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Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: results from long-term open-label study

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Abstract

Objective: This study assessed the effect of 1-year administration of diazoxide choline extended-release tablet (DCCR) on hyperphagia and other complications of Prader-Willi syndrome (PWS).

Jennifer L. Miller and Evelien Gevers are co-first authors.

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Methods: The authors studied 125 participants with PWS, age ≥ 4 years, who were enrolled in the DESTINY PWS Phase 3 study and who received DCCR for up to 52 weeks in DESTINY PWS and/or its open-label extension. The primary efficacy endpoint was Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score. Other endpoints included behavioral assessments, body composition, hormonal measures, and safety.

Results: DCCR administration resulted in significant improvements in HQ-CT (mean [SE] −9.9 [0.77], $p < 0.0001$) and greater improvements in those with more severe baseline hyperphagia (HQ-CT > 22). Improvements were seen in aggression, anxiety, and compulsivity (all $p < 0.0001$). There were reductions in leptin, insulin, and insulin resistance, as well as a significant increase in adiponectin (all $p < 0.004$). Lean body mass was increased ($p < 0.0001$). Disease severity was reduced as assessed by clinician and caregiver (both $p < 0.0001$). Common treatment-emergent adverse events included hypertrichosis, peripheral edema, and hyperglycemia. Adverse events infrequently resulted in discontinuation (7.2%).

Conclusions: DCCR administration to people with PWS was well tolerated and associated with broad-ranging improvements in the syndrome. Sustained administration of DCCR has the potential to reduce disease severity and the burden of care for families.

INTRODUCTION

Prader-Willi syndrome (PWS) is a rare, complex genetic neurobehavioral/metabolic disorder with an estimated birth incidence of 1:15,000 to 1:20,000 [1, 2]. PWS arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13 caused by a paternal deletion, maternal uniparental disomy 15, or an imprinting center defect and resulting in disruption of multiple body systems, including hypothalamic dysfunction [3]. Clinical features of PWS include hypotonia and feeding difficulties in infancy and sustained accumulation of excess body fat beginning in early childhood [4]. Hyperphagia presenting as food obsession, aggressive food seeking, and lack of satiety, with progression to severe obesity if energy intake is not restricted, occurs at a mean age of 8 years. Reduced energy requirement and obesity can occur at an earlier age [4]. PWS is also associated with intellectual disability; low muscle mass; neuroendocrine abnormalities, including growth hormone and sex hormone deficiency; behavioral problems, including aggression, anxiety, and compulsivity; and elevated risk for early mortality [5–7]. According to a 2014 survey of caregivers of patients with PWS, reducing hunger and improving food-related behaviors were the most important unmet needs in patients with PWS that should be addressed in the development of a new therapeutic [8]. There are no effective treatments for hyperphagia in PWS due to the challenge of addressing the underlying pathophysiology of the syndrome.

Diazoxide choline extended-release (DCCR) is a novel, long-acting crystalline salt formulation of diazoxide. Diazoxide is a potent activator of the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel that is capable of crossing the blood-brain barrier [9]. The DCCR formulation facilitates once-per-day dosing with very stable and predictable intraday plasma concentrations of active drug because of the increased solubility of diazoxide choline at all physiologically relevant potential of hydrogen (pH) values compared with diazoxide and its gradual release and absorption throughout the small and large intestines from the extended-release tablet formulation [10].

Activation of the K_{ATP} channel in neuropeptide Y (NPY)/Agouti related-protein (AgRP) neurons has the potential to reduce secretion of NPY and AgRP, potent endogenous appetite stimulatory neuropeptides, thereby contributing to a reduction in hyperphagia [11]. These actions of the drug are complemented by activating the K_{ATP} channel in the dorsal motor nucleus of the vagus nerve, pancreatic β cells, and adipocytes to reduce hyperinsulinemia and excess body fat and directly or indirectly improve insulin and leptin resistance, as well as satiety [11]. These effects have been confirmed in animal models of inherent or induced hyperphagic obesity including a model of PWS (Magel-2 null mouse) [11, 12].

The results of DESTINY PWS (C601), a randomized, double-blind, placebo-controlled Phase 3 study comparing DCCR with placebo in participants with PWS over a 13-week period, have recently been reported [13]. DCCR had salutary effects on multiple secondary endpoints, including body composition; however, the primary endpoint, Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score, did not differ significantly between placebo and DCCR groups. There was a significant difference between placebo and DCCR groups in a preplanned analysis of participants with more severe baseline hyperphagia (HQ-CT score > 22) [13]. Furthermore, there was a clear and

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significant relationship between circulating drug level and HQ-CT change from baseline [13]. The purpose of the current study was to investigate the long-term impact of DCCR on hyperphagia, body composition, and other aspects of behavior and physiology in people with PWS, including data obtained in the open-label extension that followed C601 (protocol C602). We hypothesized that long-term use of DCCR in people with PWS would be associated with reductions in reported HQ-CT score, improvements in body composition, and amelioration of disease severity.

