

CLINICAL REVIEW

Application Type	NDA 20-986
Submission Number	047
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Reviewer Name	Joanna K. Zawadzki, M.D.
Review Completion Date	February 26, 2008; revised March 12, 2008
Established Name	Insulin Aspart
Trade Name	NovoLog®,
Therapeutic Class	3031500 (insulin analog)
Applicant	Novo Nordisk, Inc.
Priority Designation	S
Formulation	Injection solution 3.5 mg insulin aspart (100 Units/ml) 10 ml vial for use in external insulin pumps
Dosing Regimen	Dosing is adjusted individually for each patient
Indication	Treatment of Diabetes Mellitus
Intended Population	Pediatric Patients with Type 1 Diabetes who use external insulin pumps
Related IND	IND 48,231
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Statisticians	Lee Pian, Ph.D., Reviewer J. Todd Sahlroot, Ph.D., Team Leader
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Disclaimer: Many of the tables are cited from the NDA supplement and retain the original table numbers.

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of this efficacy supplement. Specifically, this reviewer recommends approval of the following:

- the pediatric indication of continuous subcutaneous insulin infusion (CSII) by external insulin pump for treatment of hyperglycemia in patients with type 1 diabetes mellitus;
- the prescribing information for NovoLog insulin analog (Insulin Aspart (Asp) [rDNA origin]) in the revised Physician Labeling Rule (PLR) format¹, pending agreement with FDA modifications.
- a waiver for children ages three and younger, as there are inadequate number of children in this age group for study, and efficacy and safety data are not expected to differ from those observed in older children.

Additional Recommendation Regarding Pediatric Intravenous Administration of NovoLog®

The intravenous indication for NovoLog was based on an adult pharmacokinetic pharmacodynamic study and it was approved on October 21, 2005. The pediatric intravenous indication was not specifically mentioned in the approval letter for the intravenous indication. In fact, that letter stated the following:

“All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.”

Presumably the last sentence referred to the original pediatric subcutaneous indication for aspart, which was approved on September 13, 2004

Recommendation:

This reviewer recommends that we waive the requirement for the pediatric intravenous study. There is no physiologic reason to suspect intravenous insulin would act differently in the pediatric population. Intravenous insulin should be administered in a hospital setting by trained personnel, so the 'in use' aspect that is evaluated in clinical studies should also not differ. This topic was discussed with members of the FDA Pediatric Review Committee. They concurred that the product is already appropriately labeled in the pediatric population and further pediatric

¹ 21CFR201.57, Revised as of April 1, 2006.

studies for the pediatric indication are not needed. The Pediatric Review Committee has proposed the following language:

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This drug product (NovoLog®) is fully labeled for use in all appropriate pediatric populations. Therefore, no additional pediatric studies are needed at this time.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Other than the modifications in the prescribing information, no other specific risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No new Phase 4 commitments are requested.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The main focus of this supplemental NDA application is the conversion of the prescribing information into the Physician Labeling Rule (PLR) format. The NovoLog® insulin analog is the first insulin analog in the PLR format. [REDACTED]

Insulin aspart (NovoLog® or NovoRapid®, Novo Nordisk) is an analog of human insulin, in which the amino acid proline has been replaced by aspartic acid in the B-chain position 28 so that the insulin molecule is more monomeric, has less of a tendency to form hexamers, and can

be absorbed more rapidly than human insulin after subcutaneous injection. Insulin aspart subcutaneous injection, [rDNA origin] (NDA 20-986) was approved for the control of hyperglycemia in adult patients with type 1 diabetes mellitus on June 7, 2000 and in pediatric patients on September 13, 2005. Insulin aspart was approved for continuous subcutaneous insulin injection (CSII) by external pumps in adult patients with type 1 diabetes on December 21, 2001 (NDA 20-986 Supplement 003). Since April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred². As a fulfillment of this requirement, Novo Nordisk has submitted data from two pediatric studies in patients with type 1 diabetes who are using external insulin pump therapy.

