PWS children who switch from DCCR see worsening hyperphagia: Trial

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Soleno to file FDA application by mid-2024 to request treatment's approval

Prader-Willi syndrome (PWS) patients who switched from daily treatment with DCCR (diazoxide choline extended-release tablets) to a placebo experienced worsening excessive hunger, or hyperphagia, and greater body weight gains relative to those who stayed on DCCR.

That's according to top-line data from the new randomized withdrawal period of Study C602 (NCT03714373), which evaluated DCCR's long-term safety and efficacy among PWS patients who had participated in the Phase 3 DESTINY PWS clinical trial (NCT03440814).

"We are delighted with the highly statistically significant results from the randomized withdrawal phase of Study C602," Anish Bhatnagar, MD, CEO of Soleno Therapeutics, the therapy's developer, said in a company press release.

CEO 'extremely pleased' by what results may mean for PWS community

"As there are currently no approved therapies for hyperphagia in PWS, we are extremely pleased by what these results may mean for the PWS community," Bhatnagar said in an emailed statement to *Prader-Willi Syndrome News*.

The launch of the randomized withdrawal period was intended to fulfill the U.S. Food and Drug Administration's (FDA) request for additional clinical testing to provide further evidence of the therapy's efficacy.

The agency had already agreed that positive data from this new trial period could support an application seeking DCCR's approval for PWS. Soleno now plans to file such a regulatory application with the FDA by mid-2024.

"Our goal is to provide a treatment for the most burdensome symptoms of PWS, and we look forward to submitting a new drug application for the potential approval of DCCR," Bhatnagar said."

The FDA had previously granted the therapy orphan drug and fast track designations, which are both intended to speed its clinical development and regulatory review. DCCR tablets similarly received fast track designation in the European Union.

The therapy acts by blocking the release of two appetite-stimulating proteins in the brain — neuropeptide Y and agouti-related protein — that are thought to contribute to hyperphagia, one of the hallmark symptoms of PWS.

The Phase 3 DESTINY PWS trial, conducted at sites in the U.S. and the U.K., evaluated the effects of daily DCCR tablets against a placebo among 127 PWS patients, 4 years and older, over about three months. After completing the trial, 115 participants enrolled in the C602 Study, where all continued treatment with DCCR for up to four years.

DESTINY PWS failed to meet its main goal of showing the therapy significantly eased hyperphagia compared with a placebo, but it did meet key secondary endpoints related to clinician-rated improvements and reductions in body fat mass.

Additional analyses indicated the COVID-19 pandemic may have affected trial results. Looking at data collected pre-pandemic, DCCR treatment did significantly curb excessive hunger in addition to meeting key secondary goals.

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Pooled trial data show DCCR led to sustained reductions in hyperphagia

Pooled data from DESTINY PWS and C602 showed that DCCR led to significant reductions in hyperphagia and disease-related behaviors that were sustained for up to a year compared with a matched group of untreated patients in the PATH for PWS natural history study (NCT03718416).

Still, the FDA wanted to see more clinical data to support a potential regulatory application. To save time and costs, the regulators agreed that any additional clinical study could include Study C602 participants.

As such, Soleno initiated a new, randomized withdrawal period of Study C602 that involved 77 patients (43 females and 34 males) who had been on DCCR tablets for two to four years.

These participants, with a median age of 14.9 years, were randomly assigned to continue receiving DCCR tablets or to switch to a placebo for about four months.

The main goal was to measure the change in hyperphagia-related behaviors, as assessed by the caregiver-reported hyperphagia questionnaire for clinical trials (HQ-CT), in which higher scores indicate more hyperphagia.

Newly announced top-line results indicate that hyperphagia-related behaviors worsened more in those who switched to a placebo compared with those still on DCCR.

Specifically, those continuing DCCR treatment saw a 2.6-point increase in HQ-CT scores, while those on placebo saw a 7.6-point increase — a 5-point

difference that was statistically significant.

Moreover, as detailed in a recent Soleno presentation, patients who switched to a placebo showed a higher increase in mean scores for each HQ-CT question relative to those in the DCCR group, indicating greater worsening in all hyperphagia-related behaviors.

These hyperphagia-related group differences were maintained across patient subgroups, including when divided by sex, by hyperphagia scores at the start of the study's withdrawal period, and by geographical location (U.S. or U.K.).

Changes in body weight and body mass index (a ratio of height and weight) also favored DCCR, as patients switching to a placebo showed significantly greater gains in both measures.

Changes in other secondary outcomes, including clinician-rated measures of improvements and disease severity, showed strong trends favoring DCCR over a placebo, but these group differences failed to reach statistical significance.

Patients on DCCR tended to have greater reduction in PWS-related behaviors

Patients continuing on DCCR also showed trends of a greater reduction in all PWS-associated behaviors evaluated, including aggression, anxiety, irritability, compulsivity, depression, and disordered thinking, than those switching to a placebo.

"In the randomized withdrawal period of our clinical study, statistically significant and clinically meaningful differences were seen in the DCCR and Placebo groups, with Placebo subjects being markedly worse," Bhatnagar said.

As in previous studies, DCCR was generally well tolerated. No new safety concerns were identified, including no treatment-related serious adverse events or treatment discontinuations due to adverse events.

Eligible patients completing Study C602 are given the option to continue DCCR treatment for up to five additional years in the open-label extension study C614 (NCT05701774), which has enrolled 75 patients as of Sept. 23.

"We would like to thank the patients, families, investigators, study site personnel and the advocacy community involved in this study, as well as the entire Soleno team for their support of the DCCR development program," Bhatnagar said.

"We remain committed to the goal of delivering DCCR, if approved, as an effective and safe therapy to individuals with PWS as expeditiously as possible."