INTRODUCTION

Diazoxide Choline Control-Release Tablet (DCCR) is a patent-protected, once-daily tablet formulation of the choline salt of diazoxide. Diazoxide, which is approved to treat rare hypoglycemic conditions, is a K<sub>ATP</sub> channel agonist which effectively crosses the blood-brain barrier.

Prader-Willi syndrome (PWS) is a complex genetic condition which is due to the absence of normal active, paternally-expressed genes in the 15q11-15q13 region on chromosome 15. The behavioral disorder is characterized by short stature, obesity, hypogonadism, cognitive impairment, development delay, and behavioral problems, including but not limited to hyperphagia and other complicated food-related behaviors, aggressive and/or threatening behaviors, temper tantrums, and obsessive-compulsive symptoms. In a Phase II study of DCCR in PWS, treatment with DCCR was associated with statistically significant reductions in hyperphagia and aggressive behaviors as well as loss of body fat, increases in lean body mass and improvements in circadian rhythms.

Very High Triglycerides (VHTG) is a metabolic disease characterized by markedly elevated triglycerides (>277 mmol/L), in which the mechanism for triglycerides from circulatration may be saturated or impaired. VHTG patients are often obese and insulin resistant. In a Phase II study of DCCR in VHTG, DCCR showed significant reductions in circulating triglyceride levels as well as LDL and total cholesterol.

While diazoxide in its current use is indicated to normalize glucose levels in rare conditions with hyperglycemia, DCCR appears to be associated with a transient elevation of blood glucose but subsequent improvements in glucose, HbA1c and insulin sensitivity.

MECHANISM OF GLYCEMIC IMPACTS OF DCCR

Administration of DCCR exerts a range of effects on fasting and post-prandial glucose levels. One of these effects tends to elevate glucose levels while the other two counterbalance this effect.

Partial Suppression of Glucose Stimulated Insulin Secretion

Diazoxide has been approved for several decades to treat hypokinesinemic hypoglycemic conditions:

- Neonates and children - Leucine sensitivity, islet cell hyperplasia, neoplastic diabetosis, extrapancreatic malignancy, islet cell adenoma, or adenomatosis
- Adults - inoperable islet cell adenoma or carcinoma (insulinoma, or extrapancreatic malignancy).

In these conditions, all of which have disgruntled insulin secretion, administration of K<sub>ATP</sub> channel-pancreatic β-cell rodostosis normalizes insulin response to glucose, thus normalizing (increasing) glucose.

Partial Suppression of Hepatic Glycogenolysis

Kishore et al. 11) in a set of well designed studies in animals and humans documented that a central effect of diazoxide administration was the partial suppression of hepatic glycogenolysis.

Improvement of Insulin Sensitivity

Treatment with diazoxide has shown to improve insulin sensitivity and improve glycemic control in numerous obesity hyperphagic animal models (2-7) and in multiple clinical studies (8-10). This effect may be due to the diazoxide (10).

GLYCEMIC EFFECTS IN VHTG PATIENTS (CT03)

- 23 non-diabetic VHTG subjects (baseline fasting TG >277 mmol/L) treated with 20 mg of atorvastatin after washout of all other lipid lowering drugs.
- DCCR 200 mg (n=15) or placebo (n=12) for 18 weeks. Titration to target dose occurred over 4 weeks.
- Fasting glucose and insulin.
- HbA1c was measured at Baseline and Weeks 8, 12 and 18.
- Fasting insulin was measured and HOMA-IR calculated at Baseline and Week 18.

Figure 1 and 2 show the mean fasting glucose and HbA1c by visit from Baseline to Week 18.

Table 1 shows mean fasting insulin and HOMA-IR at Baseline and Week 18.

No subject discontinued from the study due to adverse event and more subjects discontinued from the placebo arm than the DCCR arm. Eighty-five subjects were treated in the DCCR arm and 54 subjects were treated in the placebo arm. Adverse events were mild.

A subset of subjects in each arm were at risk at baseline and received concomitant fenofibrate. Fenofibrate increases the disposal of circulating triglycerides to tissues increasing their fat content, and may therefore increase insulin resistance and worsen glycemic control. These subjects were excluded from this analysis.

GLYCEMIC EFFECTS IN PWS PATIENTS (PC05)

- 13 male and females, child, adolescent and adult, overweight and obese subjects with genetically confirmed PWS.
- Starting DCCR dose of about 1.5 mg/kg and titrated to 2.4 mg/kg, 3.3 mg/kg and 4.2 mg/kg.
- Treatment continued open label through Week 10, then subjects were randomized to continue their DCCR dose (n=15) or to the placebo equivalent of that dose (n=15) through week 14.
- A few subjects were treated with DCCR 290 mg for 6 months in an extension study.
- One subject enrolled in the study was a type II diabetic treated with metformin and exenatide and a second was receiving metformin to delay a progression to type II diabetes.
- Fasting glucose and insulin was measured at Baseline and weeks 2, 4, 6, 8, 10 and 14.

Figure 3 shows the changes from Baseline to Week 10 and 14 for fasting glucose. Figure 4 shows the glucose levels from Week 10 to Week 14.

HOMA-IR was calculated at Baseline and Weeks 10 and 14. Changes in fasting insulin and HOMA-IR are shown in Table 2.

Two subjects discontinued from the study due to adverse events. One due to complications of a pre-existing psychiatric disease unrelated to study drug. The second, who had impaired glucose tolerance at Baseline with a family history of type II diabetes, showed progressive worsening of glycemic control with titration. At a dose of 4.2 mg/kg the subject was discontinued from the study. The subject received insulin therapy, and returned to Baseline glycemic status and maintained it without anti-diabetic medication.

Fasting glucose showed a non significant increase over 10 weeks of DCCR treatment and no regression of body fat index in both the Placebo and DCCR treatment arms by week 14 (Figure 3). All subjects in the DCCR treatment arm were normoglycemic at Week 14. The glycemic control of subjects concurrently treated with anti-diabetic medications was uncompromised. HbA1c rose in treated subjects through Week 10 with a further increase from Week 10 to Week 14 (Figure 4). A limited number of PWS subjects were treated with DCCR 290 mg for 6 months. In these subjects, HbA1c dropped incrementally based on placebo instead of 6 months. HOMA-IR improved markedly during the first 10 weeks of treatment and improved further in those who were randomized to DCCR (Table 2).

EFFICACY IN WHTG PATIENTS (CT03)

- DCCR treatment was associated with the following placebo adjusted changes in lipid parameters:
  - Triglycerides: -30.1%
  - Total cholesterol: -8.1%
  - VLDL-Cholesterol: -44.9%
  - Non-HDL Cholesterol: -11.2%
  - HDL Cholesterol: 9.0%

EFFICACY IN PWS PATIENTS (PC05)

- DCCR treatment was associated with the following statistically significant therapeutic responses:
  - Reduction in hyperphagia. Reduction in aggressive behaviors. Reduction in body fat and waist circumference. Increase in lean body mass and the lean body mass fat mass ratio.

CONCLUSIONS

- While diazoxide is best known as the standard of care in hyperinsulinemic hypoglycemic conditions to normalize glucose levels, there are other centrally mediated effects of the drug that could contribute to the overall impact on insulin secretion.
- DCCR treatment appears to be associated with short term increases in glucose but longer term treatment is not associated with compromised glycemic control in the majority of individuals.
- Similar patterns of impact on glycemic control were observed in patients with very high triglycerides, who tended to be obese and insulin resistant, and in patients with Prader-Willi syndrome who tend to be obese, but are generally hyperinsulinemic and insulin sensitive.

REFERENCES