Pharmacokinetics of Diazoxide Choline Controlled-Release Tablets, a Once a Day Treatment Being Evaluated in Patients with Prader-Willi syndrome

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INTRODUCTION

Prader-Willi syndrome (PWS) is due to the absent expression of paternally inherited genes in the chromosome 15q11-q13 region.[1] It is characterized by hypothalamic-pituitary and behavioral abnormalities leading to features 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, aggression, 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. Upon administration diazoxide choline hydrolyzes releasing diazoxide which is absorbed and circulates. Diazoxide, which is approved to treat rare hypoglycemic conditions, is a K_{ATP} channel agonist which effectively crosses the blood-brain barrier.

CLINICAL STUDIES FOR DCCR

Key parameters of each study are provided in Table 1. Individual study results are summarized in subsequent tables.

Table 1. Clinical studies and pharmacokinetic parameters measured

Study	Subjects	n	Parameters Evaluated
PK001	Obese	30	Single dose PK of DCCR and Proglycem diazoxide oral suspension
TR002 group 7	Obese	12	Steady state PK at multiple dose levels, dose linearity
PK015	Healthy normal	9	Steady State PK
PK008	Healthy normal	12	Steady state PK and food effects
PC025	Prader-Willi syndrome	11	Steady state PK

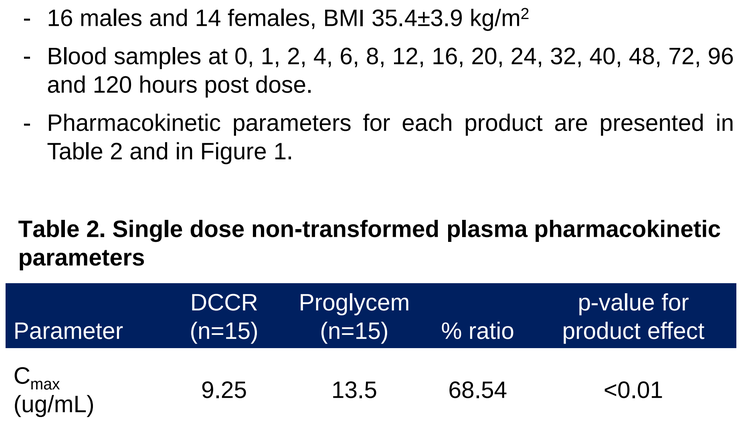
CLINICAL STUDY PK001- SINGLE DOSE PHARMACOKINETICS OF DCCR AND PROGLYCEM - TIME TO STEADY STATE AND STEADY STATE PHARMACOKINETICS OF DCCR

- Single dose Proglycem diazoxide oral suspension (n=15, 200 mg) or a single 290 mg DCCR tablet (n=15, equivalent to 200 mg of diazoxide) administered under fasted conditions,
- 16 males and 14 females, BMI 35.4±3.9 kg/m^2
- Blood samples at 0, 1, 2, 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, 72, 96 and 120 hours post dose.
- Pharmacokinetic parameters for each product are presented in Table 2 and in Figure 1.

Table 2. Single dose non-transformed plasma pharmacokinetic parameters

Parameter	DCCR (n=15)	Proglycem (n=15)	% ratio	p-value for product effect
C_{max} (ug/mL)	9.25	13.5	68.54	<0.01
AUC_{0-t} (ug*hr/mL)	553.09	643.82	85.91	0.11
$AUC_{0-\infty}$ (ug*hr/mL)	618.53	697.12	88.73	0.26
T_{max} (hr)	22.13	6.67	331.73	<0.01
$T_{1/2}$ (hr)	32.43	29.24	110.93	0.31

Figure 1. Plasma concentration 0-120 hours in clinical study PK001 (mean±SEM)



CLINICAL STUDY TR002 - DOSE LINEARITY

- 5 male and 7 female obese subjects (BMI 35.5±3.7 kg/m^2) titrated from 217.5 mg/day to 507.5 mg/day (every 7 days in 72.5 mg increments).
- PK samples predose and 6-8 hours post-dose (corresponding to Cmax at steady state, see results of PK015).
- Peak and trough levels increased linearly with dose.
- The regression of mean peak circulating drug levels on dose accounted for more than 99% of variability in mean peak circulating drug levels (y=0.1178x + 1.7854; R^2>0.99).
- The same was true for the regression of mean trough circulating drug levels on dose (y=0.1158x + 2.6399; R^2>0.99).

