Long-term Administration of Diazoxide Choline Extended-Release (DCCR) Tablets in People with Prader-Willi Syndrome: Changes in Lean Body Mass and Lean Mass Index

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INTRODUCTION

Prader-Willi syndrome (PWS) is a rare genetic neurobehavioral metabolic disorder characterized by hyperphagia, accumulation of excess fat, and behavioral/ psychological challenges.[1,2] People with PWS typically have low lean body mass and hypotonia, which affects motor development and the ability to perform daily activities, likely contributing to the increased mortality risk of the condition. Previous work showed that in growth hormone treated males lean mass index (LMI) increased by 0.28 kg/m^2/yr prior to puberty and 0.74 kg/m^2/yr during puberty.[3]

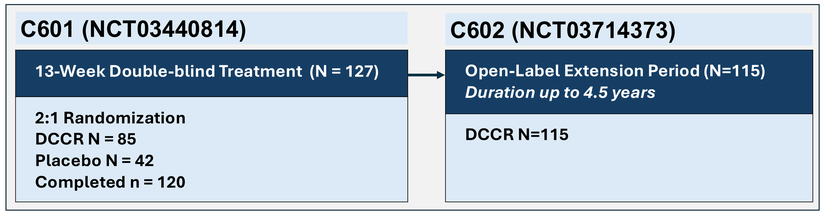
Diazoxide choline extended-release (DCCR) tablet is the first FDA-approved product for the treatment of hyperphagia in individuals 4 years and over with PWS. DCCR is a once-daily, extended-release tablet that provides for stable plasma concentrations and absorption throughout the GI tract.

The objective of this analysis was to assess long-term changes in lean body mass and LMI in participants with PWS treated with DCCR.

METHODS

Participants ≥ 4 years old with genetically confirmed PWS who had hyperphagia were randomized to receive DCCR or Placebo in a 13-week, Phase 3, double-blind, placebo-controlled study (DESTINY PWS, C601) at 29 sites in the US and UK. Participants who completed DESTINY PWS were eligible to enroll in its long-term, open-label extension study period (C602-OLE)(**Figure 1**).

Figure 1. C601/C602-OLE Study Design



Lean body mass was measured by DEXA. LMI was calculated as lean mass divided by height squared. LS Means are based on a mixed model adjusting baseline Lean Body Mass index, DCCR Baseline Age, sex, growth hormone use status and time point (Week 13, Week 52, Week 104, and Week 156). An unstructured covariance matrix was used to account for the correlation between repeated measurements.

In pediatric participants, those with BMIs ≥ 95th percentile were classified as having obesity. Those with BMI ≥ 85th percentile but < 95th percentile were classified as having overweight. For adult subjects, a BMI ≥ 30 kg/m^2 was considered obesity and a BMI ≥ 27 kg/m^2 but < 30 kg/m^2 was considered overweight.

RESULTS

- 125 participants were analyzed from Studies C601 and C602-OLE and received at least 1 dose of DCCR.
- The average age was 13.4 years; 55% were females; the average weight was 62.1 kg; and 82% were treated with growth hormone (**Table 1**).
- Median duration of DCCR administration was ~3.0 years (maximum 4.5 years):
  - 105 (84%) of participants received over 1 year,
  - 90 (72%) of participants received over 2 years, and
  - 71 (57%) of participants received over 3 years of DCCR

Table 1. Baseline Characteristics

Safety Population	N = 125
Age (mean [±SD]), years	13.4 (6.98)
Race (% WHT / BLK / MULT)	84.8 / 4.8 / 6.4
Weight (mean [±SD]), kg	62.1 (30.15)
Lean mass (mean [±SD]), kg	29.0 (13.69)
Fat mass (mean [±SD]), kg	27.7 (17.15)
Height (mean [±SD]), cm	146.7 (13.98)
BMI z-score (mean [±SD])	1.3 (1.12)
Growth hormone use (n [%])	103 (82%)
PWS Subtype (% Del / Non-del / Missing)	61.6 / 37.6 / 0.8

Abbreviations: BLK, black; BMI, body mass index; del, deletion; MULT, multiple; SD, standard deviation; WHT, white.

