Resuming Diazoxide Choline Extended-Release (DCCR) after 16-week Randomized Withdrawal is Associated with Significant Improvements in Hyperphagia and Behavioral Symptoms in PWS (Study C614)

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INTRODUCTION

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a rare genetic neurobehavioral metabolic disorder characterized by hyperphagia, accumulation of excess fat, hypotonia, and behavioral/ psychological challenges.[1,2]

Diazoxide choline extended-release (DCCR)

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

Phase 3 Program

C601, C602-OLE, and C602-RWP

Study C601 was a Phase 3 randomized (2:1 DCCR to Placebo), double blind, parallel arm study comparing DCCR to Placebo in participants with genetically confirmed PWS, ages 4 and older.

Study C602 was a Phase 3 multicenter study that consisted of an initial open-label extension (OLE) period for approximately 2 to 4 years followed by a 16-week, double-blind, placebo-controlled randomized withdrawal period (RWP). After long-term treatment with DCCR (~3 years), significant improvements in hyperphagia were observed as measured by reduction in mean Hyperphagia Questionnaire for Clinical Trials (HQ-CT) Total Score (-10.7, p<0.0001). During RWP, statistically significant worsening of HQ-CT Total Score was observed in placebo-treated participants (LS Mean change: 7.6 for placebo vs 2.6 for DCCR; difference [SE] -5.0 [1.57], p=0.002).

C614

Study C614 is an active open-label, multi-center, long-term extension study. **(Figure 1)**

METHODS

We evaluated whether resuming DCCR for 1 year (C614) improved hyperphagia and behavioral symptoms associated with PWS in 77 participants who previously received DCCR in C602-OLE, followed by DCCR or placebo in C602-RWP. Changes from baseline in hyperphagia and behavioral symptoms were assessed by HQ-CT and Prader-Willi Syndrome Profile (PWSP) questionnaires, respectively. In C614, patients and health care professionals remained blinded as to whether patients received DCCR or placebo during the RWP.

Figure 1. Phase 3 Program

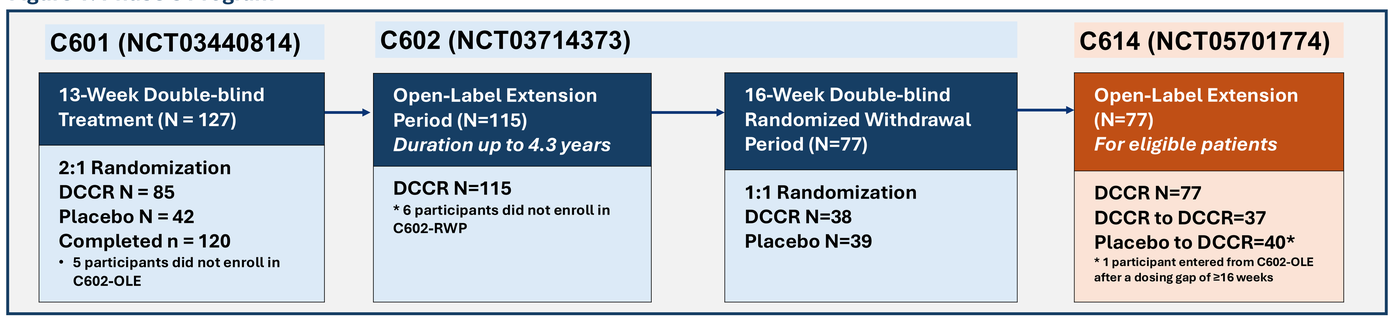


Table 1. C614 Baseline Characteristics

	C602 RWP DCCR to C614 DCCR (N = 37)	C602 RWP Placebo to C614 DCCR (N = 39)	C614 DCCR (N = 77)
Age (mean [±SD]), years	15.8 (4.76)	14.6 (4.38)	15.3 (4.63)
Sex (% male/female)	51.4 / 48.6	35.9 / 64.1	44.2 / 55.8
Weight (mean [±SD]), kg	75.0 (30.28)	64.1 (17.47)	69.7 (24.99)
BMI (mean[±SD]), kg/m2	29.0 (9.28)	26.1 (5.90)	27.4 (7.77)
BMI z-score (mean [±SD]), kg/m2	1.4 (1.24)	1.3 (0.88)	1.3 (1.06)
Hyperphagia (HQ-CT) Total Score	11.9 (7.99)	15.4 (7.81)	13.8 (8.05)
PWS Subtype (% Deletion / Non-deletion)	56.8 / 43.2	74.4 / 25.6	64.9 / 35.1
Ongoing Growth Hormone Use (% Yes / No)	78.4 / 21.6	94.9 / 5.1	87.0 / 13.0