METHODS

DESTINY PWS enrolled males and female individuals with genetically confirmed PWS, age 4 years and older with moderate to severe hyperphagia (HQ-CT score ≥ 13 out of a maximum 36) and weighing between 20 and 135 kg, in a stable care setting (no change in care setting for 6 months prior to enrollment and no planned change during the study) at 29 sites in the United States and the United Kingdom. Growth hormone treatment of children and adults was permitted. Following the completion of the double-blind study, participants in C601 were eligible to enroll in clinical study C602, a long-term, open-label extension. The 1-year analysis described in this manuscript was undertaken once the last participant had completed 52 weeks of treatment with DCCR in C602. For all participants, baseline was defined as the last assessment prior to initiating DCCR, which, for those treated with DCCR in C601, is the C601 baseline, whereas, for those treated with placebo in C601, it is the end of treatment visit in C601. Based on their baseline weight, participants were included in one of five weight bands (20 to <30 kg; ≥30 to <40 kg; ≥40 to <65 kg; ≥65 to <100 kg; and ≥100 to <135 kg), and the DCCR dose was up-titrated to the target dose within 6 weeks. The target dose for each weight band was fixed in milligrams per day (100, 150, 225, 375, and 450 mg/d for the 5 weight bands). This target dose for an individual with a weight at the midpoint of the weight band was about 4.2 mg/kg/d. After reaching their target dose, dose adjustments to optimize efficacy were allowed at the discretion of the investigator, with the maximum allowed dose being the lesser of 5.8 mg/kg/d or 525 mg/d. The primary efficacy endpoint, hyperphagia change from baseline, was measured using the HQ-CT, a nine-item, PWS-validated questionnaire that is used to assess food-related behaviors associated with hyperphagia [14].

Additional endpoints included behavioral complications of PWS, which were assessed using the PWS Profile (PWSP) questionnaire (a caregiver-completed questionnaire assessing behaviors in six domains: aggressive behaviors [9 items, range 0–18]; anxiety [11 items, range 0–22]; compulsivity [10 items, range 0–20]; depression [5 items, range 0–10]; disordered thinking [6 items, range 0–12]; and rigidity/irritability [10 items, range 0–20]) and the Developmental Behavior Checklist version 2 (DBC2) Parent edition (Western Psychological Services, Torrance, California); body composition parameters assessed using dual energy x-ray absorptiometry (fat mass and lean body mass); and hormones involved in appetite, satiety, fat metabolism, or cardiovascular health (leptin, insulin, and adiponectin), all measured at a central laboratory (Covance, Indianapolis, Indiana). The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated using fasting insulin and glucose measurements from the central lab as follows: (fasting insulin [micro international units per milliliter] × fasting glucose [millimoles per liter])/22.5. Disease severity was rated at each visit by both the clinician, using the Clinical Global Impression of Severity (Clinical GI-S, 7 categories), and the caregiver, using the Caregiver Global Impression of Severity scale (Caregiver GI-S, 4 categories) [15, 16].

The primary efficacy endpoint was analyzed using a linear mixed model for repeated measurements, including fixed effects for time, using baseline HQ-CT score as a covariate and an unstructured covariance model. The analysis included all available data from all participants.

Study Importance

What is already known?

Compared with placebo, short-term (13-week) administration of a diazoxide choline extended-release (DCCR) tablet to people with Prader-Willi syndrome (PWS) did the following:

- Significantly improved hyperphagia as measured by the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) in those with more severe baseline hyperphagia.
- Significantly reduced body fat.
- Significantly improved Clinical Global Impression of Change.

What does this study add?

This study showed that long-term administration of DCCR to children, adolescents, and adults with PWS can result in the following:

- Significant, clinically relevant improvements in hyperphagia.
- Significant improvements in other behavioral complications of the syndrome.
- Significant reductions in disease severity.

How might these results change the direction of research or the focus of clinical practice?

Were DCCR to be approved for the treatment of hyperphagia and other behavioral complications of PWS, administration of DCCR to people with PWS may reduce the following:

- The burden of the syndrome on people with PWS.
- The burden of care on the family.

