Design of a Randomized Withdrawal Period Following Long-Term Administration of Diazoxide Choline Extended-Release Tablets to People with Prader-Willi Syndrome

Evelien Gevers MD, PhD on behalf of the C601/C602 Investigators and Soleno Therapeutics

Background

Prader–Willi syndrome (PWS) is a rare, complex genetic neurobehavioral/metabolic disorder with an estimated birth incidence of 1:15,000 to 1:20,000 (1,2). PWS arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13 caused by a paternal deletion, maternal uniparental disomy 15 or an imprinting center defect, resulting in hypothalamic dysfunction (3). Clinical features of PWS include hypotonia and feeding difficulties in infancy and sustained accumulation of excess body fat beginning in early childhood (4). Hyperphagia, which occurs around an average age of 8 years, presents as food obsession, aggressive food seeking, and lack of satiety, with progression to severe obesity if calorie intake is not restricted (4). PWS is also associated with intellectual disability, low muscle mass, neuroendocrine abnormalities including growth hormone and gonadotropin deficiency, behavioral problems including aggression, anxiety and compulsivity, and elevated risk for early mortality (5). There are no effective treatments for hyperphagia or other behavioral problems in PWS.

DCCR as an extended-release tablet formulation of a highly soluble salt of diazoxide which upon administration results in release and absorption of active drug throughout the small and large intestine over 24 hours resulting in very stable intraday circulating drug levels with once-per-day dosing. Diazoxide is a potent activator of the ATP-sensitive potassium (K_{ATP}) channel.

Figure 1. Mode of Action of DCCR in PWS (6)

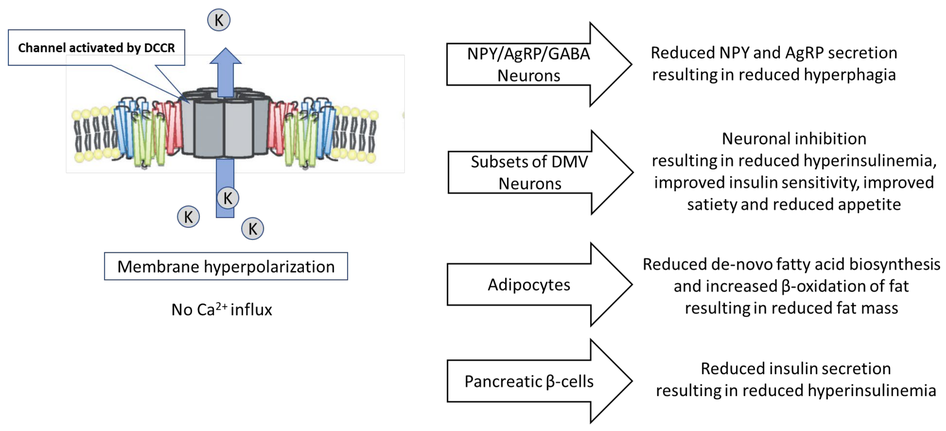
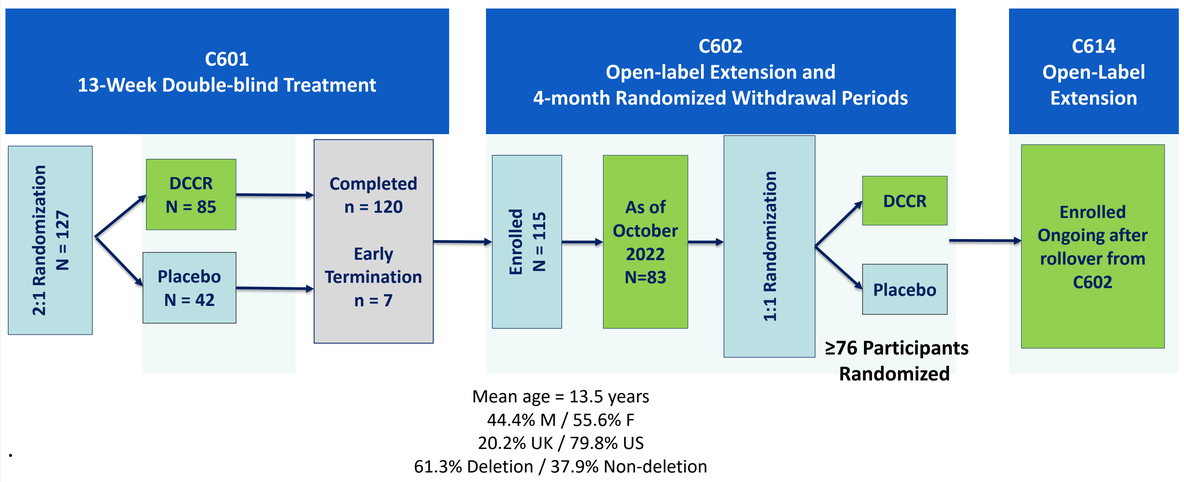


Figure 2. Flow diagram for Study C601 (DESTINY PWS): a multi-center, randomized, double-blind, placebo-controlled, parallel arm study in patients with PWS (7), and Study C602: an open-label safety extension study



Purpose of, Inputs Into, and Participants Enrolled into Randomized Withdrawal Period

Purpose

- Confirm the effects of DCCR administration on hyperphagia and other endpoints in a controlled setting
- To supplement the currently available data with further controlled data to support a regulatory filing

