^5\)

---

Carbetocin nasal spray data from a phase 3 clinical study

Levo Pharmaceuticals conducted a phase 3 trial called the CARE-PWS study¹

119 participants (7-19 years old) were treated with intranasal low-dose (3.2 mg) carbetocin or placebo 3x/day for 8 weeks

The study showed that carbetocin appeared to be well-tolerated

Low-dose carbetocin treatment showed improvement in hyperphagia and behavioral symptoms

In January 2022, the FDA denied the approval of carbetocin for PWS, citing insufficient efficacy, and recommended that an additional study confirming the efficacy of the low-dose be performed²

Carbetocin is an investigational drug. Safety and efficacy of this drug has not been established or approved by the FDA

CARE-PWS, CARbetocin Efficacy and Safety Study in Prader-Willi Syndrome
Acadia is conducting a phase 3 study

Acadia acquired Levo Therapeutics and is conducting a phase 3 trial to investigate the safety and efficacy of low-dose carbetocin for PWS

**Study design**
12-week, randomized, double-blind, placebo-controlled, parallel-group trial
Acadia has discussed this study with the FDA

**Treatment**
~170 participants (85 per group) with PWS will be treated with intranasal low-dose (3.2 mg) carbetocin or placebo 3×/day

**Outcomes**
Effects of carbetocin on hyperphagia in PWS
Participants will be eligible to enroll in an open-label extension at the end of this study

The goal is to begin enrollment later this year

THANK YOU!

www.pwsausa.org
info@pwsausa.org
(941) 312-0400
Our goal is to help people with Prader-Willi syndrome reach new heights

Learn more about KITE-PWS, a research study testing an investigational drug that may help to control appetite.

PWSA USA NATIONAL CONVENTION 2023

Presenter: Zsanett Gyongyosi-Bucsi M.D. (Supervisory Medical Monitor)
Representing: Gedeon Richter Plc. (Sponsor)
What is the purpose of the study?

- To learn about an experimental drug called RGH-706 in people with PWS that may help to control hyperphagia (increased appetite) in people with PWS.

What is RGH-706?

- An experimental drug that blocks a hormone called melanin-concentrating hormone (MCH).
- When MCH attaches to specific receptors in the brain it increases the desire to eat.
- RGH-706 aims to be the first MCH blocker to be studied in people with PWS.

KITE-PWS will help us understand if RGH-706 is safe and effective in blocking MCH and reducing appetite in people with PWS.
What are the objectives of the study?

**Primary objectives**

- To understand if RGH-706 is effective in reducing hyperphagia in people with PWS in the short- and longer run

  - Hyperphagia for Clinical Trials Questionnaire (caregiver reported)

**Secondary objectives**

- To assess safety and tolerability of RGH-706
- To assess how much and how quickly the study treatment gets into the bloodstream, (pharmacokinetics)
- To explore the effect of RGH-706 on weight, body composition and metabolic biomarkers (e.g. fasting glucose, insulin, uric acid, etc.)
- To explore the effect of RGH-706 on caregiver burden and caregiver impressions of severity and change

**Exploratory objectives**

- To explore the effect of RGH-706 on exploratory metabolic biomarkers (leptin, ghrelin, adiponectin)

KITE-PWS is a multicenter study with 25 research sites (6 sites in the USA) in 5 countries
How is the study set up? – Study duration and visits

Participants will be randomized to RGH-706 or placebo for both parts (capsules)

**Part A**
- 60 people with PWS
- 30 days Screening Period
- 6 weeks Study Treatment Period
- 13 weeks Follow-up Period
- Clinic visit
- Phone call or remote visit

**Part B**
- 100 people with PWS
- 30 days Screening Period
- 15 weeks Study Treatment Period
- 2 weeks Follow-up Period
- There is currently no open label extension available

**Interim analysis of results**
- People can only enter one study part

**Participants**
- 60 people can only enter one study part (capsules)
How is the study set up? – Visit schedule

Procedures that occur at every visit in both Part A and B

- weighing
- waist circumference measurement
- questions about any symptoms, illness and medical changes
- vital signs (blood pressure, pulse, temperature)
- questionnaire for caregiver

Visit schedule

- The primary caregiver should accompany the participant to every visit
- For blood draws, the participant should be in fasting state (no food or drink but water 10 hours before the visit)

• The sponsor of the study will pay for costs of the study drug, tests and procedures during study
• Reimbursement for travel expenses will be provided
• A participant may qualify for travel accommodations and reimbursement for out-of-pocket expenses
• A stipend for participating in the study will be provided
Who can be in the study?

- People with genetic diagnosis of PWS
- At least 17 years of age
- Body weight > 88 lbs (40 kg) and < 450 lbs (200 kg)
- Stable body weight for the past 3 months (weight change ≤5% in the previous 3 months)
- Have a consistent and reliable caregiver who can evaluate changes in participants’ hyperphagia symptoms, mood, health and behaviour during the study (caring for the participant for at least 3 months prior to study entry, is anticipated to be the participant’s primary caregiver for the duration of the study and must spend at least 4 waking hours per day on average with the participant)
- No uncontrolled diabetes or diabetes that requires insulin
- Medical history and other criteria will be reviewed to determine eligibility*

What should be considered before joining the study?

Possible risks:
- RGH-706 might not help your symptoms
- Side effects*
- Discomfort and time commitment related to study procedures

Possible benefits:
- RGH-706 might help your symptoms
- Receive regular health check-ups
- Help doctors learn about RGH-706 which may help others with PWS in the future

*for detailed information regarding study entry criteria and potential side effects please refer to the research sites and investigators participating in the study (https://clinicaltrials.gov/ct2/show/NCT05322096)
KITE-PWS has been reviewed by FDA and is open for people with PWS and their caregivers to enter.

Where can I find more information about the trial? Clintrials.gov: https://clinicaltrials.gov/ct2/show/NCT05322096

Every day, research uncovers new information about medical conditions and their treatment. Volunteer involvement in clinical studies is a key part in the development and advancement of future therapies. Results collected from clinical studies have led to thousands of medications and devices becoming available to patients all over the world.
CLINICAL TRIALS UPDATE

neuren

pharmaceuticals