Novo Nordisk has submitted data from two post-marketing pediatric Phase 3b studies, Study ANA-2181 and Study ANA 1507, which evaluated the use of continuous subcutaneous insulin infusion (CSII) in 298 children ages 3-18 years and 61 children age less than 7 years, respectively, to complete the postmarketing study commitment under the Pediatric Research Equity Act (PREA). Study ANA-2181 was an open label, randomized study that compared CSII therapy with insulin aspart to CSII therapy with another insulin analog, insulin lispro (Humalog®, Eli Lilly). On the basis of this study, Novo Nordisk has proposed the following additional section in the *Clinical Studies* section of the PLR prescribing information:



Study ANA-1507 was also an open label study, but one-third of the patients were assigned to pump therapy and the remaining two-thirds of patients were randomized to subcutaneous insulin aspart or insulin lispro therapy. Because Study ANA-1507 was not fully randomized, the data from it are considered supportive in the safety analysis.

The submission of an efficacy supplement for this NDA requires the conversion of the prescribing information for insulin aspart to the revised Physician Labeling Rule (PLR) format³. The FDA-revised label is attached to this review. The conversion of the label to the PLR format was the major effort in this NDA supplement review.

1.3.2 Efficacy

The primary efficacy comparison was non-inferiority of CSII of aspart to insulin lispro in HbA_{1c} change from baseline to Week 16 using a margin of 0.4%.

The data for the primary efficacy comparison were reviewed by the FDA statistician, Lee Piang, Ph.D.

Table 2 displays the mean HbA_{1c} at baseline and week 16 and mean HbA_{1c} change from baseline.

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 bound of the 95% confidence interval, 0.07% is less than the 0.4% non-inferiority margin which indicated the pump treatment with insulin aspart is non inferior to insulin lispro in HbA_{1c} change from baseline (Table 2). ANCOVA results from the per protocol (PP) population were similar.

Table 2. Mean change (SD) from baseline in HbA_{1c} (%) at Week 16

(full analysis set, last observation carried forward)

Treatment	N	Baseline	Week 16	Change
aspart	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 3. Least squares mean change from baseline in HbA_{1c} (%) at Week 16 – ANCOVA* (LOCF)

Treatment	LSMean	StdErr	Lower CL	Upper CL
aspart	-0.24	0.08	-0.40	-0.07
lispro	-0.13	0.10	-0.33	0.06
Aspart minus lispro	-0.10	(0.09)	[-0.27	0.07]

³ 21CFR201.57, Revised as of April 1, 2006.

*ANCOVA (analysis of covariance) model included treatment group and age group as fixed effect and Baseline HbA_{1c} as covariate

1.3.3 Safety

Safety assessments in Study ANA-2181 included reports of adverse events and episodes of hypoglycemia, hyperglycemia, and diabetic ketoacidosis; physical examination findings; laboratory test results for hematology, blood chemistry, and insulin antibody binding. No deaths were reported during the clinical studies. No significant differences in rates of hypoglycemia with central nervous system symptoms requiring assistance of a third person were observed between the aspart and lispro treatment groups. No significant differences in rates of diabetic ketoacidosis or infusion site reactions were observed. Data observed in the pediatric pump studies were similar to data observed in adult pump studies.

1.3.4 Dosing Regimen and Administration

Insulin doses, including those of insulin analogs such as aspart (NovoLog®), must be individualized – whether administered by multiple subcutaneous doses or by continuous subcutaneous insulin infusion.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Insulin aspart (NovoLog® or NovoRapid®, Novo Nordisk) is an analog of human insulin, in which the amino acid proline has been replaced by aspartic acid in the B-chain position 28 so that the insulin molecule is more monomeric, has less of a tendency to form hexamers, and can be absorbed more rapidly than human insulin after subcutaneous injection. Insulin aspart injection, [rDNA origin] (NDA 20-986) was approved for the control of hyperglycemia in adult patients with type 1 diabetes mellitus on June 7, 2000 and in pediatric patients on September 13, 2005. Insulin aspart was approved for continuous subcutaneous insulin injection (CSII) by external pumps in adult patients with type 1 diabetes on December 21, 2001 (NDA 20-986 Supplement 003). Since April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred⁴. As a fulfillment of this requirement, Novo Nordisk has submitted data from two pediatric studies in patients with type 1 diabetes who are using external insulin pump therapy. Insulin aspart has also been approved for intravenous use in October 21, 2005 (NDA 20-986 Supplement 032).

