Abstract 2739 Therapeutic Response to DCCR (Diazoxide Choline) Extended-Release Tablets in Patients with Prader-Willi Syndrome Prior to the Onset of the COVID-19 Pandemic

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Objective

The objective of this analysis was to evaluate the therapeutic response of participants with Prader-Willi syndrome to DCCR (Diazoxide Choline) Extended-Release Tablet prior to the onset of the COVID-19 pandemic.

Background

Prader-Willi syndrome (PWS), a rare genetic neurobehavioral-metabolic disease, is characterized by hyperphagia, accumulation of excess fat, hypotonia, and behavioral/psychological complications. Patients with PWS and their families were significantly disrupted by the COVID-19 pandemic. There are no approved treatments for hyperphagia in PWS. In the analysis of the full dataset (pre-COVID + COVID) the primary endpoint, HQ-CT, trended toward significance while 2 of three secondary endpoints, Clinical Global Impression of Improvement [CGI-I] and body fat mass were significant.

Methods

DESTINY PWS Study

- 13-week, double-blind, placebo-controlled, parallel arm study
- 29 sites in the US and UK
- Randomized 127 subjects with genetically confirmed PWS ages 4 and older with hyperphagia of whom 124 had a post-baseline assessment of primary endpoint (necessary for MMRM analysis)
  - Stratified by growth hormone use and Baseline HQ-CT score
- Endpoints
  - Primary – Hyperphagia Questionnaire for Clinical Trials (HQ-CT)
  - Secondary
    - Clinical Global Impression of Improvement (CGI-I), Caregiver Global Impression of Change (Caregiver GI-C), and Body fat mass by DXA
  - Exploratory – behavioral assessment and cardiometabolic markers

COVID-19

- The COVID-19 pandemic caused significant disruptions in the lives of participants as well as their caregivers making it more difficult to control access to food and manage behavioral issues, with increased caregiver stress and could have affected the efficacy results.[1,2]
- March 1, 2020 cutoff used prior to any significant effect of the pandemic

Analysis

- Primary - HQ-CT – Mixed Model for Repeat Measures
- CGI-I and Caregiver GI-C - Cochran-Mantel-Haenzsel (CMH) test with modified ridit scores, stratified by randomization strata
- Body fat – ANCOVA
- Exploratory behavioral endpoints – Wilcoxon-Mann-Whitney test
- Cardiometabolic markers – ANCOVA
- All analyses were conducted with windowed visit data

1. Wieting J, et al. Behavioural change in Prader-Willi syndrome during COVID-19 pandemic. J Intellect Disabil 2021; Mar 22 online ahead of print.
2. PWS Registry Data: Impact of COVID-19 on PWS Families [INFOGRAPHICS] (fpwr.org)

Results

Table 1. Demographic and Baseline Characteristics

	DCCR (N=82)	Placebo (N=42)	Overall (N=124)
Age (years) Mean (SD)	13.4 (6.8)	13.6 (7.4)	13.5 (7.0)
Sex n (%)			
Male	36 (43.9)	19 (45.2)	55 (44.4)
Female	46 (56.1)	23 (54.8)	69 (55.6)
Height (cm) Mean (SD)	146.3 (18.5)	147.5 (20.1)	146.7 (19.0)
Weight (kg) Mean (SD)	62.2 (30.4)	60.4 (29.6)	61.6 (30.0)
HQ-CT Mean (SD)	23.0 (6.03)	21.9 (5.08)	22.6 (6.57)
Body fat mass (kg) Mean (SD)	27.67 (16.62)	26.47 (17.58)	27.25 (16.90)
Lean body mass (kg) Mean (SD)	29.25 (14.16)	28.31 (12.52)	28.92 (13.56)
Cardiometabolic parameters			
Leptin (ng/mL) Mean (SD)	37.6 (28.6)	36.3 (28.6)	37.2 (28.5)
Adiponectin (ng/mL) Mean (SD	11213 (6978)	10414 (6087)	10947 (6680)
Acylated ghrelin (pg/mL) Mean (SD)	242.0 (149.8)	276.7 (253.7)	253.7 (163.5)
Fasting Insulin (µIU/mL) Mean (SD)	12.07 (15.25)	9.74 (5.99)	11.28 (12.90)
PWS Genetic Sub-Type, n (%)			
Deletion	48 (58.5)	28 (66.7)	76 (61.3)
Non-deletion	33 (40.2)	14 (33.3)	47 (37.9)
Not available	1 (1.2)	0 (0.0)	1 (0.8)
Country, n (%)			
United Kingdom	19 (23.2)	6 (14.3)	25 (20.2)
United States	63 (76.8)	36 (85.7)	99 (79.8)
Growth Hormone Status, n (%)			
Currently Treated	69 (84.1)	35 (83.3)	104 (83.9)
Not Currently Treated	13 (15.9)	7 (16.7)	20 (16.1)

