



# P1-1161 Efficacy and Safety of Diazoxide Choline Controlled-Release Tablet in Patients with Prader-Willi syndrome, an Updated Analysis

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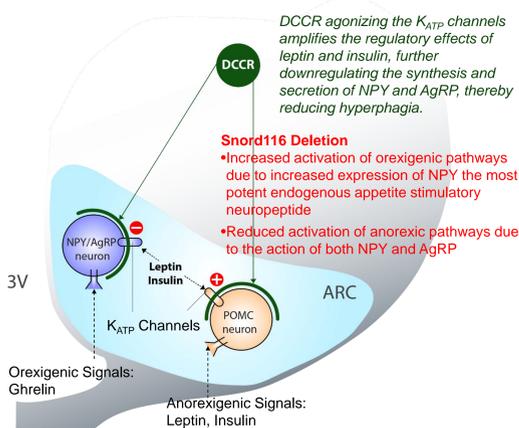
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## INTRODUCTION

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.<sup>1</sup> 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

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<sub>ATP</sub> channel agonist which effectively crosses the blood-brain barrier. The only available formulation currently needs to be administered 2-3 times per day.

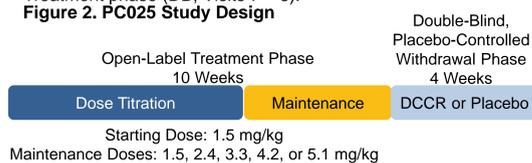
Figure 1. DCCR Mode of Action – Hyperphagia in PWS



## STUDY DESIGN

Clinical study PC025 consisted of a 10-week Open-Label Treatment phase (OL, Visits 2 - 7), followed by a 4-week randomized, Double-Blind, Placebo-Controlled Withdrawal Treatment phase (DB, Visits 7 - 8).

Figure 2. PC025 Study Design



Subjects with an improvement in hyperphagia and/or an increase in resting energy expenditure during the OL were eligible to enter the DB, in which they were randomized equally to remain at the DCCR dose they received at Visit 7 or its placebo equivalent.

## KEY ELIGIBILITY CRITERIA

- Signed written informed consent and assent.
- Males or females aged 10-22 years with genetically-confirmed PWS.
- BMI consistent with obesity or elevated body fat content.

## DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Thirteen subjects were enrolled; 11 subjects completed the OL, were classified as responders, and were randomized into DB (DCCR: 5; Placebo: 6).

Table 1. Demographics and Baseline Characteristics (n=13)

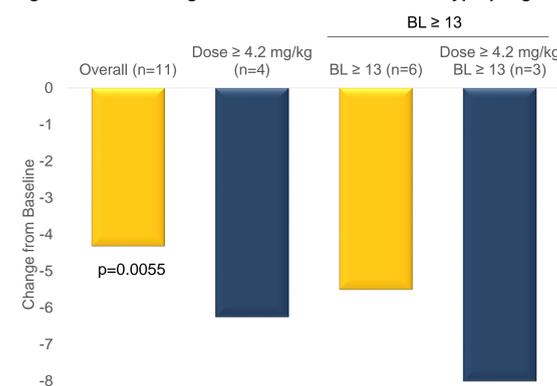
Mean Age (years)	16.00 (11.59-21.62)
Sex (n, %)	
Male	8 (61.5%)
Female	5 (38.5%)
Race (n, %)	
Asian	1 (7.7%)
White	11 (84.6%)
Multiracial	1 (7.7%)
Ethnicity (n, %)	
Hispanic or Latino	7 (53.8%)
Not Hispanic or Latino	6 (46.2%)
PWS Genetic Subtype (n, %)	
Deletion	12 (92.3%)
Uniparental Disomy	1 (7.7%)
Growth Hormone (n, %)	
Treated	7 (53.8%)
Naïve	6 (46.2%)
Mean Percent Body Fat (%)	51.7 (36.4 - 60.7)
Mean BMI (kg/mg <sup>2</sup> )	38.14 (24.7 - 53.5)
Mean Weight (kg)	89.58 (56.4 - 134.1)
Mean Hyperphagia Score (0-34)	16.23 (3.0 - 29.0)