2.2 Currently Available Treatment for Indications

Currently available recombinant DNA human insulins and insulin analogs are available for the treatment of type 1 and type 2 diabetes mellitus and gestational diabetes. Animal-derived (beef and/or pork) insulins are no longer marketed. A list of types of human insulins and insulin analogs and adult and pediatric indications are included in the table below. Of note, insulin lispro has been approved for adult continuous subcutaneous insulin infusion (CSII) pump therapy but not specifically for pediatric continuous subcutaneous insulin infusion (CSII) pump therapy.

⁴ 63 FR 66632 <http://www.fda.gov/ohrms/dockets/98fr/042401a.htm> accessed February 26, 2008.

Table 4. Approval of Insulins and Insulin Analogs for Adult and Pediatric Use⁵

Insulin Product	Indications	Adult Approval	Pediatric Approval
Aspart (NovoLog, NovoNordisk)	<ul style="list-style-type: none"> • subcutaneous • continuous subcutaneous insulin infusion • intravenous 	6/7/2000 12/21/01 10/21/05	9/13/05 Pending this review Recommend waiver
Detemir (Levemir, NovoNordisk)	<ul style="list-style-type: none"> • subcutaneous 	6/16/2005	?date
Glargine (Lantus, Sanofi Aventis US)	<ul style="list-style-type: none"> • subcutaneous 	4/20/2000	?date
Glulisine (Apidra, Sanofi Aventis US)	<ul style="list-style-type: none"> • subcutaneous • continuous subcutaneous insulin infusion • intravenous 	4/16/04 4/16/04 4/12/07	Not approved
Lispro (Humalog, Lilly)	<ul style="list-style-type: none"> • subcutaneous • continuous subcutaneous insulin infusion 	6/14/1996 6/2/04	4/4/00
Human recombinant insulin (Humulin R and N, Lilly)	<ul style="list-style-type: none"> • subcutaneous 	10/28/1982	
Human recombinant insulin (Novolin R, Novo Nordisk)	<ul style="list-style-type: none"> • subcutaneous 	6/25/1991	
Human recombinant insulin (Novolin N, Novo Nordisk)	<ul style="list-style-type: none"> • subcutaneous 	7/1/1991	
Human recombinant (Exubera, Pfizer)	<ul style="list-style-type: none"> • inhaled 	1/27/2006	Not approved

⁵ Drugs@FDA. The most recent available labeling information is cited; accessed 11/28/06

2.3 Availability of Proposed Active Ingredient in the United States

Insulin aspart is available in the United States.

2.4 Presubmission Regulatory Activity

Novo Nordisk had submitted a pediatric plan for the use of the insulin analog NovoLog® (aspart) in external insulin pumps (5/06/02) and a revised pediatric plan (8/18/03). The applicant had initially proposed a 16-week study in 94 children ages 6-17 with DM1 and at least 3-month use of a pump in a 3:2 randomization to aspart and lispro (Humalog). The primary FDA recommendation was the use of buffered human insulin as a control, as lispro has not been approved for pump use. A 3-arm trial was suggested as an option. The sponsor stated that buffered human insulin was not an appropriate control, as rapid acting insulin analogs were the standard of care in children and adolescents, including in external insulin pump therapy.

The applicant submitted a revised draft synopsis, which incorporated the FDA recommendations (other than the selection of the comparator), for an open-label, randomized 16-week study in 250 children (ages 2-18) with type 1 diabetes mellitus and HbA1c < 12% and at least 3 months of prior pump therapy to be randomized 1:1 to external insulin pump therapy with aspart or lispro. The primary objective was to demonstrate the non-inferiority of aspart treatment to lispro, as measured by HbA1c. The non-inferiority margin of 0.4% in HbA1c change, 80% power, 1-side alpha level of 0.025, and a drop-out rate of 20% were used to calculate the sample size.