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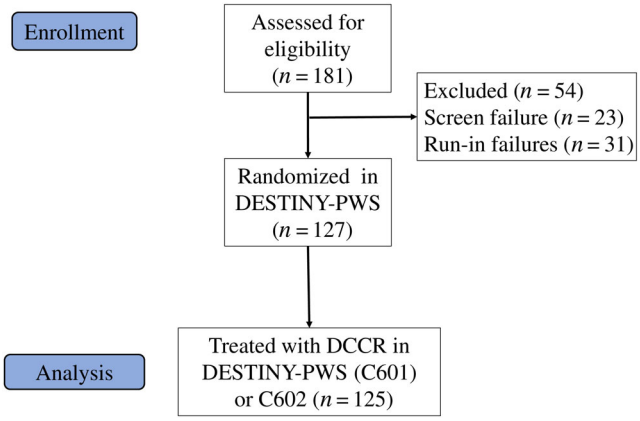

FIGURE 1 CONSORT (Consolidated Standards of Reporting Trials) diagram for clinical studies C601 and C602. DCCR, diazoxide choline extended-release tablet. [Color figure can be viewed at wileyonlinelibrary.com]

Hormonal, endocrine, body composition, and behavioral parameters were analyzed using the same approach as the primary endpoint, with the baseline value for the parameter as a covariate. Caregiver Global Impression of Severity and Clinical Global Impression of Severity were analyzed using the Wilcoxon signed rank test.

Prior to initiation of the study, ethics committee review and approval of the protocol and study related materials were completed. Participants or their parents/guardians provided informed consent and, as appropriate, assent prior to being enrolled in the study.

RESULTS

From May 2018 until January 2020, 181 individuals with PWS were screened for the study, 158 of whom were enrolled in a 2-week single-blind, placebo-treated run-in, and 127 were randomized in DESTINY PWS (C601), having met the criteria for randomization at the end of the run-in (Figure 1). Participants completing C601 were eligible for enrollment in C602, an open-label extension study to C601. A total of 125 participants received DCCR either in C601 or C602 and were included in this analysis (the intent-to-treat [ITT] population). For these 125 participants, the mean ± standard deviation (SD) age was 13.4 ± 7.0 years (range, 4–44; 20%, 18+ years), weight was 62.1 ± 30.2 kg (range, 20.5–143.5 kg), body fat mass was 27.7 ± 17.2 kg (range, 4.6–78.2 kg), and HQ-CT score was 21.5 ± 6.7 (range, 4–34); 55.2% were female (Table 1), and all participants lived with their families. Mean body mass index (BMI) for children and adolescents at baseline was above the 90th percentile for age and sex, with BMI *z* scores of 1.542 ± 1.045 for children ($n = 100$), and, for adults, it was 1.505 ± 1.198 ($n = 25$). A total of 74 participants received DCCR in both C601 and C602, 10 only received it in C601 (due to early termination in C601 or a decision not to enroll in C602), and 41 only received it in C602 (placebo-treated in C601). Height *z* score in growth hormone-treated children was −0.0976 ± 1.1468 at baseline and −0.0851 ± 1.0421 at 52 weeks, suggesting that 52 weeks of DCCR administration did not adversely affect linear growth in growth hormone-treated children with PWS.

TABLE 1 Demographics and baseline characteristics of participants with PWS treated with DCCR long-term

	ITT population ($N = 125$)
Age (y)[a]	13.4 (6.98) [4–44]
Race, *n* (%)	
White	106 (84.8)
Black or African American	6 (4.8)
Asian	1 (0.8)
American Indian or Alaska Native	1 (0.8)
Native Hawaiian or Other Pacific Islander	1 (0.8)
Other	2 (1.6)
Multiple	8 (6.4)
Ethnicity, *n* (%)	
Hispanic or Latino	12 (9.6)
Not Hispanic or Latino	111 (88.8)
Not reported	2 (1.6)
Gender, *n* (%)	
Male	56 (44.8)
Female	69 (55.2)
Height (cm)[a]	146.7 (19.0) [103–199]
Weight (kg)[a]	62.06 (30.15) [20.4–143.5]
BMI[a]	27.56 (9.63) [13.1–58.9]
HQ-CT[a]	21.5 (6.7) [4–34]
HQ-CT for HQ-CT > 22[a]	27.7 (3.23) [23–34]
Body fat mass (kg)[a]	27.7 (17.15) [4.6–78.2]
Lean body mass (kg)[a]	29.0 (13.69) [10.2–57.9]
Hormonal and endocrine parameters	
Serum leptin (ng/mL)[a]	38.2 (29.9) [1.5–136.7]
Serum adiponectin (μg/mL)[a]	10.65 (6.36) [1.87–48.32]
Fasting insulin (μIU/mL)[a]	11.09 (12.78) [0.84–45.78]
HOMA-IR[a]	2.56 (3.44) [0.17–10.63]
PWS genetic subtype, *n* (%)	
Deletion	77 (61.6)
Non-deletion	47 (37.6)
Not available	1 (0.8)
Country, *n* (%)	
United Kingdom	25 (20.0)
United States	100 (80.0)
Growth hormone status, *n* (%)	
Currently treated	103 (82.4)
Not currently treated	22 (17.6)

Abbreviations: DCCR, diazoxide choline extended-release tablet; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HQ-CT, Hyperphagia Questionnaire for Clinical Trials; ITT, intent-to-treat; PWS, Prader-Willi syndrome.
[a]Mean (SD) [range].

