# RF24 / P441: Long-Term Safety of Diazoxide Choline Extended-Release (DCCR) Tablets in Patients with Prader-Willi Syndrome

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## INTRODUCTION

Prader-Willi syndrome (PWS), a rare genetic neurobehavioral-metabolic condition, characterized by hyperphagia, accumulation of excess fat, hypotonia, and behavioral/psychological complications.[1,2] Aside from growth hormone to treat short stature, there are no FDA-approved treatments to manage the significant, life-threatening aspects of PWS.

Diazoxide is a potent activator of the ATP-sensitive $K^+$ ($K_{ATP}$) channel, crosses the blood-brain barrier, and activates the channel in hypothalamic neurons, thereby contributing to reductions in hyperphagia.[3]

DCCR is a once daily, extended-release tablet formulation of diazoxide choline, which provides for continuous release and absorption throughout the GI tract and stable plasma concentrations. DCCR is currently under investigation as a therapy to reduce hyperphagia and improve behavior in PWS.

## METHODS

Participants with genetically-confirmed PWS ≥4 years old with hyperphagia were treated with oral daily DCCR in multi-center studies conducted at 29 sites in the US and the UK: a 13-week, Phase 3, double-blind, placebo-controlled study (DESTINY PWS, C601) and its long-term, open-label extension study (C602).

The safety summary was based on all safety data available following the last patient reaching 1 year of treatment. Baseline was the last assessment prior to the first dose of DCCR.

## C601/C602 SAFETY POPULATION

125 participants received at least 1 dose of DCCR; 103 participants received DCCR for 52 weeks.

## RESULTS

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%) and female (55.2%).

Treatment-emergent adverse events (TEAEs) occurred in 98.4% of participants with 80% experiencing at least one drug related TEAE. TEAEs infrequently resulted in discontinuation of study drug. Twenty participants experienced serious adverse events (SAEs), two of which were considered drug-related (one patient with peripheral / pulmonary oedema and another with fluid retention) but expected. 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 oedema, and hyperglycaemia (Table 2, Table 3). The majority of adverse events (AEs), (77.6%) were grade 1 or 2 severity. These results are consistent with the observed safety profile of DCCR from prior studies.

Nearly all of peripheral oedema cases resolved while treatment continued (~90%), infrequently required dose adjustment (7%), or needed for diuretic treatment (1.6%). Most cases of hypertrichosis (>80%) were mild and only once resulted in discontinuation. About 35% of cases of hypertrichosis were resolved/resolving at Week 52.

At baseline, both mean fasting glucose (FG) and mean HbA1c were in the upper end of the normal range. Consistent with the expected AE of hyperglycaemia, mean FG rose through 26 weeks (mean change from baseline ± SD mmol/L = 0.35±0.81) and returned nearly to baseline by 65 weeks (0.11±0.61) (Figure 1); mean HbA1c followed a similar pattern (Figure 2). In participants experiencing hyperglycaemia, the AE resolved with continued treatment in about half of cases and 14 (11.2%) of subjects started a new anti-hyperglycaemic agent, which in a few cases could be discontinued.

**Table 1. Summary of treatment emergent adverse events**

| Event | N (%) of Subjects (n=125) |
|---|---|
| TEAE | 123 (98.4%) |
| TEAE related to study drug | 100 (80.0%) |
| TEAE leading to premature study discontinuation | 9 (7.2%) |
| SAE | 20 (16.0%) |
| SAE related to study drug | 2 (1.6%) |
| SAE leading to premature study discontinuation | 3 (2.4%) |

**Table 2. TEAEs related to study drug report in ≥ 5 subjects**

| Adverse Event (Preferred Term) | N (%) of Subjects (n=125) |
|---|---|
| Hypertrichosis | 75 (60%) |
| Oedema Peripheral | 38 (30.4%) |
| Hyperglycaemia | 28 (22.4%) |
| Hirsutism | 23 (18.4%) |
| Blood Glucose Increased | 10 (8.0%) |
| Headache | 9 (7.2%) |

**Table 3. Three most common TEAEs related to study drug, by severity**

| TEAE (Preferred Term) | DCCR Treated Subjects (N = 125) | | | |
|---|---|---|---|---|
| | Severity (n [%]) | | | |
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hypertrichosis | 61 (48.8%) | 14 (11.2%) | 0 (0.0%) | 0 (0.0%) |
| Oedema peripheral | 27 (21.6%) | 9 (7.2%) | 2 (1.6%) | 0 (0.0%) |
| Hyperglycaemia | 20 (16.0%) | 8 (6.4%) | 0 (0.0%) | 0 (0.0%) |

**Figure 1. Mean fasting glucose over 65 weeks**

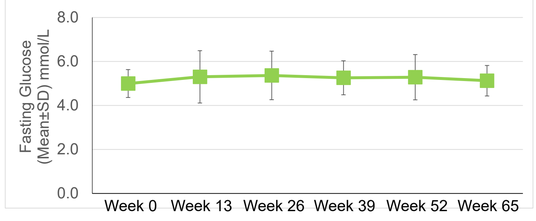
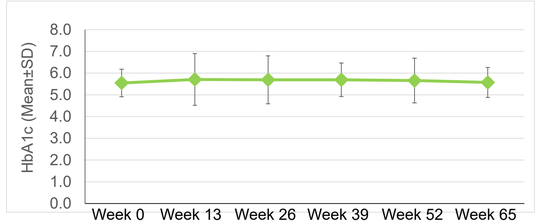



**Figure 2. Mean HbA1C over 65 weeks of DCCR**




## CONCLUSIONS

DCCR was well tolerated in long-term use. The majority of TEAEs (77.6%) were grade 1 or 2 severity. Most common TEAEs were expected based on prior studies of DCCR. These included hypertrichosis, peripheral edema and hyperglycemia, which were typically mild and resolved without intervention in most cases. Mean fasting glucose and HbA1c levels vary minimally over 52 weeks of DCCR treatment. Overall, the safety profile of DCCR is consistent with that of diazoxide-equivalent doses and the prior DCCR use.

## REFERENCES

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