Comparison of hyperphagia and problem behaviors in participants with Prader-Willi syndrome (PWS) receiving Diazoxide Choline Extended-Release (DCCR) with matched participants in PATH for PWS (PfPWS)

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Abstract

Background: PWS is a rare neurodevelopmental genetic disorder characterized by hyperphagia, obesity, hormonal deficiencies, and problem behaviors for which there are no approved treatment. DCCR administration (100-525 mg/day) up to 52 weeks in participants with PWS improved hyperphagia, behavior, body composition and metabolic markers.

Objective: The objective of this study was to compare changes in hyperphagia (using Hyperphagia Questionnaire for Clinical Trials [HQ-CT]) and PWS-related behaviors (via PWS Profile Questionnaire [PWSP]) between 114 participants enrolled in DCCR placebo-controlled, double-blind (C601, NCT03440814) and open-label extension (C602, NCT03714373) studies (sponsored by Soleno Therapeutics) and a matched subcohort from PfPWS sponsored by Foundation for Prader-Willi Research, NCT03718416) (n=229) who did not receive experimental treatment.

Methods: C601/C602 and PfPWS studies were conducted concurrently. The creation of the PfPWS subcohort was conducted prospectively by an independent group prior to receiving the results from either study. Participants from both groups had genetically confirmed PWS and their caregivers completed the HQ-CT and PWS-P questionnaires prior to enrollment. Availability of participant-level data in PfPWS allowed for the creation of a propensity matched control cohort (n=195) similar to the C601/C602 study population by applying the defined inclusion criteria (age, gender, baseline HQ-CT score, baseline weight, and data collection time points).

Results: Statistically significant reductions in HQ-CT score for C601/C602 compared to PfPWS sub-cohort at Week 26 were observed for propensity-adjusted [Difference (C601/C602 – PfPWS), Adjusted Least-Square means, SE (standard error), 2-sided 95% CI = -5.7 (-7.43, -3.95)] and non-propensity-adjusted analyses [Difference = -5.9 (-7.53, -4.34)] (all p<0.001), which were sustained at Week 52 [Difference (C601/C602 - PfPWS) = -5.5 (-7.39, -3.64) for propensity-adjusted; = -5.9 (-7.65, -4.23) for non-propensity-adjusted; (all p<0.001). The difference in HQ-CT score between the two cohorts was consistent across age, sex, baseline HQ-CT, PWS genotype, geographical subgroups and growth hormone use.

Reduction of PWSP scores for C601/C602 were statistically significant across all domains (aggression, anxiety, rigidity/irritability, compulsivity, depression, disordered thinking) in comparison to PfPWS cohort (p<0.001 for all) at Week 26 and were maintained at Week 52 (p<0.001 to 0.03).

Conclusions: These data demonstrate that improvements in hyperphagia and other PWS-related behaviors achieved by 26 weeks and maintained through 52 weeks in subjects receiving DCCR were significantly greater than in matched controls from an untreated observational cohort, in line with previous results of C601/C602 studies. This further suggests that DCCR may be an effective treatment option for individuals with PWS.

Introduction

PWS is a rare, complex neurodevelopmental disorder that occurs in ~ 1 in 15,000 births. Hyperphagia, cognitive rigidity, temper outbursts, anxiousness and obsessive-compulsive behaviors comprise the challenging behavioral phenotype in PWS. Currently, there are no FDA/EMA approved drugs to reduce hyperphagia in PWS.

Soleno Therapeutics is evaluating Diazoxide Choline Extended Release (DCCR) as a potential therapy to reduce hyperphagia and improve behavior in PWS. A randomized, placebo-controlled study (C601) and its ongoing, open label extension (C602) have provided evidence of DCCR's safety and efficacy.

The Foundation for Prader-Willi Research is concurrently conducting a prospective natural history study, PATH for PWS, which includes clinical outcome assessments that are used in studies C601/C602 (Hyperphagia Questionnaire for Clinical Trials [HQ-CT], and PWS Profile questionnaire [PWSP]).

Objectives

To compare changes in hyperphagia (HQ-CT) and PWS-related behaviors (PWSP) between participants enrolled in DCCR placebo-controlled, double-blind and open-label extension studies (C601/C602) and matched participants enrolled in the PATH for PWS (PfPWS) Natural History Study, who did not receive experimental treatment, at 26 weeks (primary) and at 52 weeks.