Figure 2. C614 HQ-CT Total Score (0-36) By Week

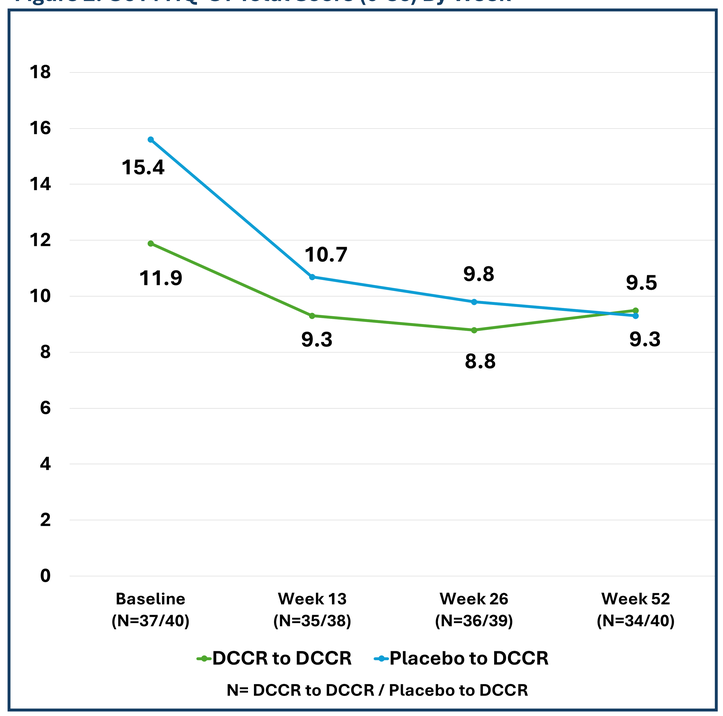
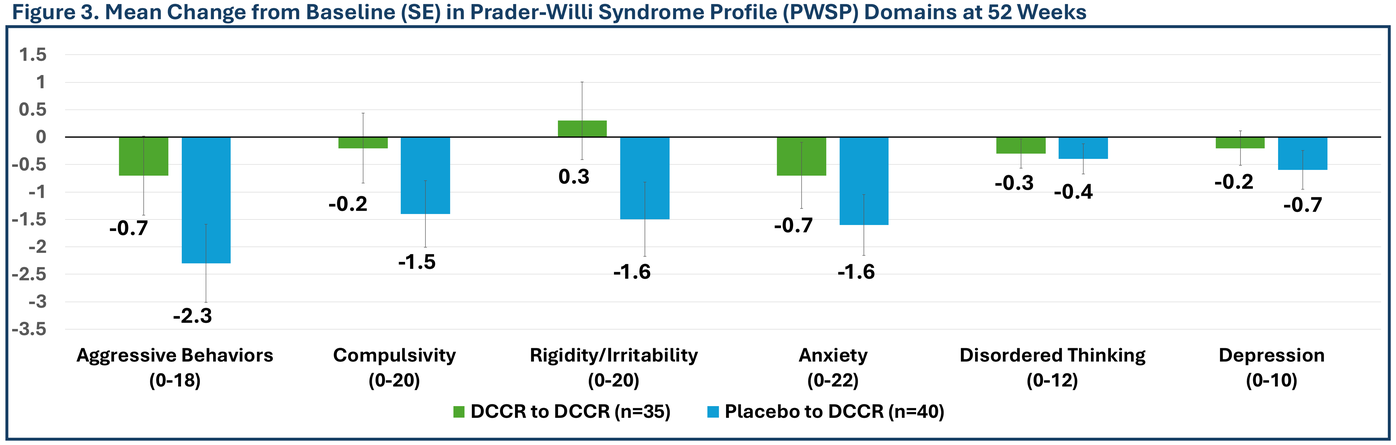


Figure 3. Mean Change from Baseline (SE) in Prader-Willi Syndrome Profile (PWSP) Domains at 52 Weeks



RESULTS

- At C614 Baseline, mean (SD) age was 15.3 (4.63) years, 55.8% were female **(Table 1)**.
- Mean (SD) HQ-CT Total Scores were 15.4 (7.81) and 11.9 (7.99), for participants who restarted DCCR after placebo or remained on DCCR, respectively.
- Participants who restarted DCCR following placebo treatments in C602-RWP showed marked improvements in HQ-CT Total Score by 13 weeks (mean [SD], -4.7 [6.3]) that further improved by 26 weeks and 1 year (-5.5 [7.0] and -6.3 [8.0], respectively) **(Figure 2)**.
- As expected, participants remaining on DCCR showed smaller improvements after 13 weeks (-2.7 [6.9]) that were sustained through 26 weeks and 1 year (-3.3 [5.7] and -2.1 [7.1], respectively), underscoring the benefits of continuous treatment **(Figure 2)**.
- Improvements in PWSP domain scores were seen at 13 and 26 weeks, with improvements in all 6 domains at 1 year in participants who restarted DCCR (mean [SE], aggression,-2.3 [0.71]; compulsivity, -1.5 [0.60]; rigidity/irritability, -1.6 [0.68]; anxiety, -1.6 [0.55]; disordered thinking, -0.4 [0.28]; and depression, -0.7 [0.35]) **(Figure 3)**.

CONCLUSIONS

In study C614, resumption of DCCR for 1 year after 16-week randomized withdrawal was associated with reductions in HQ-CT total scores and PWSP, indicative of significant improvements in both hyperphagia and behavioral symptoms characteristic of PWS.

REFERENCES

1. Butler MG, et al. *Curr Pediatr Rev.* 2019; 15(4): 207-244.
2. Miller JL, et al. *Am J Med Genet A*. 2011;155A(5), 1040–1049.

ACKNOWLEDGMENTS

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CONTACT INFORMATION

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ELECTRONIC POSTER and PLAIN LANGUAGE SUMMARY
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