Novo Nordisk had announced the discontinuation of Velosulin® BR buffered regular human insulin, effective approximately 4/30/04. This was the only marketed buffered regular human insulin. At that time, Velosulin buffered insulin and NovoLog® (aspart) were the only insulin products approved for pump use. Humalog® (lispro) was approved for pump use on June 2, 2004.

The main FDA concern was the use of lispro insulin analog as the comparator, as lispro had not yet been approved for use in external insulin pump therapy. Most patients with Type 1 diabetes mellitus were using the rapid acting insulin analogs. However, FDA had sent comments to the applicant indicating that approval of NovoLog insulin for pump therapy in the pediatric population should be based on a comparison to an approved insulin for pump use. Velosulin® buffered insulin was the only other insulin approved for pump therapy, and this study would be the first pediatric study. The planned discontinuation of manufacture of Velosulin buffered insulin, which was recommended as a comparator in a 2-arm or 3-arm design, complicated this recommendation. FDA noted that “Though a comparison between aspart and lispro may provide clinical information, it is unlikely that such a study would result in a claim.” in a comment sent to Novo Nordisk on December 19, 2003.

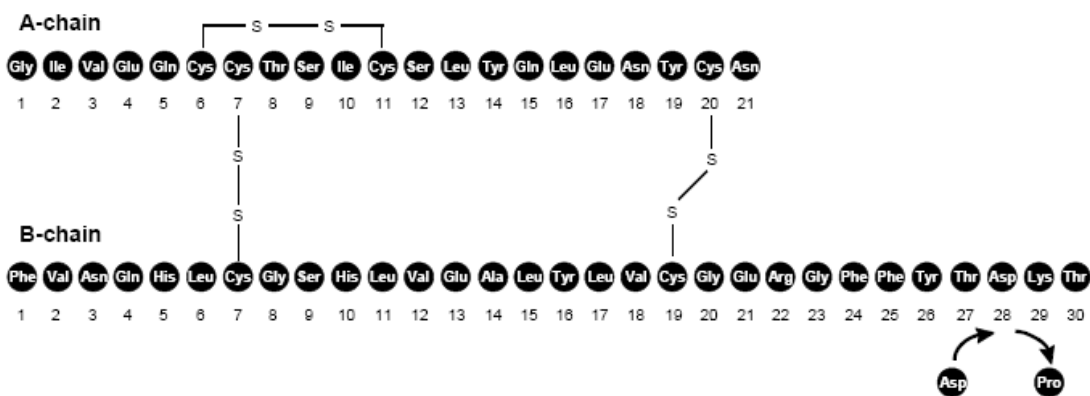
In vitro studies submitted [redacted] resulted in a significant under delivery of insulin on day one with the MiniMed pumps. Thus a comparison to lispro in the MiniMed pump could cause a potential bias, as there would be lower rates of hypoglycemia and lower efficacy. Good glycemic control would be expected three months after external pump therapy initiation; maintenance of good glycemic control would be expected during the 16-week study.

Novo Nordisk did not initiate Study ANA-2181 until lispro (Humalog®) had been approved for continuous subcutaneous insulin infusion by external pump in the adult type 1 diabetes population (6/2/04). Of note, Velosulin BR (buffered insulin recombinant human insulin) was approved July 19, 1999 for use in external pumps in a study of 20 patients with type 1 diabetes ages 24-55. No insulin or insulin analog has been previously approved for use in pediatric patients with type 1 diabetes using continuous subcutaneous insulin infusion pump therapy.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Insulin aspart (NovoLog®, Novo Nordisk) is an analog of human insulin, in which the amino acid proline has been replaced by aspartic acid in the B-chain position 28. It is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) as the production organism. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8. The structural formula is indicated below:



No new chemistry data were submitted in this supplement.

