Soleno Therapeutics (SLNO)

Updated Phase I/II Data for DCCR in PWS

On September 15th, Soleno Therapeutics (NasdaqCM: SLNO) announced the presentation of updated data from a Phase I/II study for its lead asset Diazoxide Choline Controlled-Release (DCCR) tablets for the treatment of patients with Prader-Willi Syndrome (PWS). This poster presentation was given by Dr. Virginia Kimonis, a principal investigator of the study, at the International Meeting of Pediatric Endocrinology. DCCR is a once-daily tablet formulation of diazoxide choline, a small molecule that activates adenosine triphosphate-sensitive potassium (K\(_{ATP}\)) channels. Updated data highlight numeric reductions in hyperphagia score, with a dose-dependent trend, and greater improvements in moderate to severe PWS patients. The Company plans to initiate a pivotal Phase III trial for DCCR in PWS, which is expected to begin in the fourth quarter of 2017 and yield data in mid-2018. Soleno has received Orphan Drug designation for this program in the US.

- **Updated Phase II Data for DCCR Show Dose-Dependent Reductions in Hyperphagia Score.** Soleno conducted a Phase I/II study for DCCR in patients with PWS, consisting of an open-label phase and a double-blind phase. Following 10 weeks of open-label treatment, patients that received any DCCR dose showed overall reductions in the modified Dykens hyperphagia questionnaire of 4.32 (n=11, p=0.0055), and patients that received 4.2 mg/kg DCCR or greater showed 6.25 point reductions (n=4, p=0.0816). Furthermore, patients with moderate to severe PWS, defined by a baseline hyperphagia score of 13 or greater, showed reductions in hyperphagia of 5.5 (n=6, p=0.028). These represent higher reductions than those achieved in the overall population. Finally, those with moderate to severe PWS that received the highest doses of DCCR showed hyperphagia reductions of 8 points (n=3, p=0.094), the highest of any patient subset.

Overall, we view this update favorably for two reasons: 1) although data for each independent dose were not provided, the subsets presented indicate a dose-dependent reduction in hyperphagia score, and 2) patients with more severe disease at baseline showed greater reductions in hyperphagia. While the low patient numbers and open-label nature of this study make it difficult to draw definite conclusions, we believe these findings in combination hint at the potential of DCCR in PWS. These data are graphically depicted in Figure 1.

**Expected Upcoming Milestones**

- **Q4 2017** – Initiate a pivotal Phase III study with DCCR for PWS.
- **2017** – Secure orphan drug designation for DCCR in novel indications.
- **2017** – Explore licensing options for legacy products.
- **Mid-2018** – Data from a pivotal Phase III trial with DCCR in PWS.
Figure 1. Mean Change in Hyperphagia Score from Baseline

Source: Poster Presentation

- **Quantitative Secondary Endpoints Strengthen Case for Dose Response with DCCR.** Investigators also assessed the effects of DCCR on body fat and lean body mass, which was measured with dual-energy x-ray absorptiometry (DEXA) scans. Results indicate that during the open-label phase of the study, patients receiving all doses of DCCR had ~1,250 g reductions in fat mass as compared to baseline, which was statistically significant (n=11, p=0.02). Notably, patients receiving the highest doses of 4.2 mg/kg DCCR or greater had nearly 2,500 g reductions in fat mass as compared to baseline (n=4, p=0.0592). Investigators also reported significant increases in lean body mass of approximately 2,500 g overall (n=11, p=0.003), as compared to baseline, and those receiving the highest doses of 4.2 mg/kg DCCR or greater showed increases of nearly 3,750 g (n=0.003, n=0.0197). These data are presented in Figure 2. These quantitative findings are consistent with DCCR’s observed dose-response on hyperphagia score, and further speak to the potential of DCCR and its mechanism of action in this condition.
Other parameters that were assessed include insulin sensitivity, which showed a 40.2% reduction per homeostatic model assessment insulin resistance (HOMA-IR), and significant 12.7 ng/mL reductions in leptin from baseline (p=0.007). Investigators also presented data on mean change from baseline in waist circumference, which indicated a 3.45 cm reduction from baseline through the end of the open-label treatment period (p=0.006). Biomarker data were also assessed, and indicate that treatment was associated with increases in HDL-C and reductions in TG, LDL-C, non-HDL-C, and total cholesterol. Common treatment emergent adverse events (TEAEs) include glycemic impacts (30.8%), peripheral edema (46.2%), upper respiratory tract infection (23.1%), and headache (23.1%), among others. We note one discontinuation due to the emergence of type II diabetes in a patient with a predisposition to diabetes, and another discontinuation due to deterioration of psychiatric condition which required relocation of the subject.

- **Design of Phase I/II Study for DCCR in PWS.** This was a multi-part [Phase I/II study](#) with DCCR for the treatment of patients with PWS. The trial had a 10-week open label treatment phase, followed by a 4 week randomized, double-blind, placebo controlled portion, and a 6 month open-label extension phase. The design of this study is in [Figure 3](#).
The open label portion enrolled 13 patients to receive doses of DCCR that escalated every 2 weeks, beginning at 1.5 mg/kg and progressing to 2.4, 3.3, and 4.2 mg/kg. After this portion of the study, 11 patients continued into the double-blind phase on the last dose of DCCR, or began receiving placebo. This was followed by a 6-month open-label extension. Primary endpoints were the change in hyperphagia as assessed via modified Dykens hyperphagia questionnaire and resting energy expenditure, which were measured from the beginning to the end of the double-blind phase. Secondary endpoints included changes in weight, percent body fat, and levels of serum lipids such as triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

### Key Aspects of Pivotal Trial Design Agreed Upon.

The pivotal trial for DCCR tablets in the treatment of patients with PWS will be a randomized, double-blind, placebo controlled Phase III study. The Company reported that the FDA is supportive of an endpoint focusing on change in hyperphagia score. Soleno expects to enroll 100 participants, and a dosing paradigm for DCCR has also been accepted. The FDA suggested that the Company’s pivotal trial should be a shorter 3-4 month study, followed by a long-term safety extension. Soleno plans to meet with the agency again to finalize the trial design prior to initiation. Soleno intends to begin this study in the fourth quarter of 2017, which would lead to a data readout in mid-2018 following the estimated 9-12 month timeframe for completion.

### Risk to Investment

We consider an investment in Soleno to be a high-risk investment. Soleno is currently focused on clinical-stage development and its marketed or approved products do not generate substantial revenues. Soleno has not entered Phase III clinical trials for its lead program. Failure to show convincing results in future pivotal clinical studies or failure to reach FDA or EMA approval could adversely affect Soleno’s stock price. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations. Soleno is not profitable and may need to seek additional financing from the public markets, which may result in dilution of existing shareholder value.
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