U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

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
Biometrics Division:	DB 2
Statistical Reviewer:	Lee-Ping Pian, Ph.D.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Joanna K. Zawadzki, M.D.
Project Manager:	Rachel Hartford

Keywords: NDA review, clinical studies

Table of Contents

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 $HbA_{1c} \leq 10\%$ at baseline.

The primary efficacy comparison was non-inferiority of aspart to insulin lispro in HbA_{1c} 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 HbA_{1c}. Table 2 displays the analysis of covariance (ANCOVA) results in the least squares mean (LSM) in HbA_{1c} 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 HbA_{1c} change from baseline (Table 2). ANCOVA results from the per protocol (PP) population were similar. Figure 1 displays the HbA_{1c} values by visit using PP population. completers (187 Aspart and 91 Lispro).

Table 1 Mean change (SD) from baseline in HbA_{1c} (%) at Week 16 – FAS, LOCF

Treatment	N	Baseline	Week 16	Change
IAsp	192	8.02 (0.94)	7.88 (0.93)	-0.13 (0.79)
Lispro	96	8.14 (0.85)	8.07 (0.85)	-0.08 (0.70)

Table 2 Least squares mean change from baseline in HbA_{1c} (%) at Week 16 – ANCOVA* (LOCF)

Treatment	n	LSMean	StdErr	Lower CL	Upper CL
INSULIN ASPART	192	-0.24	0.08	-0.40	-0.07
INSULIN LISPRO	96	-0.13	0.10	-0.33	0.06
ASPART minus LISPRO		**-0.10**	**(0.09)**	**[-0.27**	**0.07]**

*ANCOVA model included treatment group and age group as fixed effects and Baseline HbA_{1c} as covariate

Figure 1 Mean HbA_{1c} (%) by visit - Completers

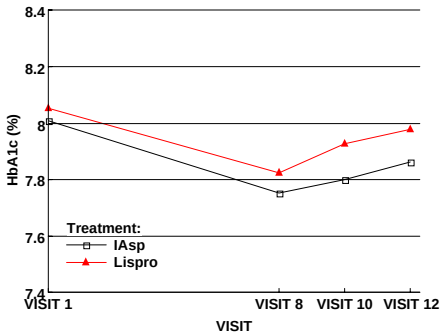
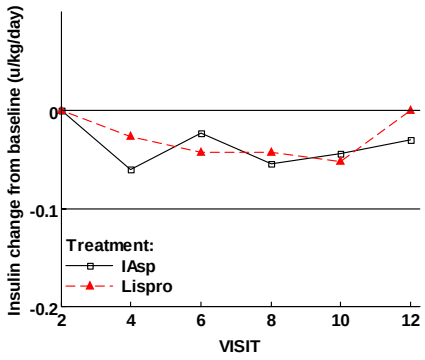


Figure 2 Mean insulin change from baseline by visit - Completers



1.2 Data Sources

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

2. LABELING COMMENTS