Long-Term Safety of Diazoxide Choline Extended-Release (DCCR) Tablets in Participants with Prader-Willi Syndrome from the Completed C601 Randomized Double-Blind Placebo-Controlled Study (DESTINY PWS) and C602 Open Label Extension (OLE) Study

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INTRODUCTION

Prader-Willi syndrome (PWS) is a rare genetic neurobehavioral-metabolic disorder, characterized by hyperphagia, accumulation of excess fat, hypotonia, and behavioral/psychological complications.[1,2] People with PWS are at high risk of developing impairment of glycemic control and diabetes.[3] No approved medications exist for treating hyperphagia in PWS. DCCR is a once daily, extended-release tablet formulation of diazoxide choline, which provides for continuous release, stable plasma concentrations, and absorption throughout the GI tract. DCCR is currently under development as a potential treatment for children and adults with PWS who have hyperphagia. The objective of this analysis was to evaluate the long-term safety of DCCR from two completed PWS studies.

METHODS

At 29 sites in the US and UK, 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). Participants who completed DESTINY PWS were eligible to enroll in its long-term, open-label extension study period (C602-OLE). Participants who completed C602-OLE were then eligible to enroll in a 16-week, randomized withrawal period (C602-RWP).

C601/C602 SAFETY POPULATION

In Studies C601 and C602-OLE, 125 participants received at least 1 dose of DCCR. Mean duration of DCCR administration was 2.5 years (maximum: 4.5 years) with 105 participants administered DCCR >1 year and 90 participants administered DCCR >2 years.

Baseline mean (±SD) age, weight, height and BMI of participants were 13.4 ± 6.98 years, 62.06 ± 30.15 kg, 146.7 ± 18.98 cm, 27.558 ± 9.62 kg/m^2, respectively. The majority of participants were white (84.8%).

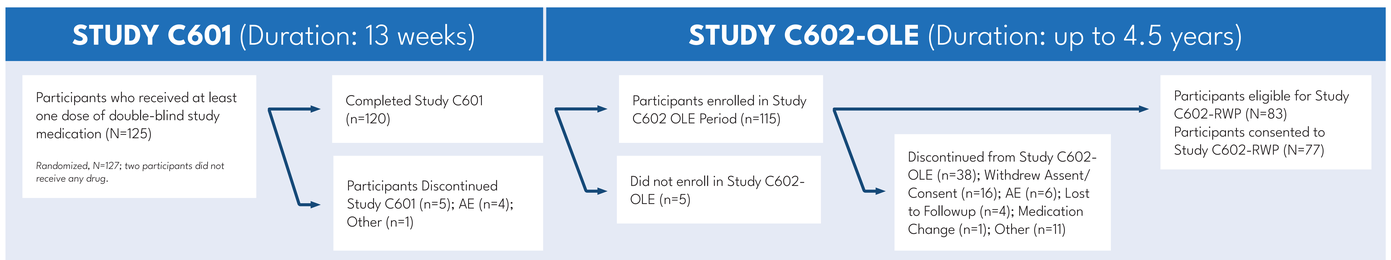

FIGURE 1: Mean Hemoglobin A1C (%) by Week of DCCR Administration

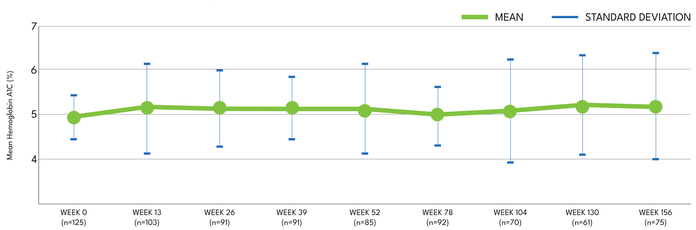

FIGURE 2: Mean Fasting Plasma Glucose (mg/dL) by Week of DCCR Administration

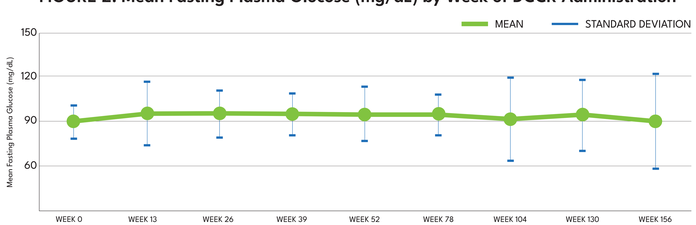

TABLE 1: Summary of Treatment Emergent Adverse Events (TEAE)

Event	n (%) of Subjects (N=125)
TEAE	123 (98.4%)
TEAE related to study drug	111 (88.8%)
TEAE leading to premature study discontinuation*	10 (8.0%)
Grade 1 or 2	94 (75.2%)
SAE	20 (16.0%)
SAE related to study drug	2 (1.6%)
SAE leading to premature study discontinuation	3 (2.4%)

*The two most common TEAEs leading to premature study discontinuation were peripheral edema (2.4%) and hyperglycemia (1.6%)

TABLE 2: TEAEs Occurring in ≥ 20% of Patients

TEAE	n (%) of Subjects (N=125)	≥ Grade 3 Events
Hypertrichosis	87 (68.8%)	0
Peripheral Edema	43 (34.3%)	2 (1.6%)
Hirsutism	34 (27.2%)	0
Hyperglycemia	34 (27.2%)	0
Headache	29 (23.2%)	0
Upper Respiratory Tract Infection	27 (21.6%)	0
COVID-19	25 (20.0%)	0

RESULTS

Treatment-emergent adverse events (TEAEs) occurred in 98.4% of participants with 88.8% experiencing at least one drug-related TEAE. TEAEs infrequently resulted in discontinuation of study drug (8.0%), with peripheral edema (2.4%) and hyperglycemia (1.6%) being the most common reasons. Twenty participants experienced serious adverse events (SAEs); two of these SAEs were considered drug-related (one patient with peripheral/pulmonary edema in the setting of an unrelated concurrent pneumonia and another with fluid retention). There were no SAEs leading to death and no suspected, unexpected, serious adverse reactions (SUSARs) reported (Table 1).

The most common TEAEs were hypertrichosis, peripheral edema, hirsutism and hyperglycaemia (Table 2). Most participants with hypertrichosis, peripheral edema or hirsutism resolved (or were resolving) with continued DCCR dosing through the end of the study. DCCR dose adjustments or short courses of diuretics for peripheral edema were prescribed as needed to manage participants experiencing these TEAEs.

Of the 34 participants who experienced TEAEs of hyperglycemia, all were grade 1 or 2 in severity. Among these participants, 22 started a new antihyperglycemic agent (e.g. metformin), which in a few cases could be discontinued. Longitudinal mean fasting glucose (FG) and HbA1c increased slightly over the initial 6-9 months but stabilized or returned to near-baseline levels upon continued DCCR dosing (Figure 1 and Figure 2).

CONCLUSIONS

DCCR was generally well-tolerated in participants with PWS after long-term exposure for up to 4.5 years. The most common TEAEs were hypertrichosis, peripheral edema, hirsutism and hyperglycemia, which were typically mild and often resolved without medical intervention. Although diabetes is a common comorbidity associated with PWS, hyperglycemia TEAEs were generally manageable with DCCR dosing adjustments and/or the introduction of oral antihyperglycemic agents. The overall observed safety profile of DCCR in patients with PWS is consistent with the known safety profile of diazoxide in other indications.

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