STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 20-986/SE5-047
Drug Name: NovoLog (insulin aspart [rDNA origin] injection)
Indication(s):
- Treatment of patients (children and adults) with diabetes mellitus
- Subcutaneous infusion by external insulin pumps (children and adults)
- Intravenous administration

Applicant: Novo Nordisk
Date(s): Received 5/11/07; user fee (10 months) 3/14/08
Review Priority: Standard

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Keywords: NDA review, clinical studies
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This supplemental application provided the required clinical data to fulfill a pediatric postmarketing study commitment for the external insulin pump use (supplement S-003, letter dated December 21, 2001).

Study ANA-2181 was an open-label, randomized, parallel group, multicenter study of 16 weeks to assess external continuous subcutaneous infusion (CSII) of Insulin Aspart (NovoLog) versus Insulin Lispro (Humalog) in children and adolescents 3 to 18 years of age with Type 1 Diabetes who had HbA1c ≤ 10% at baseline.

The primary efficacy comparison was non-inferiority of aspart to insulin lispro in HbA1c change from baseline to Week 16 using a margin of 0.4%.

A total of 298 patients were randomized; 198 to Aspart and 100 to Lispro. 187 patients in the Aspart group and 91 in the Lispro group completed the study. The per protocol population included 252 (85%) of the randomized patients (172 Aspart and 80 Lispro). Table 1 displays the descriptive statistics of HbA1c. Table 2 displays the analysis of covariance (ANCOVA) results in the least squares mean (LSM) in HbA1c changes from baseline to week 16 for the full analysis set (FAS) using last observation carried forward (LOCF) to impute missing data. The upper confidence interval, 0.07% is less than the 0.4% non-inferiority margin which indicated the pump treatment of Aspart is non inferior to Lispro in HbA1c change from baseline (Table 2). ANCOVA results from the per protocol (PP) population were similar. Figure 1 displays the HbA1c values by visit using PP population, completers (187 Aspart and 91 Lispro).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline</th>
<th>Week 16</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspart</td>
<td>192</td>
<td>8.02 (0.94)</td>
<td>7.88 (0.93)</td>
<td>-0.13 (0.79)</td>
</tr>
<tr>
<td>Lispro</td>
<td>96</td>
<td>8.14 (0.85)</td>
<td>8.07 (0.85)</td>
<td>-0.08 (0.70)</td>
</tr>
</tbody>
</table>

Table 2 Least squares mean change from baseline in HbA1c (%) at Week 16 – ANCOVA* (LOCF)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>L SMean</th>
<th>StdErr</th>
<th>Lower CL</th>
<th>Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSULIN ASPART</td>
<td>192</td>
<td>-0.24</td>
<td>0.08</td>
<td>-0.40</td>
<td>-0.07</td>
</tr>
<tr>
<td>INSULIN LISPRO</td>
<td>96</td>
<td>-0.13</td>
<td>0.10</td>
<td>-0.33</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**ASPART** minus **LISPRO**

| ASPART** minus **LISPRO** | -0.10 | (0.09) | [-0.27 | 0.07] |

*ANCOVA model included treatment group and age group as fixed effects and Baseline HbA1c as covariate
1.2 Data Sources

Datasets are located at `\CDSESUB1\N20986\S_047\2007-05-11\m5\datasets\2181`

2. LABELING COMMENTS