Figure 2. LS Mean (± SE) Increase in Lean Mass (kg) from Baseline

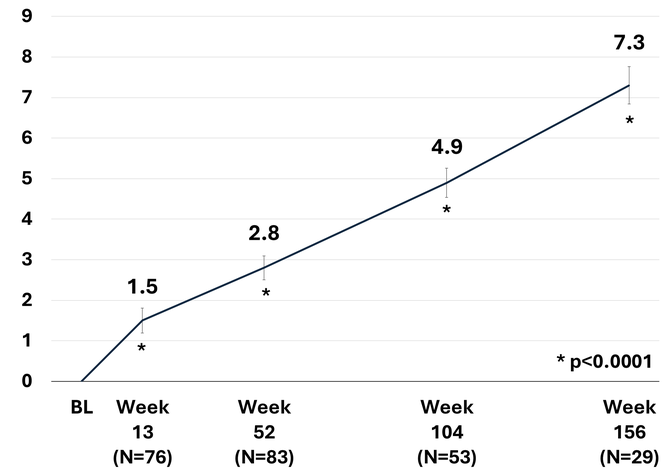


Figure 3. LMI LS Mean (±SE) Change from Baseline at 52 Weeks by Age

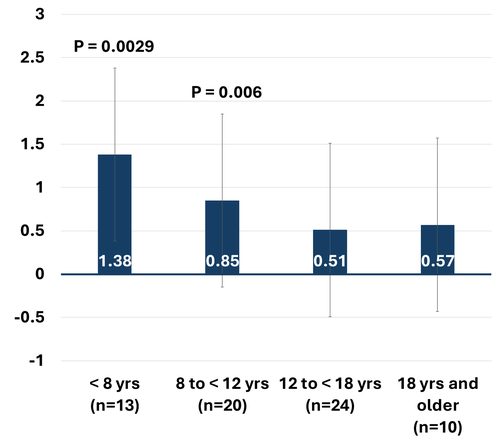


Figure 4. Lean Mass Percent Change from Baseline in C601+C602 Safety Population

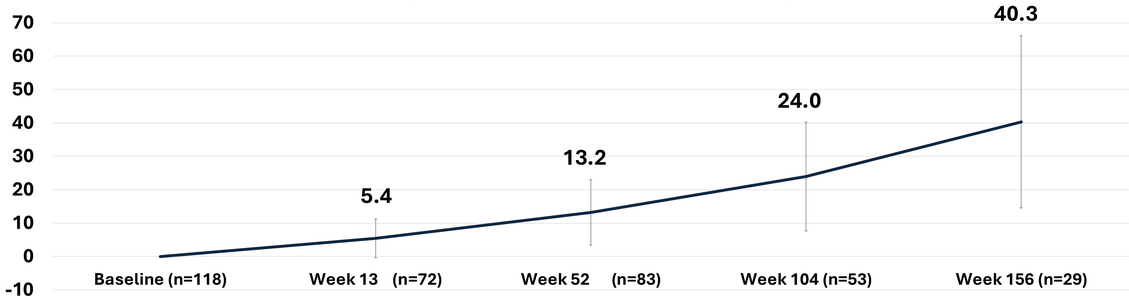


Figure 5. Lean Mass Percent Change from Baseline in Population with Overweight or Obesity