Methods

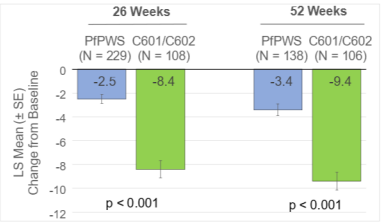
- PfPWS participants met key inclusion criteria for C601 (age, baseline hyperphagia score, weight, and caregiver involvement) and had at least 2 consecutive HQ-CT assessments 26 weeks apart
- HQ-CT and PWSP were compared at 26 weeks and 52 weeks
- Propensity scores were calculated using a logistic regression model accounting for differences in baseline characteristics: age, gender, baseline weight, baseline HQ-CT total score, growth hormone status (currently taking vs. not), region (US vs OUS, and PWS genetic subtype (deletion vs. non-deletion)
- The definition and creation of the PfPWS cohort and analyses were conducted prospectively by an independent statistical group prior to long-term results being available for the C601/C602 cohort
- For the responder analysis, a responder was defined as having a decrease in hyperphagia score (HQ-CT) of at least 7 points

Results

Table 1. Demographics and Baseline Characteristics for DCCR and PfPWS

Parameter	C601 / C602 N=125	PATH for PWS N=229
Age (years)		
Mean ± SD	13.4 ± 6.98	17.9 ± 9.49
Sex		
Female	55.2% (69/125)	52.0% (119/229)
Male	44.8% (56/125)	48.0% (110/229)
Weight (kg)		
Mean ± SD	62.1 ± 30.15	66.7 ± 26.72
BMI (kg/m²)		
Mean ± SD (n)	27.6 ± 9.62	28.9 ± 9.76 (212)
HQ-CT (Baseline)		
Mean ± SD (N)	21.5 ± 6.70	18.2 ± 4.99

Figure 1. Six-month and one-year comparisons of changes in hyperphagia total scores from baseline



Statistically significant reductions in HQ-CT total scores in subjects from the C601/C602 cohort compared to the PfPWS cohort at 26 and 52 weeks 1 year (Figure 1, p < 0.001). A significantly greater proportion of subjects in the C601/C602 cohort had a reduction in their HQ-CT total score that met the definition of a responder (reduction in total score of at least 7 points) compared to subjects in the PfPWS study (Figure 2, p < 0.001). Propensity score-adjusted analyses yield similar results for changes from baseline in HQ-CT total score at 26 weeks for C601/C602 cohort compared to the PfPWS cohort (Figure 3, p < 0.001). Statistically significant differences in reductions of common PWS behaviors as assessed by the PWSP for the C601/C602 cohort compared to the PfPWS cohort were seen at Week 52 (Figure 4, all p < 0.001 to 0.03)

Figure 2. Responder analysis – percent of participants who had a decrease in hyperphagia scores of at least 7 points on the HQ-CT at Week 26 compared to baseline

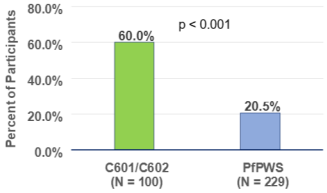


Figure 3. Mean change from baseline in HQ-CT total score at Week 26, propensity score-adjusted results

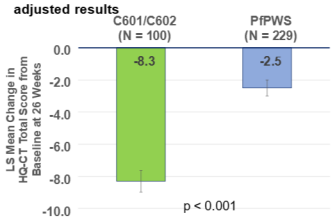
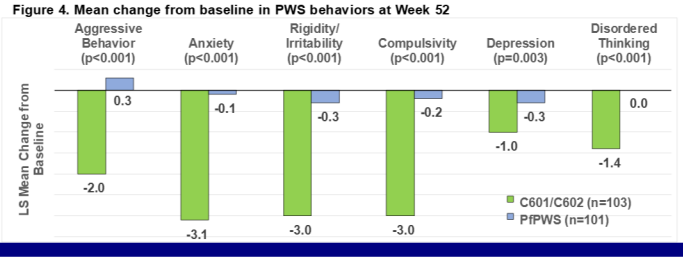


Figure 4. Mean change from baseline in PWS behaviors at Week 52



Conclusions

Compared to participants in PATH for PWS Natural History Study, participants treated with DCCR for 26 weeks and 52 weeks showed:

- A significantly greater reduction in hyperphagia score in all subjects, as well as propensity adjusted analysis
- A significantly greater percentage of participants with a clinically-meaningful HQ-CT score reductions of at least 7 points
- Significantly greater reductions across all behavioral domains in the PWS Profile (aggression, anxiety, compulsivity, rigidity/irritability, depression and disordered thinking)

These data suggest a potential long-term, beneficial effect of DCCR on hyperphagia and other behaviors in participants with PWS when compared with the natural history of the disease as characterized in the PATH for PWS participants.

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