Comparison of hyperphagia and behavioral features in Prader-Willi Syndrome (PWS) patients receiving Diazoxide Choline Extended-Release (DCCR) with matched participants in PATH for PWS Study (PfPWS NHS)

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Disclosures: A. Bhatnagar is an employee of Soleno Therapeutics

ABSTRACT

Background: PWS is a rare genetic disease characterized by hyperphagia, abnormal weight gain, and behavioral issues for which there is no approved treatment. DCCR administration (100-525 mg/day) in participants with PWS up to 52 weeks has been shown to improve hyperphagia, behavioral features, body composition and metabolic markers.

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

Methods: All studies, C601/C602 and PfPWS NHS, were conducted concurrently, enrolled participants with genetically confirmed PWS, and included the completion of HQ-CT and PWSP by the participants' caregivers. Availability of participant-level data in PfPWS NHS allowed for the creation of a control cohort similar to the C601/C602 study population by applying defined inclusion criteria that included age, baseline HQ-CT score, baseline weight, and data collection timepoints. 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 from either study.

Results: Highly statistically significant reductions in HQ-CT total score for C601/C602 compared to PfPWS cohort at Week 26 were observed for propensity-adjusted and non-propensity-adjusted analyses (all $p < 0.001$), which were sustained at Week 52 (all $p<0.001$). The reduction of HQ-CT total score between the two cohorts was consistent across age, baseline HQ-CT, PWS subtype, region subgroups or growth hormone use.

Reduction of PWS-P scores for C601/C602 were statistically significant across all domains (aggression, anxiety, rigidity/irritability, compulsivity, depression, disordered thinking) in comparison to PfPWS NHS ($p<0.001$ for all) at Week 26 and were maintained at Week 52 ($p<0.001$ to 0.003).

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 PfPWS, suggesting 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
- Characteristics include hypotonia / failure to thrive in infancy, with increasing interest in food during early childhood, typically progressing to hyperphagia and aggressive food seeking by mid-childhood
- Additional clinical concerns include endocrinopathies, sleep disturbances, and a challenging behavioral phenotype [cognitive rigidity, temper outbursts, anxiousness and obsessive-compulsive behaviors]
- Currently, there are no FDA 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) has 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 (PWS-P)]
- **Objective:** To compare changes in hyperphagia (HQ-CT) and PWS-related behaviors (PWS-P) 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* (PATH) natural history study, who did not receive experimental treatment

METHODS

- *PATH for PWS* participants who met inclusion criteria for C601/602 were included in the analysis [criteria included: age, baseline hyperphagia score, weight and caregiver involvement]
- HQ-CT and PWS-P were compared at 26 weeks (6 mo) and 52 weeks (1 year)
- Propensity matching was applied for relevant analyses
- Analysis was done by an independent contract research organization

RESULTS

DEMOGRAPHICS

	C601 / C602 N=114	PATH for PWS N=229
Age Mean ± SD (years)	13.1 ± 6.2	17.9 ± 9.5
Sex		
Female	57.9%	52.0%
Male	42.1%	48.0%
Weight Mean ± SD (kg)	60.3 ± 29.7	66.7 ± 26.7
BMI Mean ± SD (kg/m²)	26.8 ± 9.3	28.9 ± 9.8
PWS Genetic Type		
Deletion	62.3%	57.9%
Non-Deletion	37.7%	42.1%
Growth hormone use at both visits	83.3%	56.8%
HQ-CT Mean ± SD	21.3 ± 6.7	18.2 ± 5.0

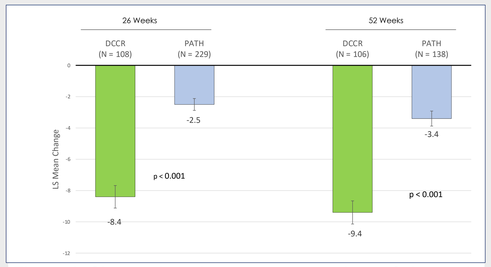

Figure 1. Six month and one year comparison of change in hyperphagia scores, compared to baseline.

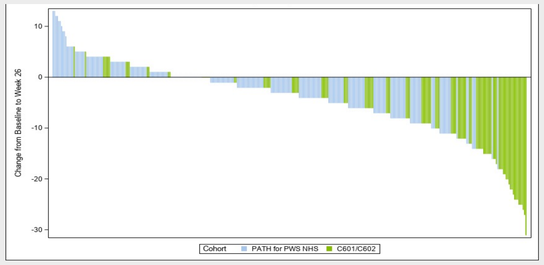

Figure 2. Waterfall plot of change in hyperphagia scores at six months, compared to baseline (all participants).

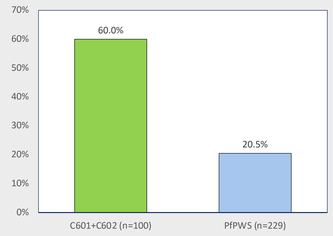

Figure 3. Responder Analysis – Percent of participants who had a decrease in hyperphagia scores of at least 7 points on the HQ-CT, at 6 months compared to baseline.

Propensity Matching: used a logistic regression model accounting for:

- Age
- Gender
- Baseline weight (kg)
- Baseline HQ-CT
- Growth hormone status (currently taking vs. not)
- Region (US vs. OUS)
- PWS genetic type (deletion vs. non-deletion)

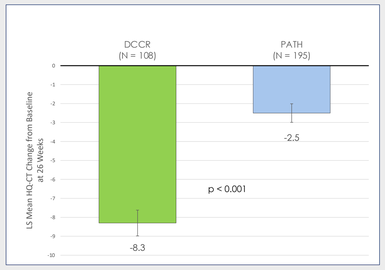

Figure 4. Change in HQ-CT score at week 26 compared to baseline, propensity score adjusted results

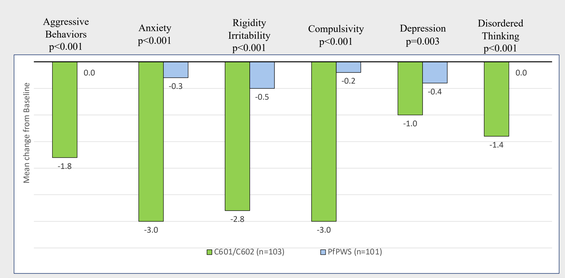

Figure 5. Changes in PWS-associated behaviors compared to baseline, as measured by the PWS Profile at week 52 (all participants)

CONCLUSIONS

Compared to participants in PATH for PWS, participants treated with DCCR for 1 year showed:

Highly significant improvements in hyperphagia at 26 and 52 weeks (all subjects, as well as propensity matched analysis)

Significantly greater improvements across all behavioral domains in the PWS profile [aggression, anxiety, compulsivity, rigidity/irritability, depression and disordered thinking]

These data show a long term, beneficial effect of DCCR on hyperphagia and other behaviors in participants with PWS when compared with the natural history of the disease.

ACKNOWLEDGEMENTS

PATH for PWS Study Investigators

C601/C602 "DESTINY PWS" Study Investigators

Participants in the C601/C602 and *PATH for PWS* studies, and their families