Figure 2. Clinical Global Impression of Improvement

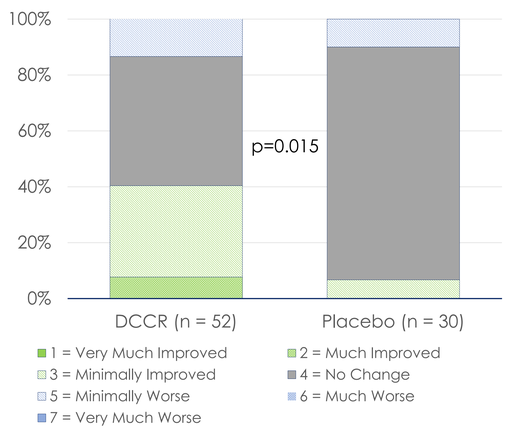

Figure 3. Caregiver Global Impression of Change

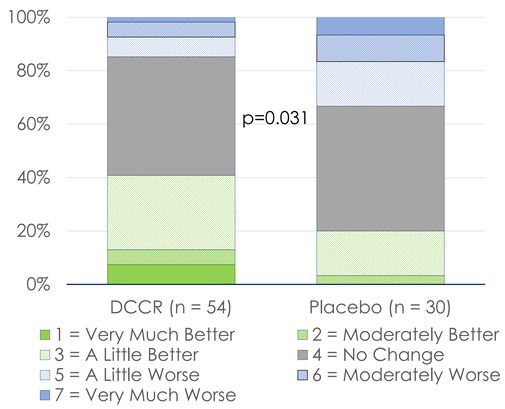

Figure 1. HQ-CT Change from Baseline

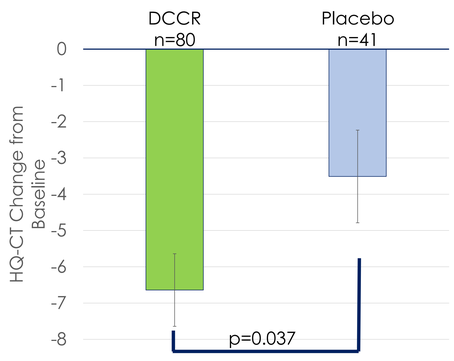

Figure 1. Body Fat Change from Baseline

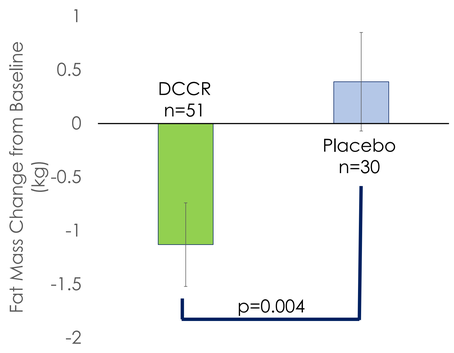

Table 2. Behavioral Endpoints

Prader-Willi Syndrome Profile Questionnaire Domain	DCCR Mean ± SD	Placebo Mean ± SD	p-value DCCR vs Placebo
Aggressive Behaviors	-1.5 ± 4.35	-0.2 ± 3.18	**0.048**
Anxiety	-3.6 ± 5.39	-1.0 ± 4.04	**0.018**
Rigidity, Irritability	-3.4 ± 4.74	-0.4 ± 3.53	**0.003**
Compulsivity	-2.8 ± 3.45	-0.5 ± 3.11	**0.008**
Depression	-0.9 ± 1.97	-0.3 ± 1.51	0.185
Disordered Thinking	-1.5 ± 2.24	-0.3 ± 1.59	**0.011**
Developmental Behavior Checklist – 2			
Total Score	-10.2 ± 18.1	-3.4 ± 21.3	**0.009**
Communication Disturbance	-1.7 ± 2.58	+0.2 ± 3.10	**0.003**
Social Relating	-1.2 ± 2.54	-0.1 ± 2.17	**0.008**

Table 3. Cardiometabolic Endpoints

Cardiometabolic Endpoint	LSmean difference (95% CI)	p-value DCCR vs Placebo
Leptin (ng/mL)	-16.3 (-23.1, -9.4)	**<0.0001**
Insulin ((µIU/mL)	-2.31 (-4.56, -0.06)	**0.0449**
Acyl Ghrelin (pg/mL)	-76 (-132.4, -19.7)	**0.0089**
Adiponectin (µg/ML)	-3.50 (2.05, 4.99)	**<0.0001**

Safety

	DCCR (n=84) N (%)	Placebo (n=42) N (%)
TEAE	67 (79.8%)	31 (73.8%)
TEAE related to study drug	49 (58.3%)	21 (50.0%)
SAE	6 (7.1%)	0 (0.0%)
SAE related to study drug	1 (1.2%)	0 (0.0%)
TEAE leading to premature study discontinuation	4 (4.8%)	1 (2.4%)
TEAEs occurring in more than 5% of subjects in either arm ordered by overall incidence		
Hypertrichosis	25 (29.8%)	6 (14.3%)
Peripheral edema	15 (17.9%)	4 (9.5%)
Upper respiratory tract infections	9 (10.7%)	5 (11.9%)
Headache	5 (6.0%)	6 (14.3%)
Hyperglycemia	9 (10.7%)	0 (0.0%)
Hirsutism	6 (7.1%)	3 (7.1%)
Diarrhea	1 (1.2%)	4 (9.5%)
Viral infections	0 (0.0%)	3 (7.1%)
TEAEs that are common complications and comorbidities of PWS	12 (14.3%)	12 (28.6%)

Key Points

- In the pre-COVID analysis, compared to placebo, DCCR treatment resulted in statistically significant improvements in hyperphagia, CGI-I and Caregiver GI-C and body fat
- There were statistically significant improvements with DCCR treatment compared to placebo in behavioral and cardiometabolic exploratory endpoints
- The frequency of TEAEs and drug related TEAEs were comparable
- Although there were more SAEs reported in the DCCR arm compared to placebo, only one was considered related to DCCR and was expected

Conclusions

In this pre-COVID analysis, compared to placebo, DCCR significantly improved a range of behaviors, body composition, and cardiometabolic endpoints and Global Impressions of the subject reported by caregivers and clinicians. DCCR may contribute to improved outcomes and quality of life of patients with PWS.

Acknowledgements

The DESTINY PWS Investigators thank the PWS patients and their families who participated in this clinical study for their commitment, diligence and sacrifice, which made the study possible.