# T-P-LB-3765 Agonizing the $K_{ATP}$ Channel with DCCR Results in Fat Loss in Prader-Willi Syndrome Patients

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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 Prader-Willi critical 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]

PWS patients have ectopic fat deposition. They accumulate excess body fat, however the majority of this excess fat accumulation is subcutaneous. This is in contrast to the pattern of accumulation of excess body fat in similarly obese non-PWS subjects, the majority of which is visceral. Growth hormone treatment, which is common in children and adolescents with PWS, limits the accumulation of visceral fat but not subcutaneous[4].

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. Diazoxide predominantly agonizes the SUR1 containing isotype of the $K_{ATP}$ channel.

Agonizing the $K_{ATP}$ channel in NPY/AgRP/GABA neurons in the arcuate nucleus of the hypothalamus reduce secretion of NPY and AgRP, reducing hyperphagic drive. Agonizing the $K_{ATP}$ channel in adipocytes increases β-oxidation of fat and reduces de-novo fatty acid biosynthesis. Both of these tissues contain the SUR1 isotype of the channel.

In multiple hyperphagic obese animal models, agonizing the $K_{ATP}$ channel results in the loss of body fat.[5-8] In multiple clinical studies agonizing the $K_{ATP}$ channel in obese subjects on a reduced calorie diet for 6 months or 1 year, resulted in significant weight loss, nearly all of which was accounted for by loss of body fat (95+%).[9-11]

## METHODS

- Clinical study PC025 included a 10-week open-label treatment phase followed by a 4 week double-blind, placebo-controlled treatment phase.
- The study enrolled 13 male and female subjects with genetically confirmed PWS between the ages of 10 and 22.
- Subjects had to have a BMI ≥ 95$^{th}$ percentile of the age specific BMI value on the CDC BMI charts or have body fat ≥ 35%.
- Subjects were titrated up on dose from 1.5 mg/kg to 4.2 mg/kg at the discretion of the investigator over 6 weeks and then treated stably for the remaining 4 weeks.
- To evaluated body fat mass and distribution, whole body DEXA scans were completed at Baseline and again at the end of open label treatment
- Two-tailed paired t-tests were used to assess statistical significance of changes in body fat.

## RESULTS

Table 1 shows Baseline characteristics of subjects (n=11) who completed the 10-week open label treatment period.

**Table 1. Clinical study PC025 Baseline characteristics of subjects completing the open-label treatment phase**

| Parameter | Subjects completing open-label treatment (n=11) mean±sd |
|---|---|
| Male/female | 6/5 |
| Age | 15.9±2.8 |
| Weight (kg) | 90.4±25.4 |
| BMI (kg/m$^2$) | 38.2±10.7 |
| Body fat (%) | 51.8±6.6 |
| Body fat (kg) | 47.6±16.6 |
| Fat mass arms (kg) | 6.4±2.7 |
| Fat mass legs (kg) | 18.1±5.3 |
| Fat mass trunk (kg) | 21.9±8.8 |
| Waist circumference (cm) | 113.2±20.4 |

DCCR treatment resulted in a statistically significant improvement in hyperphagia as measured using a modified Dykens hyperphagia questionnaire.[2] There was greater improvement in hyperphagia at the highest dose and greater improvement in subjects with moderate to severe hyperphagia at Baseline. In parallel, there were statistically significant decreases in body fat and increases in lean body mass.[2] Given the loss of body fat and increases in lean body mass, there was no statistically significant change in weight at 10 weeks. DCCR treatment was also associated with a statistically significant improvement in aggressive behaviors.[2] Additionally there were improvements in circulating lipids and a trend towards improvement in insulin sensitivity.[2]

## CHANGES IN BODY FAT

Figure 1 shows the effects of 10 weeks of DCCR treatment on body fat for the whole body and various body segments.

Tables 2 and 3 summarize the body fat results by body region for all subjects who completed the 10 week open-label treatment phase and for those who were treated with the 4.2 mg/kg dose. There was a statistically significant reduction in body fat (-1.59 kg, -3.77%, p=0.02). The results by body segment did not reach statistical significance. Subjects treated with the 4.2 mg/kg dose (n=4) lost more body fat (-2.31 kg, -6.09%), and lost more in each body segment than did the overall population (Table 2). The 4.2 mg/kg dose appeared to preferentially reduce visceral fat (3.28x) and subcutaneous fat in the legs (4.09x) compared to the whole population (calculated as: change from Baseline 4.2 mg dose/change from Baseline overall population).

