28-Day Dosing with Avexitide Improves Hyperinsulinemic Hypoglycemia in Patients with Severe, Refractory Post-Bariatric Hypoglycemia:

The PREVENT Study

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Disclosures

I have consulted for XOMA and Xeris Pharmaceuticals and have been a site investigator for Eiger Pharmaceuticals.
Sample Case

• 50 year-old woman with obesity (BMI 45 kg/m²)
• Underwent Roux-en-Y gastric bypass and lost nearly 100 pounds within a year
• New onset postprandial hypoglycemia 2 years after surgery
• Severe episodes leading to confusion, visits to the ED and no longer able to drive or work due to risks to self and/or others
• Prior workup included
  - 75 gram oral glucose tolerance test: glucose of 87 mg/dL at baseline, 33 mg/dL at 120 min with confusion
  - Unremarkable CT abdomen
  - Normal ACTH stimulation test
  - No focal hypersecreting insulin producing lesion on selective arterial calcium stimulation test
Post-Bariatric Hypoglycemia (PBH)

- Normal fasting glucose
- Hypoglycemia 1-3 h after eating
- Often debilitating
- Glucose <55 mg/dL may trigger neuroglycopenic symptoms (e.g. dizziness, blurred vision, syncope)
- May impact 5-10%\textsuperscript{1,2} of Roux-en-Y patients
- No approved pharmacotherapy; many patients refractory to diet and off-label meds

\textsuperscript{1} Gribsholt et al. JAMA 2016; \textsuperscript{2} Lee et al. Obesity 2015
Etiology of PBH: Critical Role of GLP-1

Altered Nutrient Transit Triggers an Exaggerated Incretin Effect via GLP-1

ALTERED NUTRIENT TRANSIT POST ROUX-EN-Y GASTRIC BYPASS → HYPERSECRETION OF GLP-1 → HYPERSECRETION OF INSULIN → SYMPTOMATIC HYPOGLYCEMIA

GLP-1 secretion increased by 10-15X

Autonomic
- Sweating
- Shaking
- Palpitations
- Hunger

Neuroglycopenic
- Blurred vision
- Confusion
- Drowsiness
- Odd behavior
- Speech difficulty
- Incoordination
- Dizziness
- Inability to concentrate

Craig et al. Diabetes, Obesity and Metabolism 2018
Pharmacologic Blockade of GLP-1 Receptor
A Targeted Therapeutic Approach Reduces Hyperinsulinemia and Prevents Hypoglycemia

Avexitide

- 31 amino acid fragment of exenatide (registered name for Byetta)
- A GLP-1 receptor antagonist
- Used as investigational agent
- >300 patients reported dosed worldwide

PREVENTION OF HYPOGLYCEMIA

1 Craig et al. Diabetes, Obesity and Metabolism 2018; 2 Clinicaltrials.gov
**Placebo-Controlled Crossover IV Infusion Study**

8 Patients with PBH Received Placebo or Avexitide Infusion During OGTT Provocation

Avexitide infusion:
- 100% reversal of hypoglycemia
- Increased the plasma glucose nadir by 70% (matching non-surgical controls)
- Ameliorated hyperinsulinemia despite earlier and equally high peak plasma glucose concentrations
- Did not alter fasting insulin or insulin clearance

Patients rescued at glucose ≤50 mg/dL
A Phase 2, Multicenter, Randomized, Placebo-Controlled Cross-over Study to Assess the Efficacy and Safety of Avexitide in Patients with PBH
Primary Efficacy Endpoint: Magnitude of postprandial hypoglycemia defined as the plasma glucose nadir during MMTT provocation
## Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>30 BID – 60 QD</th>
<th>60 QD – 30 BID</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.5 (7.45)</td>
<td>43.4 (12.04)</td>
<td>44.3 (10.04)</td>
</tr>
<tr>
<td>Sex, # female (%)</td>
<td>8 (100)</td>
<td>10 (100)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.01 (3.06)</td>
<td>29.28 (4.87)</td>
<td>29.61 (4.07)</td>
</tr>
<tr>
<td>History of LOC due to PBH, # (%)</td>
<td>3 (37.5)</td>
<td>5 (50.0)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>History of Seizure due to PBH, # (%)</td>
<td>0 (0.0)</td>
<td>2 (20.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>History of hospitalization due to PBH, # (%)</td>
<td>1 (12.5)</td>
<td>2 (20.0)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Frequency of Symptoms of Hypoglycemia</td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>Daily, # (%)</td>
<td>3 (37.5)</td>
<td>4 (40.0)</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Weekly, # (%)</td>
<td>5 (62.5)</td>
<td>5 (50.0)</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>Following medical nutrition therapy, # (%)</td>
<td>8 (100.0)</td>
<td>10 (100.0)</td>
<td>18 (100.0)</td>
</tr>
<tr>
<td>History of pharmacotherapy for PBH, # (%)</td>
<td>5 (63.0)</td>
<td>10 (100.0)</td>
<td>15 (83.0)</td>
</tr>
<tr>
<td>History of surgery for PBH, # (%)</td>
<td>1 (5.6)</td>
<td>2 (11.1)</td>
<td>3 (16.7)</td>
</tr>
</tbody>
</table>