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3.2 Animal Pharmacology/Toxicology

No new toxicology data were submitted in this supplement.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This efficacy supplement was submitted electronically to the Electronic Document Room (EDR). The submissions were accessed at the following addresses:

\\CDSESUB1\N20986\S_047\2007-05-11

\\CDSESUB1\N20986\S_047\2007-08-08 patent info

\\CDSESUB1\N20986\S_047\2007-08-29 labeling

<\\CDSESUB1\NONECTD\3166888> requested tables submitted 101007 SE5 BZ

<\\CDSESUB1\NONECTD\3863910> proposed PLR submitted 111207 SE5 BL

<\\CDSESUB1\EVSPROD\NDA020986\0000> submitted 011608

<\\Cdsub1\evsprod\NDA020986\0003\m1\us> proposed/revised labeling - response to FDA labeling

4.2 Tables of Clinical Studies

Table 1–1 Trial Characteristics–Insulin Aspart Paediatric CSII Trials

Trial ID	Design	Treatment	Primary Endpoint	Subjects
Pivotal Trial in Children and Adolescents (3 to 18 Years of Age)				
ANA-2181	OL, randomised (2:1), parallel-group, active-control, multi-centre study (45 sites in the US). Study duration: 16 wks	<ul style="list-style-type: none"> • Insulin aspart CSII • Insulin lispro CSII 	HbA _{1c} change from baseline at Wk 16	298 children and adolescents (3-18 years [youngest subject enrolled was 4 years]) with T1D ≥ 1 yr, HbA _{1c} ≤ 10% and treated continuously for the previous 3 months with insulin aspart or insulin lispro CSII.
Supportive Trial in Children (< 7 Years of Age)				
ANA-1507	OL, 3-arm (2 arms 1:1 randomised, 1 arm fixed allocation [insulin aspart CSII]), parallel-group, multi-centre (5 sites in Poland) study. Study duration: 29 wks total (3-wk run-in, 26 wk treatment)	<ul style="list-style-type: none"> • Insulin aspart CSII • Insulin aspart MIT (+ basal NPH) • Regular HI MIT (+ basal NPH) 	HbA _{1c} 26 wks after randomisation	61 children < 7 yrs with T1D, HbA _{1c} < 12%, on > 2 injections/day of regular HI and NPH insulin (MIT).

OL = open-label; CSII = continuous subcutaneous insulin infusion; MIT = multiple injection therapy; T1D = type 1 diabetes; HI = human insulin.

4.3 Review Strategy

The submitted study reports were reviewed. The FDA statistician confirmed the primary efficacy data for Study ANA-2181. The major effort in this review was the conversion of the prescribing information into the Physician Labeling Rule (PLR) format. For more details about the labeling review strategy, please see Section 9.4 Labeling Review.

4.4 Data Quality and Integrity

Data quality and integrity appeared adequate. No site inspections were conducted for this NDA supplement.

4.5 Compliance with Good Clinical Practices

The study appeared to comply with good clinical practices.

4.6 Financial Disclosures

In compliance with the Final Rule on Financial Disclosure by Clinical Investigators (published 2/2/98 (63 FR 5233; revised 12/31/98 (63 FR 72171)), the financial certification disclosure, OMB Form No. 0910-0396, is signed by Anders Desgaard, and paragraph (1) is checked, certifying that there were no financial agreements between the sponsor and the investigators where compensation was linked to study outcome (as defined in 21 CFR 54.2(a), and that no clinical investigator reported any proprietary interest in this product or significant equity in the sponsor (as defined in 21 CFR 54.2(b), or the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). The Novo Nordisk certifications signed by the individual investigators specified that the total payment (including research grants, equipment donations, retainers, honoraria, etc.) to each investigator or institution would not exceed \$25,000, exclusive of the cost of conducting the clinical trial.

5 CLINICAL PHARMACOLOGY

No new clinical pharmacology studies with insulin aspart have been submitted with this NDA supplement.