**Figure 1. Changes in fat mass by body region clinical study PC025**

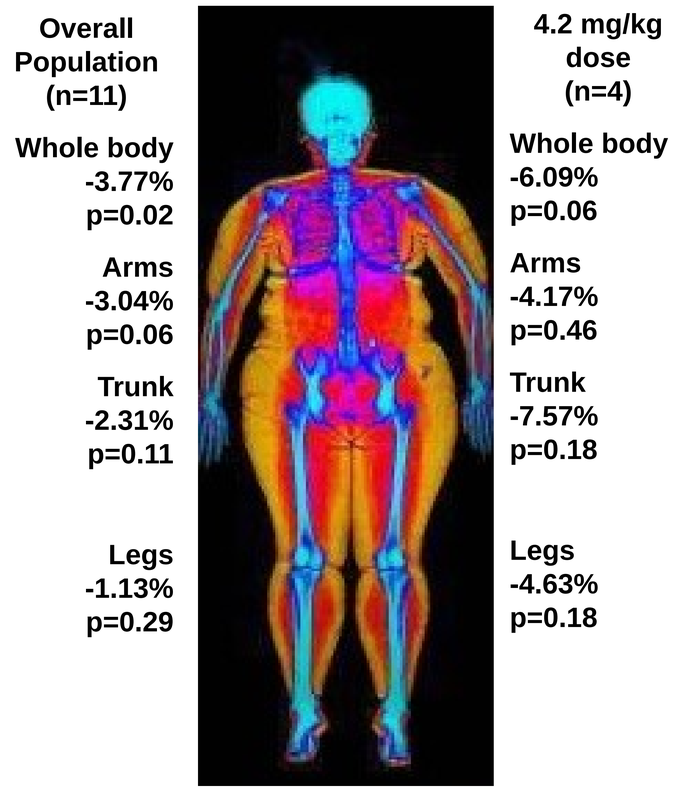



**Table 2. Overall population (n=11) changes in body fat and fat mass by body region clinical study PC025**

| Parameter | Baseline (mean±sd) | Change | P-value | Range | Percent change (mean±sd) |
|---|---|---|---|---|---|
| Body fat mass (kg) | 47.6±16.6 | -1.59 | 0.02 | -4.66 to 1.14 | -3.77%±4.75% |
| Trunk fat mass (kg) | 21.9±8.8 | -0.93 | 0.11 | -3.77 to 0.77 | -2.31%±6.51% |
| Legs fat mass (kg) | 18.1±5.3 | -0.28 | 0.29 | -1.68 to 1.28 | -1.13%±3.91% |
| Arms fat mass (kg) | 6.4±2.7 | -0.37 | 0.06 | -0.87 to 0.30 | -3.04%±6.06% |

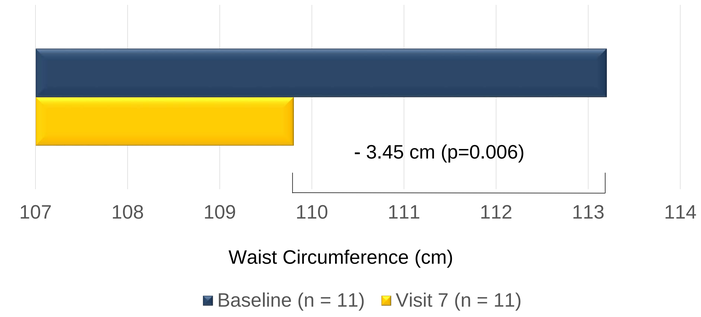
**Table 3. Subjects treated with the 4.2 mg/kg dose (n=4) changes in body fat and fat mass by body region clinical study PC025**

| Parameter | Baseline (mean±sd) | Change | P-value | Range | Percent change (mean±sd) |
|---|---|---|---|---|---|
| Body fat mass (kg) | 38.2±12.9 | -2.31 | 0.06 | -3.84 to -0.58 | -6.09%±3.95% |
| Trunk fat mass (kg) | 17.5±6.1 | -1.46 | 0.18 | -3.25 to 0.77 | -7.57%±7.50% |
| Legs fat mass (kg) | 14.6±3.8 | -0.67 | 0.18 | -1.68 to 0.18 | -4.63%±5.55% |
| Arms fat mass (kg) | 4.8±1.5 | -0.20 | 0.46 | -0.87 to 0.20 | -4.17%±7.43% |

## CHANGES IN WAIST CIRCUMFERENCE

Figure 2 shows the effects of 10 weeks of DCCR treatment on waist circumference. Consistent with the significant loss of visceral fat, there was a statistically significant reduction in waist circumference.

**Figure 2. Changes in waist circumference clinical study PC025**




## CONCLUSION

In obese hyperphagic animal models agonizing the $K_{ATP}$ channel results in significant loss of body fat. In clinical studies in obese subjects on reduced calorie diet, agonizing the $K_{ATP}$ channel results in significant weight loss, which is almost exclusively attributable to the loss of body fat.

In Prader-Willi syndrome patients, who experience ectopic accumulation of excess body fat, 10 weeks of treatment with DCCR without caloric restriction resulted in statistically significant loss of body fat. Loss of both visceral and subcutaneous fat appeared to have occurred.

Use of the 4.2 mg/kg dose resulted in greater loss of body fat, and appeared to result in the preferential loss of visceral fat and subcutaneous fat from the legs.

While hyperphagia and food related behaviors are often identified as the most problematic aspects of PWS, obesity and its cardiometabolic complications are by far the leading cause of death in PWS patients. DCCR has shown statistically significant improvements in hyperphagia and aggressive behaviors. These data provide evidence of the substantial impact of DCCR on body fat, a very desirable outcome in PWS. DCCR is currently being evaluated in a Phase III study in PWS patients, the Destiny-PWS study.

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