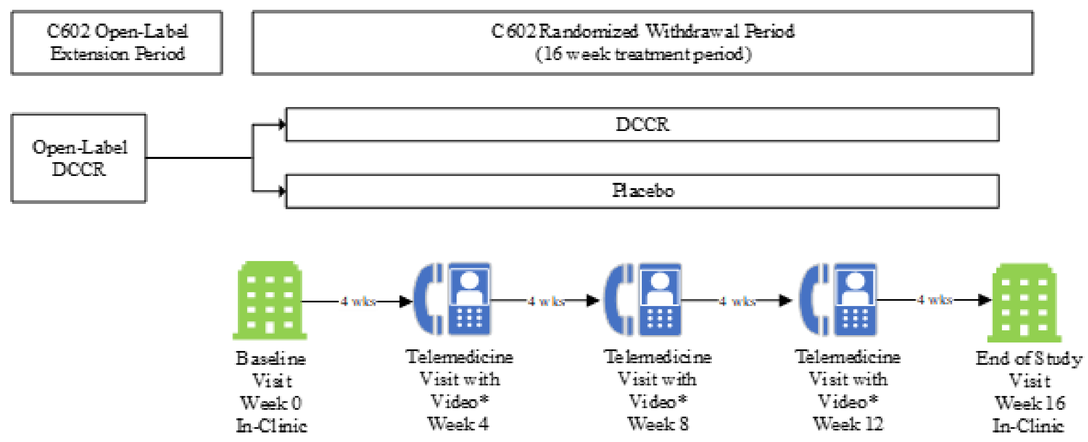
Inputs

- Input into the design, conduct and analysis of the RW period were sought from patients, caregivers, clinicians and from the FDA

Participants

- All subjects who were enrolled in C602 open label extension study were eligible to be randomized into the Randomized Withdrawal (RW) Period
- All had been treated for at least 2 years with DCCR, with some treated as long as 4.5 years
- More than 90% of eligible participants consented to enroll in the RW Period and randomization is complete

Design of the Randomized Withdrawal Period



Efficacy Endpoints

Primary
- HQ-CT Change from Baseline

Key Secondary
- Clinical Global Impression of Improvement
- Clinical Global Impression of Severity (CGI-S) Change from Baseline

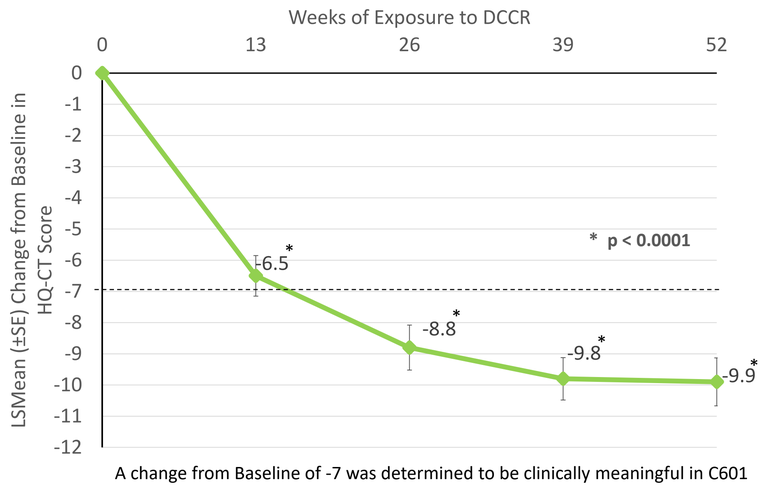
Exploratory
- Prader Willi syndrome Profile Questionnaire domains Change from Baseline
- Weight Change from Baseline
- BMI Change from Baseline
- Caregiver Global Impression of Change
- Caregiver Global Impression of Severity

Blinding
- Double-blind

Powering
- A sample size of at least 74 participants would have at least 85% power to detect a statistically significant difference between DCCR and Placebo if the underlying difference in change scores is 5.0 points.

Results from C601/C602

Figure 3. Change in Hyperphagia Questionnaire for Clinical Trials (HQ-CT) from Baseline



A change from Baseline of -7 was determined to be clinically meaningful in C601

Significant improvements in
- Compulsivity
- Anxiety
- Aggressive behaviors
- Rigidity
- Depression
- Hormonal parameters
- Lean body mass
- Clinician and caregiver assessed disease severity

References

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The C601/C602 Investigators include: Jennifer L. Miller MD, Jack A. Yanovski MD, PhD, Nicola Bridges DM, Parisa Salehi MD, Kathryn S. Obrynba MD, Eric I. Felner MD, Lynne M. Bird MD, Ashley H. Shoemaker MD, Moris Angulo MD, Jorge Mejia-Corletto MD, Merlin G. Butler MD PhD, David Stevenson MD, Anthony P. Goldstone MD PhD, John Wilding MD, Melissa Lah MD, M. Guftar Shaikh MD, Elizabeth Littlejohn MD, M. Jennifer Abuzzahab MD, Amy Fleischman MD, Urmi Das MD, Shawn E. McCandless, MD, Timothy Barrett MD, Tony Holland MD, Verghese Mathew MD, Heidi Shea MD, Katerina Harwood MD, Virginia Kimonis, MD, Laura Konczal MD, and David Viskochil MD

Soleno Therapeutics Team includes: Anish Bhatnagar MD, Patricia Hirano, Kristen Yen, Shaila Ballal, Michael Woloschak MD, Neil M. Cowen PhD

evelien.gevers@nhs.net