Table 3. Trough and peak circulating drug levels at steady state by dose in clinical study TR002 (mean±SD)

Dose	Trough (µg/mL)	Peak (µg/mL)	Peak-to-trough swing (µg/mL)	Trough as a percent of peak
217.5 mg	22.77±5.35	27.68±6.75	4.90±4.22	83.9%±14.2%
290 mg	30.25±8.55	35.94±10.52	6.23±6.98	85.7%±17.2%
362.5 mg	39.50±8.51	44.58±7.81	4.20±7.03	90.9%±17.7%
435 mg	48.70±9.38	51.88±10.03	4.03±6.73	92.6%±13.6%
507.5 mg	55.54±11.80	62.42±11.75	6.08±5.05	90.8%±7.9%

CLINICAL STUDY PK015 - TIME TO STEADY STATE AND STEADY STATE PHARMACOKINETICS OF DCCR

- 8 male and 1 female healthy normal subjects, BMI 28.8±3.67
- 290 mg of DCCR once daily for 10 days.
- PK samples pre-dose on days 1, 3, 5, 7, 9 and 10.
- Day 10 subjects were sampled at 2, 4, 6, 8, 10, 12, 15, 24, 48, 72, 96 and 120 hours post dose.
- Steady state for DCCR was reached on Day7.
- Steady state pharmacokinetic parameters for DCCR are shown in Figure 2 and Table 4.

Figure 2. Plasma intraday concentrations of DCCR in clinical study PK015 (mean±SEM)

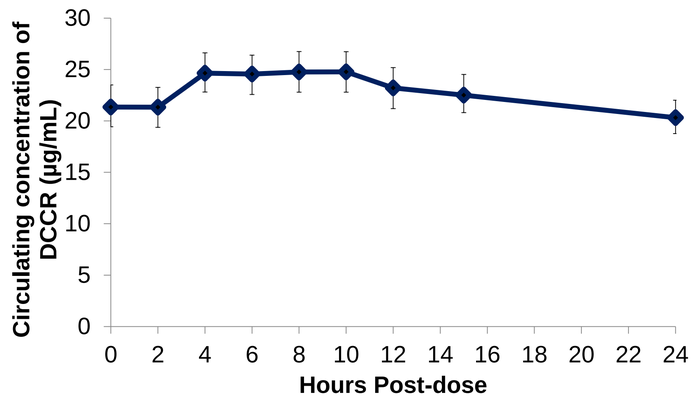


Table 5. Steady state pharmacokinetic parameters for DCCR

DCCR			
Parameter	**Mean**	**SD**	**%CV**
$C_{max(ss)}$ (µg/mL)	25.91	6.17	23.8
T_{max} (hr)	6.00	2.24	37.3
AUC_{0-t} (µg·hr/mL)	1594	484.0	30.4
$C_{av(ss)}$ (µg/mL)	22.73	5.673	25.0
$t_{1/2}$ (hr)	35.39	14.10	39.8
Peak-to-Trough Swing (µg/mL)	6.276	1.541	24.6

CLINICAL STUDY PK008 - FOOD EFFECTS

- 9 male and 3 female healthy normal subjects BMI 28.6±2.7 kg/m^2
- 435 mg of DCCR once daily for 8 days.
- On Days 7 and 8 PK sampling occurred within 5 minutes prior to dosing (0 hour) and after dose administration at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours.
- On day 7 subjects were dosed following an overnight fast and continued to fast for 4 hours after dose administration.
- Day 8 subjects were dosed following a standardized meal. Table 6 summarizes steady state pharmacokinetic parameters under fed and fasted conditions. There appears to be no food effect for DCCR.

