Once-Weekly Exenatide in Youth with Type 2 Diabetes: A Pivotal Phase III Randomized Study

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Disclosures


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Background

- The incidence and prevalence of type 2 diabetes in children and adolescents is increasing, particularly among minority racial and ethnic groups: this is partially due to the global epidemic of childhood obesity.1–4
- The few available approved pharmacologic treatments—metformin, insulin, and liraglutide—have limitations.1,3,5–7
- To date, no once-weekly injectable drug has been approved by the United States and European regulatory agencies for use in youth with type 2 diabetes.
- Exenatide, a glucagon-like peptide-1 receptor agonist, is the first drug approved in adults with type 2 diabetes that can be administered once weekly.8,9
- This study evaluated the efficacy and safety of once-weekly exenatide injections for the treatment of children and adolescents with type 2 diabetes.

Study Design

Parallel-group, Phase III study

Randomized

Exenatide 2 mg

Placebo

5:2

United States
14 sites

Mexico
5 sites

Hungary
3 sites

Israel
3 sites

Bulgaria
1 site

Kuwait
1 site

Hungary
5 sites

United States
14 sites

Israel
3 sites

Bulgaria
1 site

Kuwait
1 site
Study Design (cont’d)

• 24 week, double-blind, placebo-controlled assessment period followed by a 28-week, open label extension period.

• Youth with type 2 diabetes aged between 10 and <18 years with HbA1c 6.5% to 11% for participants not taking insulin or a sulfonylurea and 6.5% to 12.0% for participants taking insulin or a sulfonylurea.

• Randomization was stratified by HbA1c at screening (<9.0% or ≥9.0%).

• No titration was performed when starting the 2-mg once-weekly dose of exenatide; dosing adjustments during the trial were prohibited.

• **Primary endpoint:** change in HbA1c from baseline to week 24 in the exenatide and placebo groups.
Results – Primary Endpoint

• 83 participants were randomized (once weekly exenatide, 59; placebo, 24) and entered the double-blind controlled assessment period
  – of these, 72 (86.7%) completed 24 weeks of treatment (once-weekly exenatide, 49; placebo, 23).

Change in HbA1c (%) from Baseline to Each Visit Between Baseline and Week 24 Using a Mixed Model with Repeated Measures Analysis; Least Squares Mean (Evaluable Analysis Set)

<table>
<thead>
<tr>
<th>Week</th>
<th>Exenatide (N=58)</th>
<th>Placebo (N=24)</th>
<th>2-sided P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.5</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>−0.1</td>
<td>0</td>
<td>0.033</td>
</tr>
<tr>
<td>8</td>
<td>−0.3</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>12</td>
<td>−0.4</td>
<td>0</td>
<td>0.012</td>
</tr>
<tr>
<td>18</td>
<td>−0.5</td>
<td>0</td>
<td>0.017</td>
</tr>
<tr>
<td>24</td>
<td>−0.6</td>
<td>0</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Between group LS mean difference at week 24: −0.85
95% CI: −1.51, −0.19
P=0.012
Results – Secondary Endpoints

Proportions of Participants Meeting HbA1c <7.0% at Week 24 and at Each Intermediate Visit

<table>
<thead>
<tr>
<th>Week</th>
<th>Exenatide n</th>
<th>Placebo n</th>
<th>2-sided P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>54</td>
<td>24</td>
<td>0.085</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>24</td>
<td>0.009</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>23</td>
<td>0.008</td>
</tr>
<tr>
<td>18</td>
<td>47</td>
<td>23</td>
<td>0.019</td>
</tr>
<tr>
<td>24</td>
<td>48</td>
<td>22</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Results – Secondary Endpoints (cont’d)

**Fasting Plasma Glucose**

- **Exenatide**
  - N=58
  - LS mean: −5.2
  - LS mean change from baseline (mg/dL)
  - Between group LS mean difference: −21.6
  - 95% CI: −49.0, 5.7
  - P=0.119

- **Placebo**
  - N=24
  - LS mean: 16.5

**Body Weight**

- **Exenatide**
  - N=58
  - LS mean: −0.59

- **Placebo**
  - N=24
  - LS mean: 0.63

Between group LS mean difference: −1.22
95% CI: −3.59, 1.15
P=0.307
## Results – Safety

### Number (%) of Participants with Adverse Events – On Treatment Controlled Assessment Period (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Event</th>
<th>Exenatide (N=59)</th>
<th>Placebo (N=23)</th>
<th>Total (N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>36 (61.0)</td>
<td>17 (73.9)</td>
<td>53 (64.6)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>2 (3.4)</td>
<td>1 (4.3)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Any SAE with outcome of death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any AE related to treatment</td>
<td>15 (25.4)</td>
<td>5 (21.7)</td>
<td>20 (24.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>13 (22.0)</td>
<td>6 (26.1)</td>
<td>19 (23.2)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>8 (13.6)</td>
<td>1 (4.3)</td>
<td>9 (11.0)</td>
</tr>
<tr>
<td>Major</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minor</td>
<td>1 (1.7)</td>
<td>1 (4.3)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (13.6)</td>
<td>1 (4.3)</td>
<td>9 (11.0)</td>
</tr>
</tbody>
</table>
Conclusions

• This study demonstrated the superiority of once-weekly exenatide versus placebo in reducing HbA1c levels at week 24 in children and adolescents with type 2 diabetes.

• Once-weekly exenatide allowed a greater proportion of patients to achieve strict glycemic targets after 24 weeks of treatment.

• Improved glucose control was observed in conjunction with trends toward decreased fasting plasma glucose levels and reduced body weight.

• There were low rates of hypoglycemia despite insulin use, and good gastrointestinal tolerability even in the absence of titration of the exenatide dose when starting treatment.