Values represent mean (SD) or number (%) as applicable
Metabolic Responses to MMTT

Significantly Reduced Hyperinsulinemic Hypoglycemia; Reduced Requirement for Rescue

True placebo nadir likely lower due to higher rate of rescue:

Rescue was administered at the earlier of:

- Glucose ≤ 50 mg/dL + neuroglycopenia

OR

- Glucose ≤ 40 mg/dL +/- neuroglycopenia

**P<0.01

***P<0.001
## Clinical Improvements in the Outpatient Setting

Reduction in Rates\(^1\) of Hypoglycemia, Severe Hypoglycemia and Rescue as Collected by SBGM + eDiary

<table>
<thead>
<tr>
<th>Rate</th>
<th>Placebo</th>
<th>30 mg BID</th>
<th>60 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of Hypoglycemia(^2)</td>
<td>4.03</td>
<td>2.81</td>
<td>1.56</td>
</tr>
<tr>
<td>Change from Placebo</td>
<td>NA</td>
<td>-1.24 ((p=0.0720))</td>
<td>-2.51 ((p=0.0014))</td>
</tr>
<tr>
<td>Rate of Severe Hypoglycemia(^3)</td>
<td>2.36</td>
<td>1.45</td>
<td>0.99</td>
</tr>
<tr>
<td>Change from Placebo</td>
<td>NA</td>
<td>-0.89 ((p=0.0267))</td>
<td>-1.35 ((p=0.0020))</td>
</tr>
<tr>
<td>Rate of Rescue(^4)</td>
<td>4.87</td>
<td>3.34</td>
<td>1.83</td>
</tr>
<tr>
<td>Change from Placebo</td>
<td>NA</td>
<td>-1.60 ((p=0.0614))</td>
<td>-3.13 ((p=0.0013))</td>
</tr>
</tbody>
</table>

\(^1\) Rate is defined as number of episodes in a 14 day period

\(^2\) Hypoglycemia is defined as hypoglycemia symptoms confirmed by SBGM concentrations of <70 mg/dL

\(^3\) Severe hypoglycemia is defined as neuroglycopenic symptoms confirmed by SBGM concentrations <55 mg/dL

\(^4\) Rescue is defined as requiring self- or third-party administration of oral or g-tube intake to prevent or treat hypoglycemia
Glycemic Improvements in the Outpatient Setting

Reduction in Diurnal\(^1\) % Time and # of Episodes\(^2\) <70 and <55 mg/dL as Measured by CGM

\(^1\)Diurnal is defined as 8AM to midnight.

\(^2\)Episodes are per 14-day period, and are defined as CGM values sustained below threshold for at least 10 min within a 3-hour period.
SAFETY AND TOLERABILITY

- Avexitide was well-tolerated
- No treatment-related SAEs and no participant withdrawals
- One non-treatment related SAE
- AEs were typically mild to moderate in severity and transient
- Most common AEs were injection site bruising, nausea, headache
  - All occurred with higher frequency during placebo than active treatment
- Low occurrence of development of anti-drug antibodies (ADA)
  - 1 of 18 participants showed low positive titers for ADA
  - No associated AEs and no apparent effect on efficacy
CONCLUSIONS

• GLP-1 plays a critical role in mediating hyperinsulinemic hypoglycemia in PBH

• Avexitide is a targeted therapeutic approach with POC demonstrated in 4 clinical trials

• 28-days of treatment in outpatient setting demonstrated clinically meaningful improvements:
  o Reductions in the magnitude of postprandial hyperinsulinemic hypoglycemia
  o Reductions in the rates of hypoglycemia and severe hypoglycemia
  o Reductions in the rates of rescue
  o Reductions in the percent time in hypoglycemia and number of hypoglycemic episodes

• Avexitide was well-tolerated, with no significant safety concerns

• Avexitide has shown consistent benefits across clinical and metabolic parameters
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