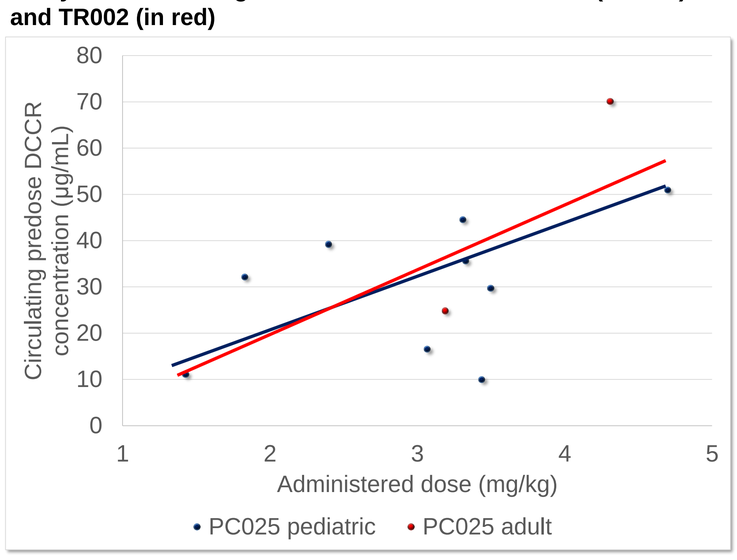
Table 6. Steady state pharmacokinetic parameters under fed and fasted conditions in clinical study PK008

Geometric means, ratios of means and 90% confidence intervals ln-transformed data				
Parameter	**Fasting conditions**	**Fed Conditions**	**Ratio**	**90% CI**
$AUC_{0-t(ss)}$ (µg*hr/mL)	984.46	936.24	1.05	100.62, 109.88
$C_{max(ss)}$ (µg/mL)	45.66	44.91	1.02	95.12, 108.71
$C_{min(ss)}$ (µg/mL)	34.66	32.33	1.07	100.46, 114.4
$C_{av(ss)}$ (µg/mL)	41.02	39.01	1.05	100.62, 109.88

CLINICAL STUDY PC025 - CIRCULATING DRUG LEVELS IN PRADER-WILLI SYNDROME PATIENTS

- 11 patients with PWS aged 11-21, BMI 38.2±10.7 kg/m^2, were initiated on a DCCR dose of about 1.5 mg/kg
- 9 of the 11 subjects in PC025 were pediatric, while 2 were adults
- Titrated every 14 days to about 2.4 mg/kg, 3.3 mg/kg, and 4.2 mg/kg at the discretion of the investigator.
- PK sample predose at at Week 10.
- The relationship between administered dose and predose circulating drug levels was examined by linear regression. For comparison, dose TR002 was converted from mg/day to mg/kg/day based on the subjects weight at each visit.
- Figure 3 compares the actual circulating predose drug level from clinical study PC025 with the predicted circulating drug level using the regression equations from both PC025 and TR002.

Figure 3. Predose circulating drug levels at Week 10 of clinical study PC025 with regressions based on PC025 data (in blue) and TR002 (in red)



CONCLUSIONS

- Single dose and steady state pharmacokinetics of DCCR are well characterized across these 5 studies
- DCCR is suitable for once daily dosing (Study PK015)
- There do not appear to be any food effects on steady state pharmacokinetics of DCCR (Study PK008)
- Given the lower C_{max} for a similar AUC, DCCR may lower the frequency and severity of C_{max} related adverse events compared to diazoxide oral suspension (Study PK001)
- Trough circulating drug levels are comparable between pediatric and adult PWS subjects and similarly obese non-PWS adult subjects suggesting the pharmacokinetic data generated in non-PWS adult subjects is relevant and applicable to the use of DCCR in pediatric and adult PWS patients (Studies TR002 and PC025)
- The constant intraday circulating drug level that follows from the continual absorption of drug from DCCR likely results in a consistent therapeutic response in treated PWS patients (Study PK015)

REFERENCES

1. Driscoll DJ, Waters MF, Williams CA, et al. A DNA methylation imprint, determined by the sex of the parent, distinguishes the Angelman and Prader-Willi syndromes. Genomics 1992;13:917–24.

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