Glycemic Impact of Long-Term Use of Diazoxide Choline Controlled-Release Tablets in Patients with Prader-Willi syndrome or with Very High Triglycerides

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INTRODUCTION

Diazoxide Choline Controlled-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_{ATP} 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 normally active, paternally-expressed genes in the chromosome 15q11-q13 region. This neurobehavioral disorder is characterized by short stature, obesity, hypogonadism, cognitive impairment, development delays, 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 circulating lipids.

Very High Triglycerides (VHTG) is a metabolic disease characterized by markedly elevated triglycerides (>27.7 mmol/L), in which the clearance mechanism for triglycerides from circulation 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 hypoglycemia, 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 hyperinsulinemic hypoglycemic conditions:

- Neonates and children - Leucine sensitivity, islet cell hyperplasia, nesidioblastosis, 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 dysregulated insulin secretion, agonizing the K_{ATP} channel in the pancreatic β-cell restores normal insulin response to glucose, thus normalizing (increasing) glucose.

Partial Suppression of Hepatic Gluconeogenesis

Kishore et al. (1) 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 gluconeogenesis.

Improvement of Insulin Sensitivity

Treatment with diazoxide has been shown to improve insulin sensitivity and improve glycemic control in numerous obese hyperphagic animal models (2-7) and in multiple clinical studies (8-19). This effect may also be centrally regulated (10).

GLYCEMIC EFFECTS IN VHTG PATIENTS (CT013)

- 23 non-diabetic VHTG subjects (baseline fasting TG >27.7 mmol/L) treated with 20 mg of atorvastatin after washout of all other lipid lowering drugs.
- DCCR 290 mg (n=11) or placebo (n=12) for 18 weeks. Titration to target dose occurred over 4 weeks.
- Fasting glucose at Baseline and weeks 2, 4, 8, 12, 14 and 18.
- HbA1C was measured at Baseline and Weeks 8, 12 and 18.
- Fasting insulin was measured and HOMA-IR calculated at Baseline and Week 18.
- Figures 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. Slightly more subjects in the placebo arm experienced an adverse event (66.7%) than in the DCCR arm (63.6%). Most adverse events were mild.

A subset of subjects in each arm were statin naïve 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.

Table 1. Fasting insulin and HOMA-IR at Baseline and Week 18 (CT013)

Treatment	Baseline n	Baseline mean±SD	Week 18 n	Week 18 mean±SD	Change BL-Week 18 n	Change BL-Week 18 mean±SD
			Fasting insulin (µIU/mL)			
Placebo	10	24.1±19.2	11	25.0±13.4	9	4.2±23.4
DCCR	11	28.2±19.8	10	13.8±5.7	10	-15.3±16.5
			HOMA-IR			
Placebo	10	7.1±7.9	11	6.8±4.1	9	0.54±10.0
DCCR	11	7.8±6.6	10	3.6±1.8	10	-4.33±5.94

Figure 1. Fasting glucose by study visit clinical study CT013 (Mean±SEM)

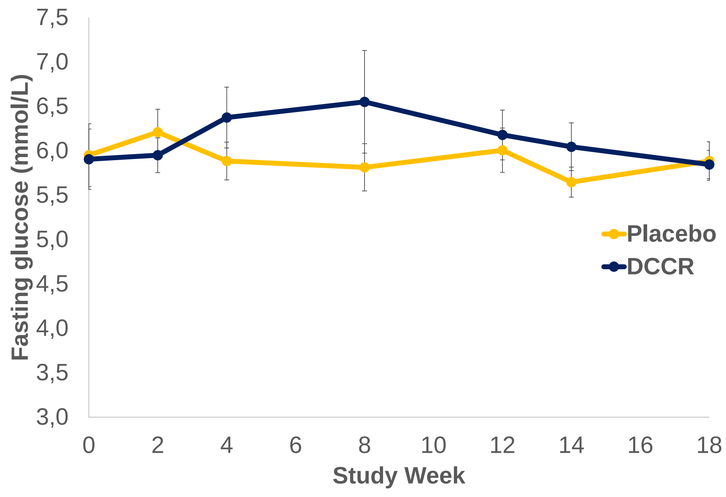
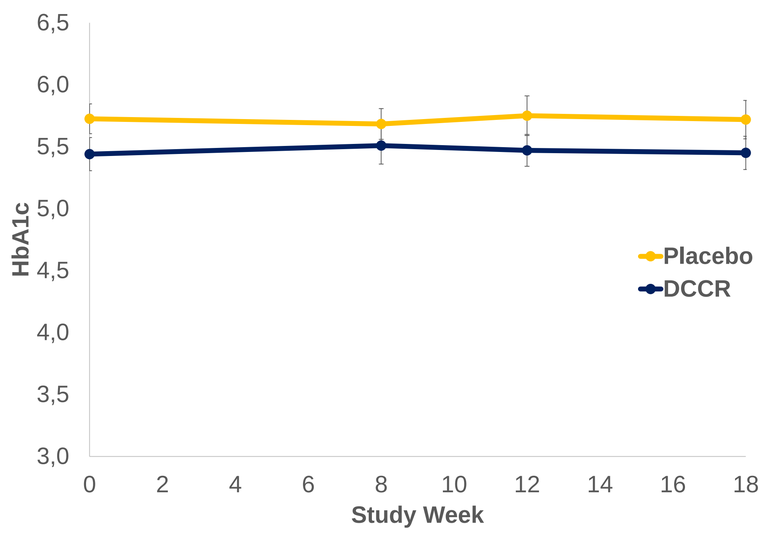