## RESULTS

### HYPERPHAGIA

- Hyperphagia assessed by the 9-item modified Dykens<sup>2</sup> questionnaire
- Hyperphagia significantly improved after 2 weeks of DCCR treatment
- Sustained and stable improvements at doses  $\geq 3.3$  mg/kg
- Change from baseline (BL) to the end of OL was highly statistically significant (Figure 3)
- The comparison between the arms for change from end of the OL to the end of DB was not significant likely because the effective half-life of DCCR persisted for a substantial period into the DB
- The comparison between the arms for change from BL to the end of DB approached significance by ANCOVA ( $p=0.108$ ) and was statistically significant by Mann-Whitney U-test ( $p=0.027$ ).
- More marked improvements were observed in subjects with moderate to severe BL hyperphagia scores ( $\geq 13$ )

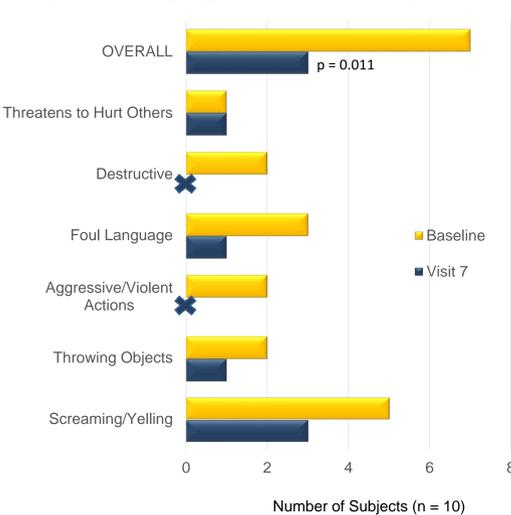
Figure 3. Mean Change From Baseline to Visit 7 in Hyperphagia



### BEHAVIORS

- The presence or absence of 23 PWS associated behaviors were evaluated at BL and again at Visit 7
- Divided into 4 categories: obsessive/compulsive, self-injurious, aggressive and threatening and other

Figure 4. Change from Baseline to Visit 7 in Numbers of Subjects Reporting Aggressive and Threatening Behaviors



### SAFETY

The safety profile of diazoxide is well-known, given the long history of use

- Dosing in approved indications tends to be at much higher doses than are required to treat PWS
- The most common treatment emergent adverse events (TEAEs) reported during the OL (regardless of relationship to study drug) were glycemic impacts (either on fasting glucose or OGTT glucose, 30.8%), peripheral edema (46.2%; includes 15.4% with AE present at BL), upper respiratory tract infection (23.1%), headache (23.1%), ear infection (15.4%), constipation (15.4%), contusion (15.4%), and somnolence (15.4%). The majority of these AEs are commonly seen in PWS patients.
- Two subjects discontinued during OL
  - Type II diabetes in a patient with a predisposition to Type II diabetes
  - Transition to a group home associated with the worsening of a pre-existing psychiatric condition (within 4 days of starting dose, unrelated to DCCR)

### DEXA AND WAIST CIRCUMFERENCE

- Statistically significant improvements (greater at higher doses) in DEXA parameters were observed (Figures 5 and 6)
- Waist circumference was significantly reduced during the OL (-3.45 cm,  $p=0.006$ ) consistent with the loss of visceral fat (Figure 7).

