Safety Profile of DCCR and Implications for PWS Study Design

Titration to Target Dose Improves the Safety Profile of Diazoxide Choline Controlled-Release Tablet (DCCR)

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INTRODUCTION

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. The result is a neurobehavioral disorder characterized by physical and mental deficiencies such as 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. The loss of SNORD116, in the 15q11-q13 region, results in hyperphagia and several other characteristics of PWS.[1]

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 potent K_{ATP} channel agonist which effectively crosses the blood-brain barrier.[2]

In a Phase II study of DCCR in PWS, treatment with DCCR was associated with statistically significant reductions in hyperphagia, and reductions in aggressive behaviors, loss of body fat, increases in lean body mass and improvements in circulating lipids.[3]

Eight clinical studies have been completed with DCCR. The overall safety profile has been consistent with the known profile of diazoxide, with the potential for a lower severity and/or frequency of common adverse events. Early studies were conducted without titration and subsequently it was noted that a 10-14 day titration between dose levels improved the tolerability of DCCR. In the Phase II and ongoing Phase III studies in PWS patients, a two week titration between dose levels is being used.

METHODS

- The adverse events from completed studies without titration are summarized. (Table 1) These studies included:
  - Three studies in 37 healthy adult volunteers with treatment periods of 7 to 16 days.
  - Two studies in 62 obese adults with treatment periods of 1 – 14 days
- Data for selected adverse events (chest pain, headache, dizziness, tachycardia, palpitations) from studies with dose titration are summarized. (Table 2) Studies with dose titration included:
  - One study in obese adults included 12 subjects assigned to dose titration study arms
  - 2 placebo-controlled studies in 90 adult patients with hypertriglyceridemia or very high triglycerides
- Glucose and HbA1c levels are summarized for patients with very high triglyceride levels

RESULTS

The adverse events reported in studies without titration are summarized by dose in Table 1. A dose-related trend was observed in chest pain, nervous system disorders (headache, dizziness), and cardiac disorders (palpitations, tachycardia). Diazoxide is a vasodilator, and, like other vasodilators, may result in headaches at the start of treatment.

Table 1. Drug-related, treatment-emergent adverse effects by dose without titration

System Organ Class Preferred Term	Target dose			
	145 mg (n=8) N (%)	290 mg (n=38) N (%)	435 mg (n=44) N (%)	580 mg (n=8) N (%)
Average duration of treatment (days)	14	37.7	12.3	7
General disorders and administration site conditions				
Peripheral edema	0 (0%)	7 (18.4%)	3 (6.8%)	4 (50%)
Chest pain	0 (0%)	0 (0%)	3 (6.8%)	1 (12.5%)
Fluid retention	0 (0%)	1 (2.6%)	0 (0%)	1 (12.5%)
Nervous system disorders				
Headache	0 (0%)	5 (13.2%)	13 (29.5%)	6 (75%)
Dizziness	0 (0%)	0 (0%)	2 (4.5%)	1 (12,5%)
Metabolism and nutrition disorders				
Decreased appetite	3 (37.5%)	1 (2.6%)	4 (9.1%)	1 (12.5%)
Hyperglycemia	0 (0%)	0 (0%)	0 (0%)	3 (37.5%)
Fluid retention	0 (0%)	0 (0%)	1 (2.3%)	0 (0%)
Cardiac disorders				
Palpitations	0 (0%)	1 (2.6%)	7 (15.9%)	2 (25%)
Tachycardia	0 (0%)	0 (0%)	1 (2.3%)	3 (37.5%)
Gastrointestinal disorders				
Nausea	0 (0%)	0 (0%)	7 (15.9%)	1 (12.5%)
Abdominal distention	0 (0%)	3 (7.9%)	1 (2.3%)	0 (0%)
Skin and subcutaneous tissue disorders				
Rash	0 (0%)	2 (5.3%)	1 (2.3%)	0 (0%)
Hirsutism	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)

Without titration, there was a dose dependent increase in frequency of several adverse events. The frequency of these events (chest pain, headache, dizziness, palpitations and tachycardia) were reduced with 7 or 10 day titration periods, (Table 2)

Table 2.
Frequency of non-titration, dose-related adverse events in studies with dose titration

	TR002 Group 7 (N = 12)	PC007 Pooled (N = 68)	CT013 DCCR Arm (N = 22)
Average target dose (mg/day)	507.5	437.1	290
Average treatment duration (days	49	56	126
Titration days / dose (No. dose steps to target)	7 (4)	7 (1 or 2)	10 (3)
Average duration of treatment (days)	49	56	126
System Organ Class Preferred Term	N (%)	N (%)	N (%)
General disorders and administration site conditions			
Chest pain	1 (8.3%)	0 (0%)	0 (0%)
Nervous system disorders			
Headache	8 (66.7%)	3 (4.4%)	0 (0%)
Dizziness	1 (8.3%)	2 (2.9%)	0 (0%)
Cardiac disorders			
Palpitations	2 (16.7%)	0 (0%)	0 (0%)
Tachycardia	0 (0%)	0 (0%)	0 (0%)

There were lower frequencies of chest pain, palpitations, and tachycardia, even at the highest doses evaluated. These data were used to design study PC025, a Phase II study in patients with PWS ages 10 years and older. PC025 included 14-day titration periods to titrate to a target dose of 4.2 mg/kg/day. In this study, there were no reports of chest pain, dizziness, palpitations, or tachycardia. There were 2 reports of headache: one in the DCCR group and one in the placebo group.