Figure 2. HbA1c by study visit clinical study CT013 (Mean±SEM)



EFFICACY IN VHTG PATIENTS (CT013)

- DCCR treatment was associated with the following placebo adjusted changes in lipid parameters:
  - Triglycerides -30.1%
  - Total cholesterol -8.8%.
  - VLDL Cholesterol -44.9%.
  - Non-HDL Cholesterol -11.2%
  - HDL Cholesterol 9.0%

GLYCEMIC EFFECTS IN PWS PATIENTS (PC025)

- 13 male and female, 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=5) or to the placebo equivalent of that dose (n=6) 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.
- HbA1C was measured at Baseline and at Weeks 10 and 14 Figure 3 shows the change from Baseline to Week 10 and 14 for fasting glucose.
- 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 regressed back to Baseline 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 concomitantly 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 from Baseline to 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).

Figure 3. Change in fasting glucose clinical study PC025 (Mean±SEM)

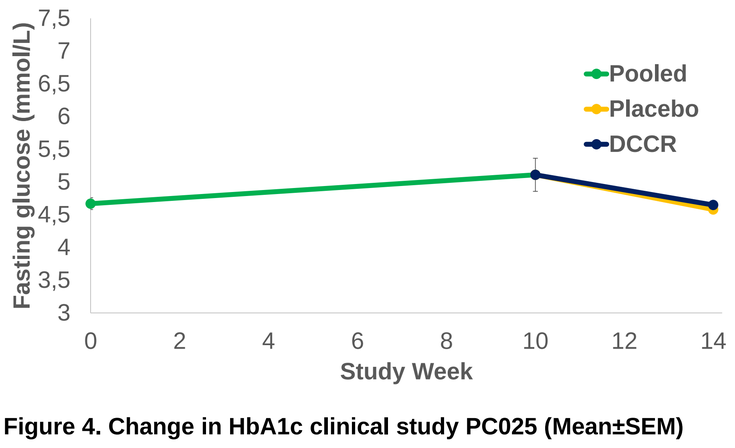


Figure 4. Change in HbA1c clinical study PC025 (Mean±SEM)

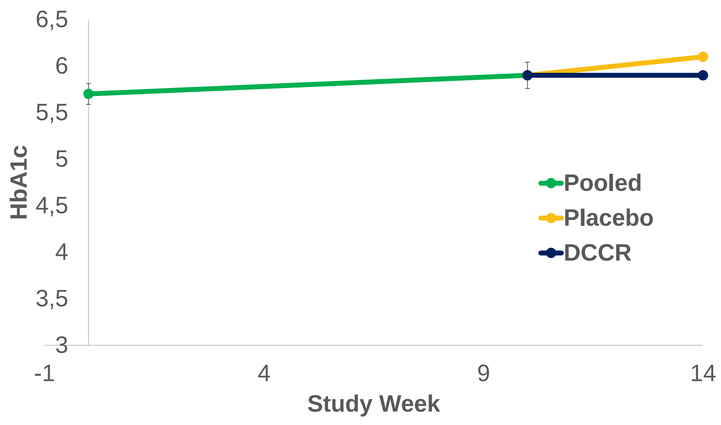


Table 2. Changes in fasting insulin and HOMA-IR clinical study PC025

Population	n	Baseline	n	Week 10	Week 14
	HOMA-IR (Mean±SD)				
All subjects	10	2.61±1.95	10	1.56±1.47	
Randomized to placebo			6	1.46±1.13	1.93±1.29
Randomized to DCCR			5	1.46±1.87	1.29±1.52
	Fasting Insulin (µIU/mL +++Mean±SD)				
All subjects	10	12.3±8.5	11	5.9±4.4	
Randomized to placebo	6		6	5.9±3.7	9.5±5.6
Randomized to DCCR	5		5	5.8±5.2	5.7±5.5

EFFICACY IN PWS PATIENTS (PC025)

- 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 counterbalance the adverse 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 hypoinsulinemic and insulin sensitive.

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Growth and syndromes (to include Turner syndrome)

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