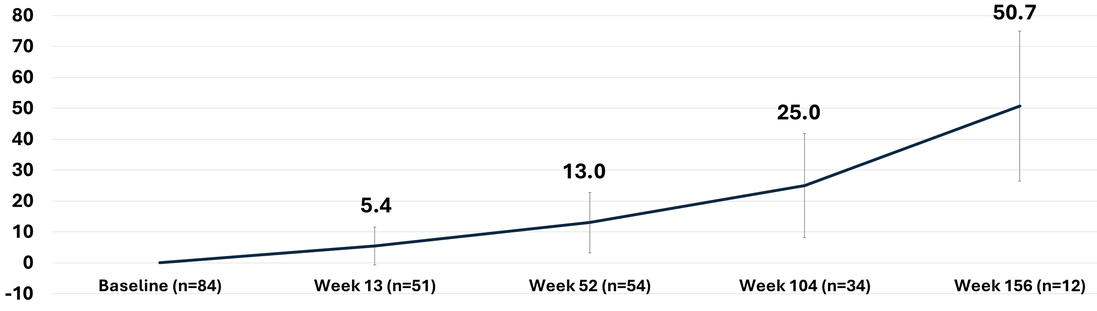
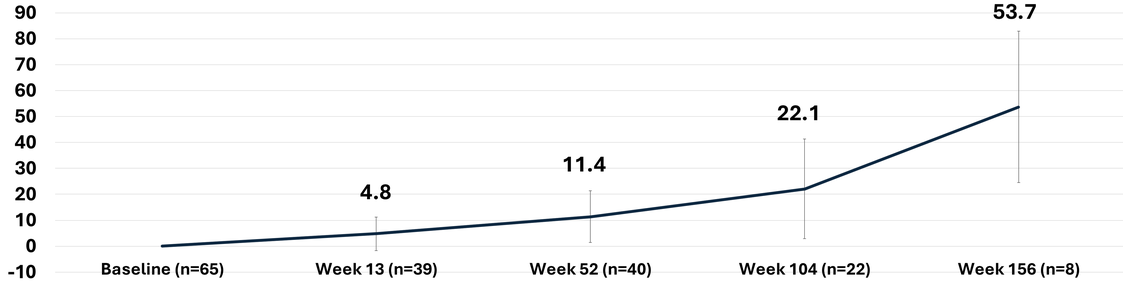


Figure 6. Lean Mass Percent Change from Baseline in Population with Obesity Only



- Corresponding LS mean lean body mass (kg) significantly increased over time in patients receiving DCCR (p<0.0001) (**Figure 2**).
- LMI increased by 0.76 kg/m^2 following 1 year of DCCR administration (p<0.0001), increasing by 1.38 ± 0.39 kg/m^2 (n=13, p=0.0029) in those < 8 years old, 0.85 ± 0.28 kg/m^2 (n=20, p=0.006) in participants 8 to < 12 years, 0.51 ± 0.39 kg/m^2 (n=24, p=0.1965) in participants aged 12 to < 18, and by 0.57 ± 0.0.29 kg/m^2 (n=10, p=0.0683) in participants 18 and older (**Figure 3**).
- Lean mass increased by 13.2 ± 9.88% at 52 weeks, 24.0 ± 16.3% at 104 weeks, and 40.3 ± 25.82% at 156 weeks of DCCR administration (**Figure 4**).
- By three years of DCCR administration, lean mass had increased by 50.7 ± 24.23% in participants who had overweight or obesity at baseline (**Figure 5**) and by 53.7 ± 29.23% in those who had obesity at baseline (**Figure 6**).

CONCLUSIONS

- **In people with PWS, DCCR administration was associated with progressive increases in lean body mass through 3 years, with greater increases realized in those who had overweight or obesity at baseline.**
- **DCCR administration appeared to increase lean mass index more than described in natural history studies of PWS, particularly in pre-pubertal children, where increases in lean mass index are limited, and in adults, where no further increases in lean mass index are expected.**
- **These increases are expected to be beneficial to people with PWS.**

REFERENCES

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2. Miller JL, et al. *Am J Med Genet A*. 2011;155A(5): 1040–1049.
3. Noordam C, et al. *J Clin Endocrinol Metab*. 2023;108(9):2299-2306.

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CONTACT INFORMATION

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