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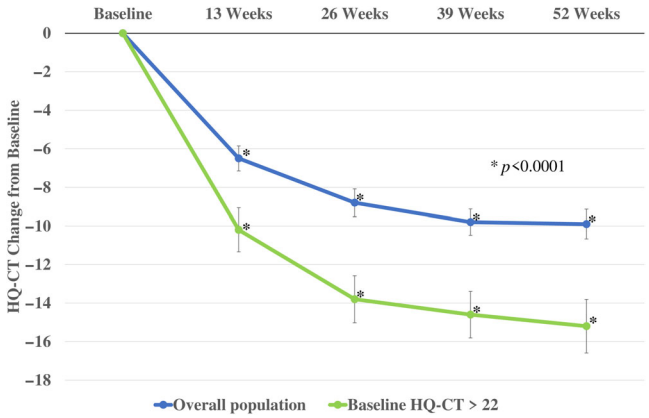

FIGURE 2 HQ-CT total score changes from baseline with DCCR over 52 weeks: primary endpoint (overall intent-to-treat population) and participants with more severe hyperphagia (baseline HQ-CT > 22). Least-squares means, SE, and *p* values were obtained from a mixed model for repeated measures analysis, including fixed effects for time, using baseline HQ-CT score as a covariate and an unstructured covariance model. C601 and C602 overall population ($N = 125$) is shown in blue and subpopulation with HQ-CT > 22 ($n = 56$) at baseline is shown in green. DCCR, diazoxide choline extended-release tablet; HQ-CT, Hyperphagia Questionnaire for Clinical Trials. [Color figure can be viewed at wileyonlinelibrary.com]

Primary endpoint

Open-label DCCR administration resulted in a progressive improvement in HQ-CT score in the ITT population, which was statistically significant at 13, 26, 39, and 52 weeks (Figure 2, 13-week, least-squares mean [standard error (SE)] −6.5 [0.65], $n = 121$; 26-week, −8.8 [0.72], $n = 107$; 39-week, −9.8 [0.68], $n = 105$; and 52-week, −9.9 [0.77], $n = 96$, all $p < 0.0001$). In a prespecified analysis focused on participants with more severe hyperphagia (baseline HQ-CT > 22), DCCR treatment resulted in a greater reduction in HQ-CT score compared with the ITT population (Figure 2, 52-week, least-squares mean [SE] −15.2 [1.39], $n = 44$, $p < 0.0001$). These changes in HQ-CT represent about a 46% improvement at 52 weeks for the ITT population and approximately a 55% improvement in those with more severe hyperphagia at baseline. In clinical study C601, a minimally clinically meaningful change in HQ-CT score was defined using distribution and anchor-based methods as a reduction from baseline of at least seven points (i.e., an improvement of at least seven points) [13]. Of the 96 participants who received DCCR for 52 weeks, 59 (61.5%) had a HQ-CT reduction from baseline of at least seven, and a substantial majority of the others still showed some degree of improvement in HQ-CT.

Long-term response in HQ-CT was predicted using nonlinear mixed effects regression employing a Michaelis-Menton model to be a function of HQ-CT baseline score (with greater improvements in those with higher baselines), circulating drug levels (with greater response in those with higher exposures), and time. There is good agreement between predicted and actual results over 1 year based on evaluation of score residual diagnostics and visual predictive checks.

Behavioral endpoints

Following 52 weeks of DCCR administration, there were significant improvements in all behavioral endpoints, including PWSP domains for aggressive behaviors, anxiety, compulsivity, depression, disordered thinking, and rigidity/irritability domains (Table 2, all $p < 0.0001$ at 52 weeks). DBC2 total score was significantly reduced at 52 weeks (Table 2, $p < 0.0001$). There were significant improvements in all DBC2 subscales, including anxiety, communication disturbance, disruptive, self-absorbed, and social relating (Table 2, all $p < 0.0001$), which were completely consistent with the significant improvement in DBC2 total score and, in the case of the anxiety subscale, consistent with the improvements seen in the PWSP anxiety domain.

Body composition endpoints

Following 52 weeks of DCCR administration, there was no change in body fat mass (Table 2, $p = 0.951$). Lean body mass increased significantly (Table 2, $p < 0.0001$), as well as weight (Table 2, $p < 0.001$). The increase in weight appears to be attributable to the change in lean body mass, as well as the normal physiological growth in younger patients. BMI *z* score at 52 weeks for children and adolescent participants was 1.574 ± 0.945 ($n = 93$), whereas, for adults, it was 1.003 ± 01.295 ($n = 19$).

Hormonal and metabolic endpoints

Fifty-two weeks of DCCR administration resulted in significant reductions in serum leptin in the absence of a change in body fat (Table 2, $p < 0.0001$), as well as in insulin (Table 2, $p = 0.0004$) and HOMA-IR (Table 2, $p = 0.0033$). Serum adiponectin was significantly increased following 52 weeks of DCCR administration (Table 2, $p < 0.0001$).

