A Phase III Study of DCCR in Prader-Willi Syndrome: Effects on Resting Energy Expenditure (REE) and Adiposity

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Introduction

- Prader-Willi Syndrome (PWS), absence of normally active, paternally expressed genes from the chromosome 15q11.2-q13 region, is characterized by low lean body mass and short stature
- Hyperphagia frequently leads to excess body adiposity and medical complications
- There are no FDA-approved treatments for PWS hyperphagia / obesity
- Once-daily oral DCCR (Diazoxide Choline Extended Release) significantly reduces body adiposity but the mechanism is not fully elucidated
- **Objective:** To investigate the effects of DCCR on resting energy expenditure in individuals with PWS

Methods

- **Clinical Study C601 (DESTINY PWS, Soleno Therapeutics):**
  - Phase III, randomized, double-blind study conducted at 29 sites in the US and UK
  - Compared once daily oral DCCR (Diazoxide Choline Extended Release, a K_{ATP} channel opener) vs. Placebo in 124 people with PWS
  - Randomized 2:1 DCCR : Placebo for 13 weeks without restriction of energy intake
- **At NICHD, NIH:**
  - **Resting Energy Expenditure:** Indirect Calorimetry at baseline and 13 weeks
  - **Body Composition:** Percent total body fat and total lean mass obtained using DXA at baseline and 13 weeks
  - Due to COVID-19, two participants were unable to complete indirect calorimetry at 13 weeks

Results

Table 1. Demographics of NIH participants

	DCCR (N=2)	Placebo (N=1)	Overall (N=3)
Age (years)	14.4 ± 2.2	8.4	12.42 ± 2.2
Gender (F/M)	2 / 0	1 / 0	3 / 0
Height (cm)	151.2 ± 2.3	124.0	142.1 ± 4.0
Weight (kg)	55.4 ± 1.06	44.0	51.6 ± 2.57
BMI (kg/m^2)	24.3 ± 1.5	28.6	25.8 ± 1.7
DXA Fat Mass (kg)	24.3 ± 0.3	23.7	24.1 ± 0.6
DXA Lean Mass (kg)	29.1 ± 1.5	19.4	25.9 ± 2.4
Growth Hormone Treated	1	1	2

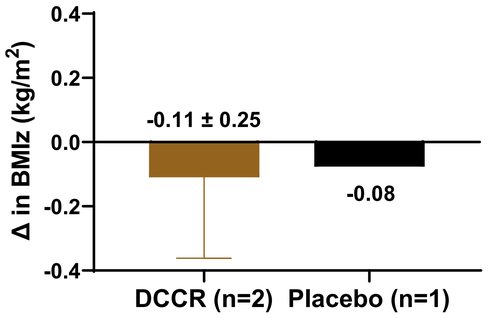

Figure 1. Decreases in BMIz were observed for both DCCR and placebo groups (DCCR: -0.110±0.25, Placebo:-0.033).

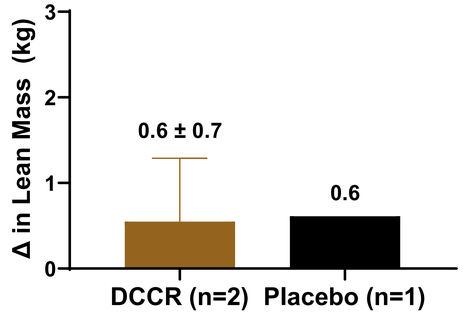

Figure 2. Small increases in lean mass were observed for both DCCR and placebo groups (DCCR: 0.548±0.739 kg, Placebo: 0.612 kg).

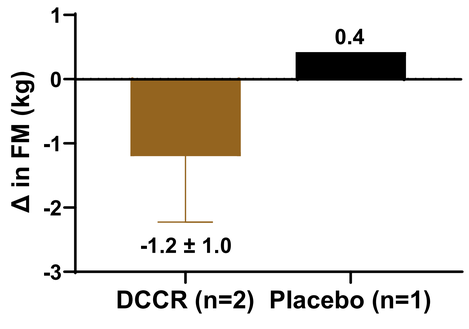

Figure 3. Decreases in fat mass were observed for those on DCCR (-1.198±0.324 kg) while an increase in fat mass was seen for placebo (+0.421 kg).

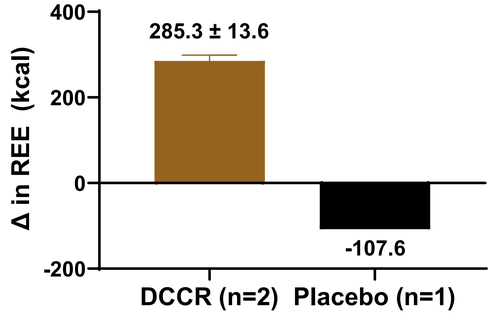

Figure 4. Large increases in REE were seen in those on DCCR (+285.3±13.6 kcal) while a decrease was seen for placebo (-107.6 kcal).

DESTINY PWS was sponsored by Soleno Therapeutics, Inc.

Results Continued

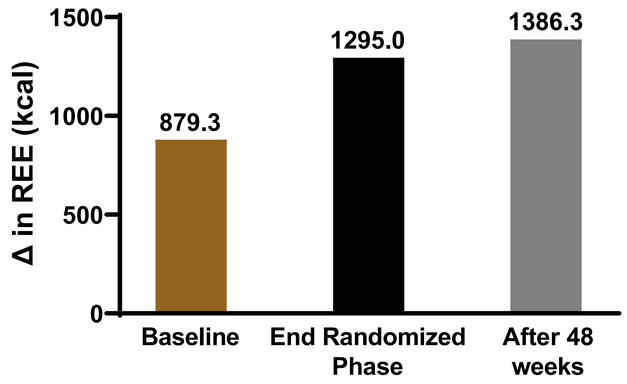

Figure 5: Case Study of one participant with PWS treated with DCCR from the beginning of the study. Steady increases in REE were observed throughout.

Conclusions

- For the two subjects with PWS seen at NIH, DCCR treatment resulted in a 285 kcal increase in REE vs. a decrease in REE in 1 placebo-treated participant.
- Those treated with DCCR also showed decreases in fat mass

Limitations

- Small total sample size at NIH (n=6)
- Smaller number of participants who completed REE testing at baseline and 13 weeks (n=3)
- Only one placebo participant at NIH

Future Directions

- Future studies should evaluate how REE changes with treatment in larger placebo-controlled trials studying the effects of DCCR, since increases of EE might assist with maintaining a lower body weight
- Other aspects of energy expenditure such as activity thermogenesis, should also be studied