Figure 5. Mean Changes from Baseline to Visit 7 in Body Composition by DEXA

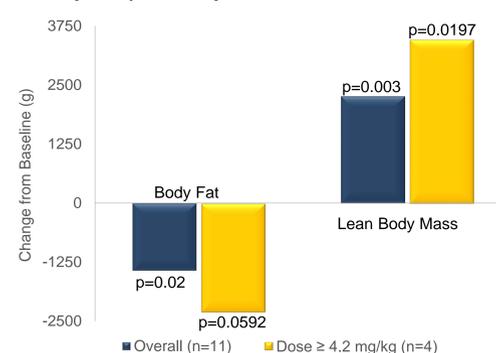


Figure 6. Mean Change from Baseline to Visit 7 in Lean Body Mass / Fat Mass (LBM/FM) Ratio

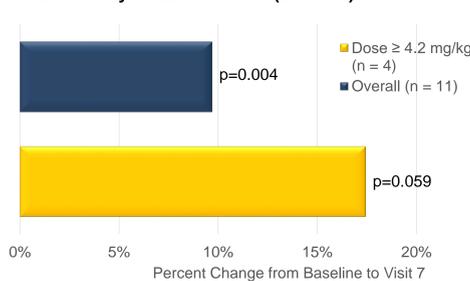


Figure 7. Mean Change from Baseline to Visit 7 in Waist Circumference



- No significant changes in mean fasting glucose at Visit 7 or Visit 8 (Table 2)

Table 2. Mean Changes in Fasting Glucose

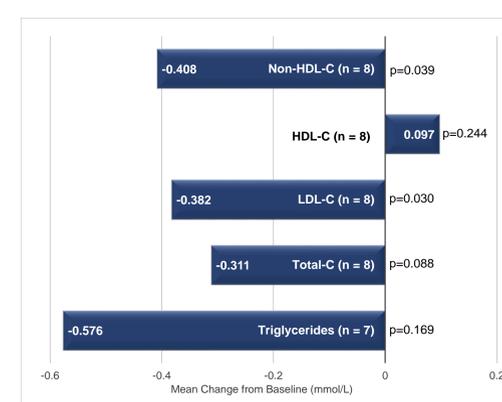
Population	n	Fasting Glucose (mmol/L)				
		BL	V7	BL - V7	V8	V7 - V8
All subjects randomized in the DB	11	4.67	5.11	0.44		
Randomized to placebo	6	4.71	5.24	0.53	4.58	-0.67
Randomized to DCCR	5	4.63	4.95	0.32	4.65	-0.30

- Overall, DCCR appeared to be well-tolerated
- Fisher's exact test comparing numbers of subjects experiencing drug-related treatment emergent adverse event (TEAE) in DB was non-significant ( $p \geq 0.999$ )

### LIPID PARAMETERS

There were statistically significant improvements in Total-C, LDL-C, and Non-HDL-C, and a marked improvement in triglycerides (Figure 8); these improvements generally persisted through the DB (data not shown).

Figure 8. Mean Changes from Baseline to Visit 7 in Lipid Parameters



### OTHER PARAMETERS

- There was an improvement in insulin sensitivity based on HOMA-IR which showed a 40.2% reduction from Baseline to Visit 7 ( $p=0.192$ ).
- Leptin was significantly reduced from Baseline to Visit 7 (-12.72 ng/mL,  $p=0.007$ ).
- Ghrelin was essentially unchanged during the OL (+9.2 pg/mL,  $p=0.93$ ).

## SUMMARY

Treatment of adolescent and adult PWS subjects with DCCR results in:

- Marked and sustained improvements in hyperphagia
- Reductions in aggressive/threatening behavior
- Reductions in body fat and increases in lean body mass
- Improvements in cardiovascular risk factors
- Reductions in waist circumference suggestive of a loss of visceral fat
- Improvements in insulin sensitivity

Safety results are consistent with the known safety profile of diazoxide. Hyperglycemic changes seen with diazoxide do not appear to be a concern with continued use of DCCR.

## CONCLUSIONS

DCCR treatment of adolescent and adult PWS patients addressed a number of the highest priority unmet needs in the disease including hyperphagia and aggressive behaviors. DCCR may represent an important new therapeutic option for PWS.

The dose response data obtained from this study provide the dose rationale for future studies. A Phase 3 study in PWS subjects is planned for initiation by the end of 2017.

## REFERENCES

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- Dykens EM, Maxwell MA, Pantino E, Kossler R, Roof E. Assessment of hyperphagia in Prader-Willi syndrome. Obesity 1997 15(7):1816-1826.

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