Disease severity

Over 52 weeks of DCCR administration, there was a significant reduction in disease severity as assessed by both clinicians and caregivers. At baseline, clinicians (Clinical GI-S) rated 39.9% normal, borderline ill, or mildly ill; 35.8% moderately ill; and 24.3% markedly or severely ill (Figure 3, $n = 123$). Following 52 weeks of DCCR administration, there was a significant change in clinician-rated disease severity, with 77.2% of participants rated as normal, borderline ill, or mildly ill; 20% moderately ill; and only 2.9% markedly ill, with none rated severely ill (severity change from baseline, −1.0, 95% confidence interval [CI]: −1.42 to −0.59; $n = 105$; $p < 0.0001$). Therefore, the proportion of participants who were moderately ill or worse dropped from 60.1% of participants at baseline to 22.9% after 52 weeks, which is more than a 60% reduction. Caregivers using the Caregiver GI-S (Figure 4) rated 14% mild, 57% moderate, and 29% severe at baseline ($n = 100$) and 55.7% mild, 37.1% moderate, and 7.2% severe at 52 weeks

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TABLE 2 Change from baseline at 52 weeks of treatment with DCCR for body composition, behavioral, and hormonal endpoints

	Baseline (ITT)		Baseline for participants with week 52 data		Change from baseline at week 52		
Parameter	*n*	Mean (SD)	*n*	Mean (SD)	*n*	LSmean (SE)	*p* value
Body composition							
Body fat mass (kg)	118	27.7 (17.2)	82	24.9 (16.1)	82	0.0 (0.6)	0.951
Lean body mass (kg)	118	29.0 (13.7)	82	29.9 (12.4)	82	2.9 (0.3)	<0.0001
Lean body mass/fat mass ratio	118	1.23 (0.52)	82	1.30 (0.58)	82	0.11 (0.30)	0.0005
Weight (kg)	125	62.1 (30.2)	112	58.7 (28.6)	112	2.1 (0.6)	0.0006
Behavioral							
PWSP aggressive behavior domain	118	7.7 (3.6)	100	7.6 (3.8)	100	−1.7 (0.3)	<0.0001
PWSP anxiety domain	118	13.0 (5.2)	100	12.9 (5.2)	100	−2.9 (0.4)	<0.0001
PWSP compulsivity domain	118	12.2 (4.9)	100	12.0 (4.9)	100	−2.8 (0.3)	<0.0001
PWSP depression domain	118	3.7 (2.3)	100	3.7 (2.4)	100	−0.9 (0.2)	<0.0001
PWSP disordered thinking domain	118	4.4 (3.3)	100	4.4 (3.3)	100	−1.3 (0.2)	<0.0001
PWSP rigidity/irritability domain	118	11.1 (5.2)	100	11.0 (5.4)	100	−2.7 (0.4)	<0.0001
DBC2 total score	116	53.8 (24.5)	95	54.4 (25.9)	95	−16.8 (1.9)	<0.0001
DBC2 subscale associated with PWS	115	5.5 (2.1)	94	3.8 (2.3)	94	−1.6 (0.2)	<0.0001
DBC2 anxiety subscale	116	5.0 (3.8)	95	3.1 (2.7)	95	−2.0 (0.2)	<0.0001
DBC2 communication disturbance subscale	116	7.7 (3.9)	95	5.1 (3.7)	95	−2.3 (0.3)	<0.0001
DBC2 disruptive subscale[a]	116	16.8 (7.7)	95	11.7 (7.9)	95	−4.8 (0.7)	<0.0001
DBC2 self-absorbed subscale[a]	116	14.8 (6.6)	95	9.7 (6.5)	95	−4.8 (0.5)	<0.0001
DBC2 social relating subscale[a]	116	5.4 (3.3)	95	3.7 (3.0)	95	−1.6 (0.3)	<0.0001
Hormonal and endocrine							
Leptin (ng/mL)	123	38.17 (29.85)	78	35.05 (29.03)	78	−11.08 (1.26)	<0.0001
Insulin (μIU/mL)	125	11.09 (12.78)	76	9.70 (7.17)	76	−2.50 (0.69)	0.0004
Adiponectin (μg/mL)	125	10.64 (6.36)	73	10.44 (6.61)	73	1.82 (0.41)	<0.0001
HOMA-IR	125	2.56 (3.44)	76	2.19 (1.74)	76	−0.50 (0.17)	0.0033

Abbreviation: DBC2, Developmental Behavior Checklist version 2; DCCR, diazoxide choline extended-release tablet; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; ITT, intent-to-treat; PWSP, Prader-Willi syndrome Profile.
[a]Change from baseline at 52 weeks, mean (SD).

(severity change from baseline −0.6, 95% CI: −0.87 to −0.28; $n = 97$, $p < 0.0001$). Therefore, the proportion of participants who were rated moderate or worse dropped from 88% at baseline to 44.3% after 52 weeks, which is nearly a 50% reduction.

