Intranasal Administration of Exenatide in Patients with Type 2 Diabetes: Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability

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Presenter Disclosure Information

Erich Blase

• Stockholder: Amylin Pharmaceuticals, Inc.
• Employee: Amylin Pharmaceuticals, Inc.
Introduction

• Exenatide, an incretin mimetic, has multiple mechanisms of action that improve glucose control in patients with type 2 diabetes:
  – Enhancement of glucose-dependent insulin secretion
  – Suppression of inappropriately elevated postprandial glucagon secretion
  – Slowing of gastric emptying
  – Reduction of food intake

• Exenatide is currently administered twice daily via subcutaneous injection prior to major meals

• Intranasal delivery of exenatide
  – Non-invasive mealtime dosing
Objective

- Examine the pharmacokinetics, pharmacodynamics, safety, and tolerability of intranasal administration of exenatide in patients with type 2 diabetes using at least one OAD
**Study Design**

- Single-blind, dose-escalation, placebo-controlled study of intranasal administration of exenatide in subjects with type 2 diabetes
  - Single dose delivered (one to three 100-μL nasal sprays)
  - Standardized breakfast given after medication
  - Blood samples prior to and during the 8 hours following medication

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening</th>
<th>Treatment (visits occurred 2-8 days apart; 28 day maximum duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Dose (n=12)</td>
<td>Screening</td>
</tr>
<tr>
<td>1</td>
<td>Screening</td>
<td>Saline IN 30 min Exen SC 5 mcg</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Placebo IN</td>
</tr>
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<td>3</td>
<td></td>
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<td>6</td>
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<tr>
<td>7</td>
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Abbreviations: IN = intranasal; SC = subcutaneous
Study Design

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<td>2</td>
</tr>
<tr>
<td>Low Dose Group (n=12)</td>
<td>Screening</td>
<td>Saline IN ↓ 30 min ↓ Exen SC 5 mcg</td>
</tr>
<tr>
<td>High Dose Group (n=8)</td>
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Abbreviations: IN = intranasal; SC = subcutaneous
## Demographics and Baseline Characteristics

**ITT Population. Data are mean ± SD, except for sex.**

<table>
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<th>Characteristics</th>
<th>All subjects (N=20)</th>
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<tr>
<td>Sex, male/female (%)</td>
<td>65/35</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55 ± 9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>93 ± 12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31 ± 3</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.1 ± 1.3</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>156.4 ± 34.6</td>
</tr>
<tr>
<td>Duration of diabetes (y)</td>
<td>9 ± 8</td>
</tr>
</tbody>
</table>

*ITT Population. Data are mean ± SD, except for sex.*
Disposition

Total Enrolled (N=20)

Low Dose Cohort
- Enrolled (N=12)
  - Intent-to-Treat (N=12)
    - Withdrew (AE) (N=1)
    - Evaluable (N=11)

High Dose Cohort
- Enrolled (N=8)
  - Intent-to-Treat (N=8)
    - Withdrew (AE) (N=2)
    - Evaluable (N=6)
Pharmacokinetic Results

Plasma Exenatide (pg/mL)

Time (min)

- 60 mcg IN
- 200 mcg IN
- 600 mcg IN
- 800 mcg IN
- 1200 mcg IN
- 1800 mcg IN

0 60 120 180 240 300 360 420 480
0 500 1000 1500 2000 2500 3000 3500
Pharmacokinetic Results

Plasma Exenatide (pg/mL) vs Time (min)

- 600 mcg IN
- 5 mcg SC
Serum Glucose

Exenatide followed by breakfast

Time (min)

Serum Glucose (mg/dL)
Serum Glucose

Exenatide followed by breakfast

Time (min)

Serum Glucose (mg/dL)

Placebo
5 mcg SC
Serum Glucose

Exenatide followed by breakfast
Serum Glucose

Exenatide followed by breakfast
Serum Glucose

Exenatide followed by breakfast

Time (min)

Serum Glucose (mg/dL)

Placebo
5 mcg SC
1800 mcg IN
1200 mcg IN
800 mcg IN
600 mcg IN
Serum Glucose

Exenatide followed by breakfast
Serum Glucose

- Placebo
- 5 mcg SC
- 1800 mcg IN
- 1200 mcg IN
- 800 mcg IN
- 600 mcg IN
- 200 mcg IN
- 60 mcg IN

Exenatide followed by breakfast.
Serum Glucose and Insulin

Serum Glucose

- Exenatide followed by breakfast

Serum Insulin

- Exenatide followed by breakfast

Exenatide

Placebo

600 mcg IN

0 30 60 90 120 150 180 210 240

Time (min)
Safety and Tolerability

• The most frequent adverse events with intranasal exenatide administration were nausea (6 patients) and vomiting (5 patients)
  – Nausea and vomiting occurred at doses ≥ 600 mcg
  – Nausea also occurred in 1 patient with placebo

• Sneezing occurred with intranasal administration of exenatide (2 patients) and placebo (1 patient)

• Intranasal administration of exenatide was generally well tolerated with no serious adverse events or hypoglycemic events
Conclusion

• Intranasal administration of exenatide in patients with type 2 diabetes was well tolerated and resulted in:
  – Therapeutic plasma exenatide concentrations
  – Enhanced glucose-dependent insulin secretion
  – Improved PPG control

• These data support the further development of intranasal exenatide delivery in the range of 600 mcg as a non-invasive treatment option for patients with type 2 diabetes
Pharmacokinetic Results

AUC<sub>0-tlast</sub> (pg·h/mL) vs Exenatide IN Dose (mcg)