Other Common Adverse Events

Peripheral edema and hyperglycemia are commonly seen in PWS patients and have been associated with diazoxide use.

While there is potential for short-term adverse glycemic impacts associated with DCCR treatment, it is generally not sustained. Fasting glucose (Figure 1) and HbA1c (Figure 2) tend to rise through titration and regress back to Baseline with longer term treatment (Figure 2). One subject, an untreated prediabetic, discontinued from clinical study PC025 due to worsening hyperglycemia.

Figure 1. CT013 Fasting glucose by study visit in statin treated subjects (Mean ± SEM)

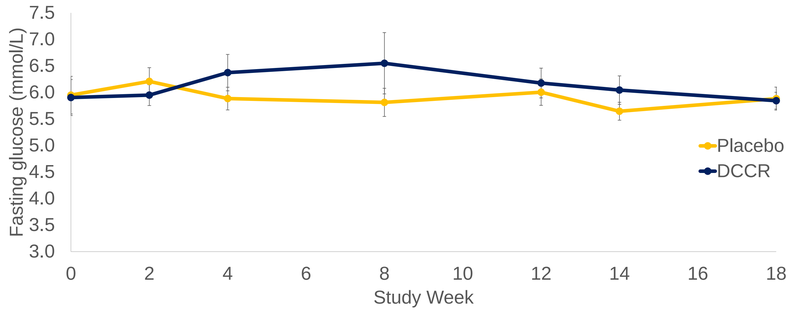
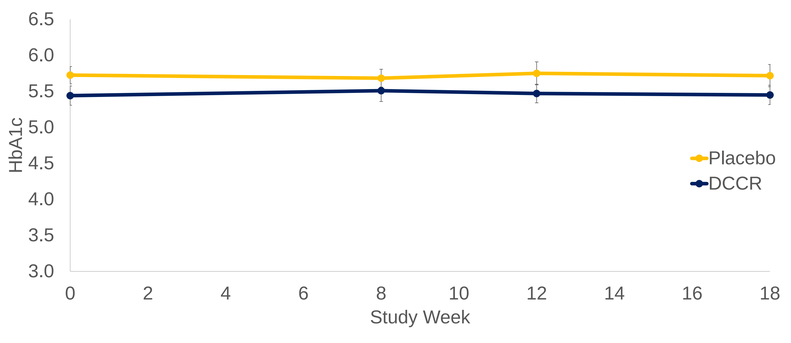


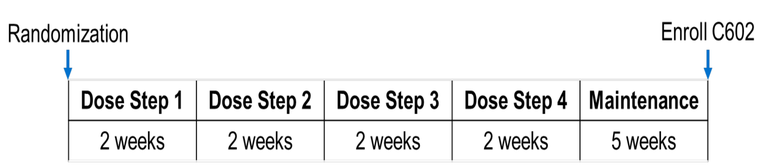
Figure 2. CT013 HbA1c by study visit in statin treated subjects (Mean ± SEM)



Peripheral edema is a common adverse event with diazoxide treatment and is likely associated with its vasodilatory action. When less aggressive titration to target dose is used, peripheral edema is less frequent and less severe, typically resolving while dosing continues, without dose adjustment or the use of diuretics, and often within days. PWS patients may have baseline peripheral edema and will be followed closely for worsening or development of de-novo edema. Diazoxide-associated peripheral edema is responsive to diuretics which may be used in PWS patients if edema does not resolve spontaneously, or with dose adjustment. While many institutions use prophylactic diuretics with diazoxide treatment for hyperinsulinism, DCCR treated patients have rarely needed diuretics and certainly do not require prophylaxis. In the Phase II PWS study, 2 of 13 patients had peripheral edema at baseline and 3 additional ones developed it during treatment. Three cases required no intervention while two (the ones who had edema at baseline) were successfully managed by either a drug holiday or a short course of diuretic. None was considered serious or resulted in discontinuation from the study.

Implications for PWS Clinical Trials

Based on the improved tolerability of DCCR with less aggressive titration, studies in PWS patients use a two-week titration schedule. In the DESTINY PWS study, patients will start with dose of 1.5 mg/kg with escalation as tolerated to 2.4 mg/kg, 3.3 mg/kg, and 4.2 mg/kg in two-week increments.



CONCLUSION

The safety profile of DCCR is consistent with the known safety profile of diazoxide; however, due to the sustained release formulation, DCCR has the potential to provide a better safety profile than the commercially-available oral suspension product. Most adverse events were mild and the frequency and severity of adverse events was improved with titration, particularly so with an extended dosing period at each titration step. Based on these data, the DESTINY PWS study, a Phase III study in PWS patients and its long-term safety extension study, has been designed to titrate subjects to their target dose. The titration occurs in up to 4 steps and the subject remains at least step for 2 weeks.

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