Exendin-(9-39): Investigational Drug for the Treatment of Hyperinsulinism

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**Exendin-(9-39)**

- Derived from exendin-4 - - Exenatide (Byetta®) approved for type 2DM
- Blocks the effects of the incretin hormone Glucagon-like peptide-1 (GLP-1)
- GLP-1 is secreted in response to ingested nutrients and is a potent stimulator of insulin secretion
Role of GLP-1 in the pathophysiology of hyperinsulinism

- Need for exogenous glucose to maintain euglycemia decreases when babies with hyperinsulinism are kept without food for a few hours
  - Suggest an enhanced "incretin" effect in hyperinsulinism
The Incretin Effect

In - cre - tin
Intestine  Secretion  Insulin

N. McIntyre  et al. Lancet 2:20-21, 1964
Incretin Hormones

- Gut-derived peptides that increase glucose-stimulated insulin secretion
- Glucose-dependent insulinotrophic polypeptide (GIP) first incretin isolated (1970)
- Glucagon-like peptide-1 (GLP-1) more potent and physiologically important incretin
- GIP and GLP-1 account for 90% of incretin response
Glucose lowering effects of GLP-1

- GLP-1 is secreted in response to ingested nutrients and is a potent stimulator of insulin secretion
- GLP-1 has other glucose lowering effect including: inhibition of glucagon, gastric emptying and appetite
- GLP-1 acts through a receptor in the pancreatic beta cells to stimulate insulin secretion
- Therapies targeting the GLP-1 receptor are now approved for the treatment of type 2 diabetes
Exendin-(9-39) inhibits amino acid-stimulated insulin secretion in HI islets

P=0.001

P=0.003

Calabria, Li, Gallagher, Stanley, De León. *Diabetes*, 2012
Preclinical proof-of-concept studies with Exendin-(9-39)

- Exendin-(9-39) prevents fasting hypoglycemia in mouse model of $K_{ATP}$ hyperinsulinism

Pilot Clinical Proof-of-Concept Study

- Pilot study to examine the effect of exendin-(9-39) on fasting blood glucose of subjects with $K_{ATP}$ Hyperinsulinism

- **Methods:**
  - 9 subjects
  - Randomized, open-label, two-period complete crossover
  - Fasted subjects received an intravenous infusion of exendin-(9-39) (100, 300 and 500 pmol/kg/min) or vehicle for 6 hours in 2 consecutive days (in random order)
  - Primary outcome: Blood glucose levels

www.Clinicaltrials.gov: NCT00571324
# Subject Characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>Mutation (ABCC8)</th>
<th>Pancreatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>F</td>
<td>delF1388 + 3992-9 G&gt;A</td>
<td>85%</td>
</tr>
<tr>
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<td>44</td>
<td>M</td>
<td>delS1387*</td>
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</tr>
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<td>M</td>
<td>S408P*</td>
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<td>4</td>
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<td>F</td>
<td>3992-9 G&gt;A</td>
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<tr>
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<td>F</td>
<td>R1353H*</td>
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<tr>
<td>9</td>
<td>37</td>
<td>F</td>
<td>R521Q*</td>
<td>None</td>
</tr>
</tbody>
</table>

*Dominant*
Exendin-(9-39) increases fasting blood glucose

Calabria and De León. Diabetes, 2012
Exendin-(9-39) suppresses plasma insulin

Calabria and De León. *Diabetes*, 2012
Exendin-(9-39) prevents protein-induced hypoglycemia in $K_{ATP}$H1

<table>
<thead>
<tr>
<th></th>
<th>Vehicle (n=8)</th>
<th>Exendin-(9-39) (n=8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose nadir (mean, SD) mg/dL</td>
<td>55.1 (2.9)</td>
<td>70.4 (5.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>AUC (mean, SD) mg/dL*min</td>
<td>12559 (2097)</td>
<td>18675 (4230)</td>
<td>0.008</td>
</tr>
<tr>
<td>% Subjects &lt; 60 mg/dL (n=8)</td>
<td>87.5%</td>
<td>37.5%</td>
<td>0.046</td>
</tr>
<tr>
<td>% Subjects &lt; 50 mg/dL (n=8)</td>
<td>37.5%</td>
<td>0%</td>
<td>0.083</td>
</tr>
</tbody>
</table>
Safety Profile

- Excellent safety profile in preclinical studies
- Well tolerated
- No significant adverse events in participating children
Summary:

- GLP-1 and its receptor may play a role in the pathophysiology of \( K_{\text{ATP}} \)HI.

- In mouse and human \( K_{\text{ATP}} \)HI pancreatic islets, exendin-(9-39) inhibits insulin secretion.

- In adolescents and adults with \( K_{\text{ATP}} \)HI, exendin-(9-39) increases fasting plasma glucose.

- Exendin-(9-39) prevents protein-induced hypoglycemia in children with \( K_{\text{ATP}} \)HI.

- Proof-of-concept single dose escalation study in neonates ongoing.
Acknowledgements

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