Safety

This safety summary extends beyond the 1-year time point, including all safety data available on participants in the ITT population at the time the last participant completed 1 year of treatment in C602. At that time, 25 participants had been administered DCCR for more than 2 years, among whom 3 had taken DCCR for more than 3 years. Patients with PWS experience frequent complications and comorbidities. Treatment-emergent adverse events (TEAEs) occurred in 98.4% of participants (Table 3). Drug-related TEAEs occurred in 80.0% of participants (Table 3). A total of 20 participants experienced one or more serious adverse events (SAEs), which, for only 2 participants, were considered drug-related (both cases were associated with a hospitalization for pneumonia or respiratory infection, which were not directly related to mechanism of action of the study drug). The most common drug-related TEAEs were hypertrichosis (60.0%), peripheral edema (30.4%), and hyperglycemia (22.4%) (Table 3). The majority of these common drug-related TEAEs were grade 1. TEAEs infrequently resulted in discontinuation of the study drug (7.2% of participants). These results are consistent with the prior safety profile of DCCR. Headache and various respiratory infections (influenza, nasopharyngitis, upper respiratory tract infections, cough, and nasal congestion) were also common TEAEs but were generally not related to the study drug. Headache and various respiratory infections were also common TEAEs in the placebo group in clinical study C601. Overall, DCCR was well tolerated. Consistent with the observation of hyperglycemia as an adverse event, fasting glucose rose through week 26 (change from baseline mean ± SD, 0.35 ± 0.81 mmol/L) and had returned nearly to baseline by 65 weeks of treatment (baseline mean ± SD, 4.997 ± 0.635 mmol/L; 65 weeks, 5.126 ± 0.692 mmol/L). Hemoglobin A1c followed a similar pattern, being elevated at week 26 (change from baseline mean ± SD, 0.19% ± 0.50%) and returned nearly to baseline

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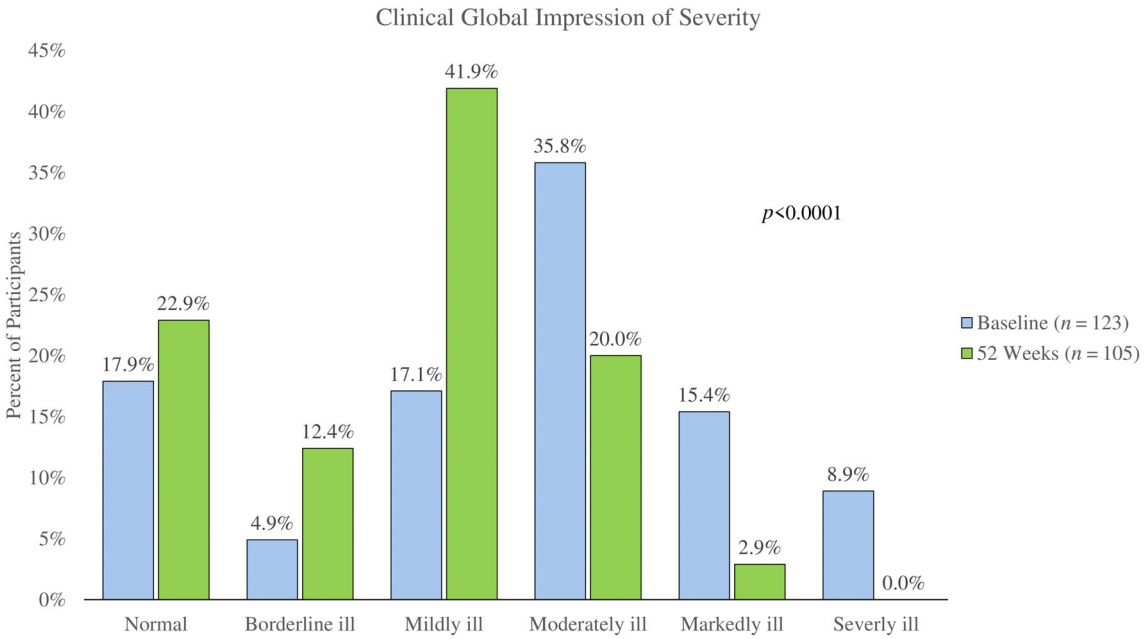

FIGURE 3 Clinical Global Impression of Severity at baseline and 52 weeks expressed as the percent of participants by score. The *p* value was computed using the Wilcoxon signed rank test. [Color figure can be viewed at wileyonlinelibrary.com]

