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

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INTRODUCTION
Diazoxide Choline Controlled-Release Tablet (DCCR) is a potent, protracted-action tablet of the cholectrol (salt of diazoxide). Diazoxide, which is approved to treat rare hypoglycemic conditions, is a P-gp channel agonist which effectively crosses the blood-brain barrier.

Prader-Willi syndrome (PWS) is a complex genetic condition which is due to an imbalance of inherited, paternally-expressed genes in the chromosome 15q11-13 region. This neurobehavioral disorder is characterized by short stature, obesity, hyperphagia, cognitive impairment, development delays, and behavioral problems, including, but not limited to hyperphagia and other complications faced, 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 (>277 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 total cholesterol is the 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 control 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 leads to elevated 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 hypereosinophilic hypoglycemic conditions:
- Neonates and children: Leucine sensitivity, islet cell hypoplasia, neodisorderia, extrapulmonary malignancy, islet cell adenoma, or adenomatosis
- Adults: inoperable islet cell carcinoma or carcinoma (insulina) or extrapulmonary malignancy.
In these conditions, patients in which they disregulated insulin secretion, a combination in the pancreatic b-cell restore normal insulin response to glucose/metabolizing (increasing) glucose.

Partial Suppression of Hepatic Glucose Oxidation
Kisher et al. (2014) in a well designed studies in animals and humans documented that a central effect of diazoxide administration was the partial suppression of hepatic glucose oxidation.

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

GLYCEMIC EFFECTS IN VHTG PATIENTS (CT013)
23 non diabetic VHTG subjects (baseline fasting TG >277 mmol/L) treated with 20 mg of atorvastatin after washout of all other lipid lowering drugs.
- DCCR 200 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, 6, 12, 14 and 18.
- HbA1c was measured at Baseline and Weeks 2, 4, 6, 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 most subjects discontinued from the placebo arm than the DCCR arm. Small changes in the placebo group experienced an adverse event (6.7%) than in the DCCR arm (6.9%). Most adverse events were mild.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline n</th>
<th>Baseline mean±SD</th>
<th>Week 18 n</th>
<th>Week 18 mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>24.1±9.2</td>
<td>11</td>
<td>25.0±13.4</td>
</tr>
<tr>
<td>DCCR</td>
<td>11</td>
<td>28.2±18.9</td>
<td>10</td>
<td>13.8±5.7</td>
</tr>
</tbody>
</table>

Fasting insulin (µIU/mL)

Placebo 10 24.1±9.2 11 25.0±13.4 9 4.2±23.4
DCCR 11 28.2±18.9 10 13.8±5.7 10 -15.3±16.5

EFFECTIVENESS OF DCCR IN PWS PATIENTS (P025)
- 13 male and female, child, adolescent and adult, overweight and obese subjects with 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=9) through Week 14.
- A few subjects were treated with DCCR 200 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 2 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.

Table 2. Changes in fasting insulin and HOMA-IR clinical study P025

<table>
<thead>
<tr>
<th>Population</th>
<th>Baseline n</th>
<th>Week 10 n</th>
<th>Week 14 n</th>
<th>HOMA-IR (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>10</td>
<td>2.61±9.5</td>
<td>6</td>
<td>1.46±1.3</td>
</tr>
<tr>
<td>Randomized to placebo</td>
<td>5</td>
<td>1.46±1.3</td>
<td>6</td>
<td>1.93±2.9</td>
</tr>
</tbody>
</table>

Fasting Insulin (µIU/mL, ±Mean±SD)

| All subjects | 10          | 12.3±5.5  | 6          | 5.9±4.4         |
| Randomized to placebo | 5          | 6          | 5.9±3.7    | 5.5±6.5         |
| Randomized to DCCR | 5          | 5          | 5.8±5.2    | 5.7±5.5         |

EFFECTIVENESS OF DPP-4 IN PWS PATIENTS (P025)
- 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 hypereosinophilic hypoglycemic conditions to normalizes glucose levels, there are other centroidally mediated effects of the drug that counterbalance the adverse suppression in insulin sensitivity.

DCCR treatment appears to be associated with short term increases in glucose but longer term treatment is not associated with improved 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 hypoglycemic and insulin sensitive.

REFERENCES