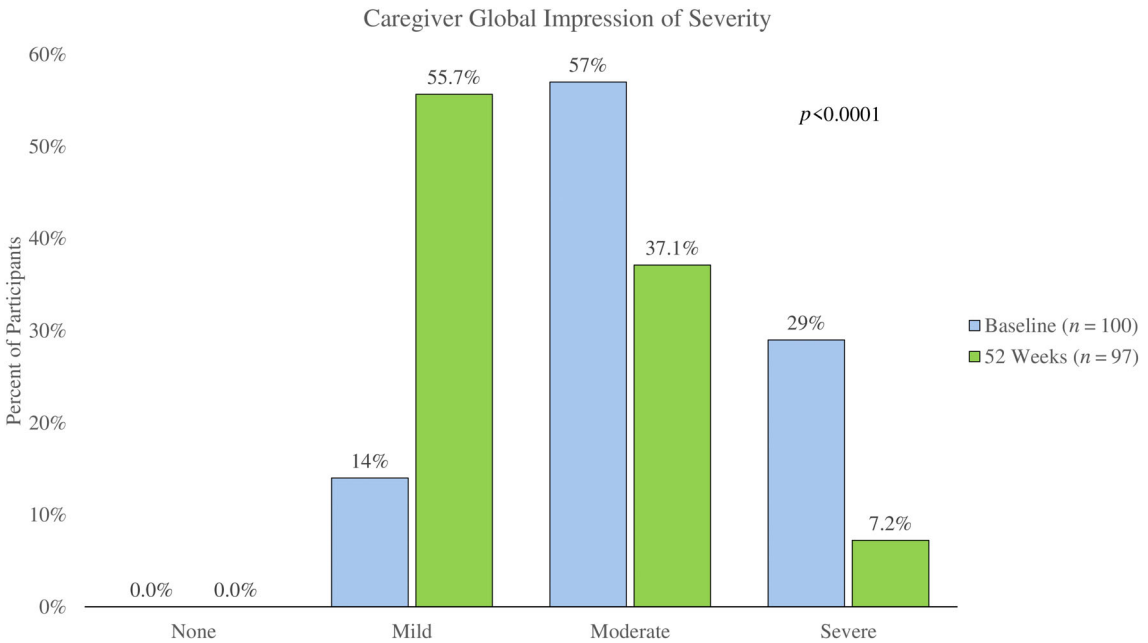

FIGURE 4 Caregiver Global Impression of Severity at baseline and 52 weeks expressed as the percent of participants by score. The *p* value was computed using the Wilcoxon signed rank test. [Color figure can be viewed at wileyonlinelibrary.com]

by week 65 (baseline mean ± SD, 5.547% ± 0.4069%; 65 weeks, 5.572% ± 0.5103%). A total of 13 participants (10.4%; median age, 17 years; median BMI, 35.8 kg/m^2) began new chronic concomitant glucose-lowering medications, primarily metformin (12 of 13) and, in one case, dulaglutide, to treat hyperglycemia or to limit the potential development of laboratory values diagnostic of type 2 diabetes. Type 2 diabetes mellitus was reported as a TEAE in one participant (17-year-old female individual, BMI, 32.6 kg/m^2). The substantial majority of cases of peripheral edema resolved without intervention and only infrequently required brief dose adjustment ($n = 3$) or brief dose interruption ($n = 3$). Short-term diuretic treatment was used to manage peripheral edema in three participants. At 1 year, the incidence of peripheral edema in participants was about the same as prior to DCCR exposure, and most cases were occurring in participants who experienced peripheral edema prior to receiving DCCR. Hypertrichosis, as a TEAE, was relatively persistent but only led to

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TABLE 3 Clinical studies C601 + C602 summary of drug-related TEAEs

	Safety population ($n = 125$; n [%])
TEAE	123 (98.4%)
TEAE related to study drug	100 (80.0%)
SAE	20 (16.0%)
SAE related to study drug	2 (1.6%)
TEAE leading to premature study discontinuation	9 (7.2%)
Drug-related TEAEs occurring in 5% or more of participants	
Hypertrichosis	75 (60.0%)
Peripheral edema	38 (30.4%)
Hyperglycemia	28 (22.4%)
Hirsutism	23 (18.4%)
Blood glucose increased	10 (8.0%)
Headache	9 (7.2%)

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

discontinuation in one instance (4-year-old female individual). Most cases (>80%) of hypertrichosis were mild. A total of 20 participants discontinued from the study prematurely. For 11 of these, the patient, caregiver, or parent withdrew consent or assent, 4 discontinued associated with an adverse event, and 5 withdrew for other reasons.

DISCUSSION

Hyperphagia, the hallmark of PWS, was improved significantly with DCCR administration at all time points through 52 weeks in the ITT population and more so in those with more severe hyperphagia at baseline. The greater improvement realized in those with more severe hyperphagia at baseline resulted in their having a mean HQ-CT score at 52 weeks that was nearly identical to the mean in those with less severe baseline hyperphagia. Although some of these improvements might conceivably be due to the participant being enrolled in a research study, we know the effects of DCCR administration on hyperphagia develop gradually over time, which is less consistent with the effect of trial participation that typically results in an apparent rapid response and may reflect a combination of direct effects of the drug in the hypothalamus and indirect effects mediated by reduced central insulin and leptin resistance. [11]. The magnitude of improvement in HQ-CT at all time points after 13 weeks of DCCR treatment with DCCR was greater than that observed during double-blind treatment (week 13) in C601 [13].

There were broad-ranging impacts on PWS-associated behaviors, which were realized at 52 weeks as measured using the PWSP and DBC2 questionnaires. Significant improvements in anxiety, compulsivity, aggressive behaviors, rigidity/irritability, disordered thinking, depression, communication disturbance, disruptive behaviors, self-absorbed behaviors, and social relating were observed. The observed reductions in hyperphagia may have contributed to improvements in other behavioral aspects of the syndrome, although we cannot rule out other direct and indirect effects of DCCR administration or changes associated with maturation of the participants.

Long-term administration of DCCR in these clinical studies was associated with significantly reduced disease severity as assessed by both clinician and caregiver. These findings are consistent with the improvements in hyperphagia and other PWS-associated behaviors. The improvements in the DBC2 subscale associated with PWS seen at 52 weeks is also suggestive of general improvement of the syndrome. The observed improvements in multiple measures of disease severity appear to be reflective of improvement in multiple features of the syndrome rather than improvement in a single or limited number of behavioral aspects of the disease, although we cannot rule out that they also reflect changes associated with maturation of the participants or biases by raters toward attributing effects to active treatment. No currently available therapeutic intervention simultaneously improves hyperphagia and other behavioral complications of the syndrome while also favorably impacting various metabolic markers of disease.

Fifty-two weeks of DCCR administration seemed to prevent the accumulation of additional body fat in contrast to the characterized natural history of the condition, whereas lean body mass continued to increase. The participants were, for the most part, growing children and adolescents. Consequently, there is an expectation of accumulation of muscle mass, weight, and fat mass over the course of 52 weeks if they are characteristically developing individuals with PWS, although prior studies of people with PWS have indicated that DCCR leads to increases in lean mass and decreases in fat mass versus placebo [13]. Diazoxide use in obese animal models has been shown to increase the benefit of exercise on muscle strength, resistance to fatigue, and muscle reactive oxygen species and redox status [17, 18].

The reductions in leptin and insulin concentrations and the improvement in HOMA-IR are consistent with the proposed mode of action of DCCR in PWS [11]. The impact of DCCR on insulin is a direct effect of the drug at the level of the β cell, whereas the impact on leptin secretion by adipocytes is probably due both to a direct effect of the drug on adipocytes and an indirect effect through reductions in insulin, resulting in substantial reductions in circulating leptin levels when expressed on a per-kilogram of body fat basis. The decrease in leptin at 52 weeks occurred in the absence of a change in body fat and may be suggestive of an improvement in leptin resistance [19]. Adiponectin concentration is increased in patients with PWS and may contribute to reduced systemic inflammation, improved insulin sensitivity, and cardiovascular health [20]. DCCR administration, resulting in further increases in adiponectin, may reinforce these benefits.

This was an open-label study, which is uncontrolled and subject to bias and other factors that may limit the applicability of the conclusions.

CONCLUSION

DCCR administration to participants with PWS was associated with significant improvement in hyperphagia and other broad-ranging

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behavioral improvements. At the same time, there were potentially beneficial changes in body composition, including the prevention of further accumulation of body fat while increasing lean body mass accrual. Additionally, there were a range of potentially beneficial hormonal and metabolic responses to DCCR administration in participants with PWS. The combined effects of these responses to treatment reduced the severity of the syndrome as assessed by both clinicians and caregivers. DCCR was well tolerated, with a relatively low rate of discontinuation due to TEAEs. Hyperglycemia may require additional treatment with antihyperglycemic agents in a small number of participants. Administration of DCCR may result in reduced disease severity and improved quality of life for these patients and a reduced burden of care for their families, thereby benefitting people with PWS and their families with a favorable risk benefit profile.

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CONFLICT OF INTEREST STATEMENT

Patricia Hirano, Kristen Yen, Neil M. Cowen, and Anish Bhatnagar are employed by Soleno Therapeutics. The institution of each author received funding from Soleno to support the conduct of the clinical trial. Lynne M. Bird reports that the support provided to the organization that she is associated with for the conduct of the clinical trial also included some salary support. Evelien Gevers reports receipt of lecturing and consulting fees from Soleno. Jack A. Yanovski reports grant support from Soleno Therapeutics and from Rhythm Pharmaceuticals for obesity-related projects, as well as material support for research from Hikma Pharmaceuticals plc and Versanis Bio. Jennifer Miller reports research funding from Rhythm Pharmaceuticals for obesity-related trials and from Harmony Biosciences for treatment trials for excessive daytime sleepiness in PWS. The other authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

Some or all of the data sets generated and/or analyzed during the current studies are not publicly available but are available from Soleno Therapeutics for further research on reasonable request.

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