6 INTEGRATED REVIEW OF EFFICACY

Study titles:

Study ANA-2181

“External Continuous Subcutaneous Infusion of Insulin Aspart (NovoLog) versus Insulin Lispro (Humalog): An Open-Label, Randomised, Parallel Group, Multicentre Study in Children and Adolescents with Type 1 Diabetes”

Study ANA-1507

“A multicentre open label 29 weeks three armed efficacy and safety study with two arms randomised and one arm with fixed allocation to CSII comparing insulin NovoRapid multiple injection or CSII with Actrapid multiple injection in diabetes type 1 children below 7 years of age”

Study ANA-2181 is the major study discussed in this review. The other study, **Study ANA-1507**, was not randomized and the efficacy data are described briefly. Study ANA-1507 was an open label study, but one-third of the patients were assigned to pump therapy and the remaining two-thirds of patients were randomized to subcutaneous insulin aspart or insulin lispro therapy. The data from Study ANA-1507 were reviewed primarily as supportive safety data. The studies are summarized in the sponsor’s table below.

Table 1–1 Trial Characteristics–Insulin Aspart Paediatric CSII Trials

Trial ID	Design	Treatment	Primary Endpoint	Subjects
Pivotal Trial in Children and Adolescents (3 to 18 Years of Age)				
ANA-2181	OL, randomised (2:1), parallel-group, active-control, multi-centre study (45 sites in the US). Study duration: 16 wks	<ul style="list-style-type: none"> Insulin aspart CSII Insulin lispro CSII 	HbA _{1c} change from baseline at Wk 16	298 children and adolescents (3-18 years [youngest subject enrolled was 4 years]) with T1D ≥ 1 yr, HbA _{1c} ≤ 10% and treated continuously for the previous 3 months with insulin aspart or insulin lispro CSII.
Supportive Trial in Children (< 7 Years of Age)				
ANA-1507	OL, 3-arm (2 arms 1:1 randomised, 1 arm fixed allocation [insulin aspart CSII]), parallel-group, multi-centre (5 sites in Poland) study. Study duration: 29 wks total (3-wk run-in, 26 wk treatment)	<ul style="list-style-type: none"> Insulin aspart CSII Insulin aspart MIT (+ basal NPH) Regular HI MIT (+ basal NPH) 	HbA _{1c} 26 wks after randomisation	61 children < 7 yrs with T1D, HbA _{1c} < 12%, on > 2 injections/day of regular HI and NPH insulin (MIT).

OL = open-label; CSII = continuous subcutaneous insulin infusion; MIT = multiple injection therapy; T1D = type 1 diabetes; HI = human insulin.

6.1 Indication

Treatment of type 1 diabetes mellitus in children and adolescents with continuous subcutaneous insulin infusion (CSII) by external pump.

6.2 Methods

6.2.1 General Discussion of Endpoints

Primary Objective of Study ANA-2181:

To demonstrate non-inferiority, as measured by HbA_{1c} after 16 weeks of continuous external infusion (CSII) of aspart in comparison with insulin lispro in children and adolescents with type 1 diabetes

Efficacy endpoint

HbA_{1c} change from baseline after 16 weeks of treatment was the primary efficacy endpoint in the non-inferiority analysis. Secondary efficacy assessments included self-monitoring of blood glucose (SMBG) measurements, fasting plasma glucose, and fasting lipid parameters.

Secondary Objectives:

Efficacy

- Glucose variability as determined by subject's self glucose monitoring
- Four-point self-monitored blood glucose (SMBG) daily (results were captured for the two days prior to each office visit.)
- Percentage of subjects with HbA1c < 7.0% and ≤ 6.5 %
- Fasting plasma glucose (FPG)
- Fasting lipid profile

Safety

- Incidence and frequency of hypoglycemia (blood glucose (BG) ≤ 56 mg/dL or 3.1 mmol/L)
- Incidence of diabetic ketoacidosis (DKA)
- Incidence and frequency of hyperglycemia (BG > 300 mg/dL or 16.6 mmol/L)
- Clinical evaluations (physical examination and vital signs)
- Urine screen and laboratory tests (haematology and chemistry)
- Change in funduscopy from baseline (this information was not collected in the CRFs or analysed.)
- Change in insulin antibodies from baseline
- Adverse events

Other

- Total daily insulin requirements
- Local infusion site reactions
- Infusion set duration (this information was not collected in the CRFs or analysed)

6.2.2 Study Design of **Study ANA-2181**

Study design (*p 20 of study report*)

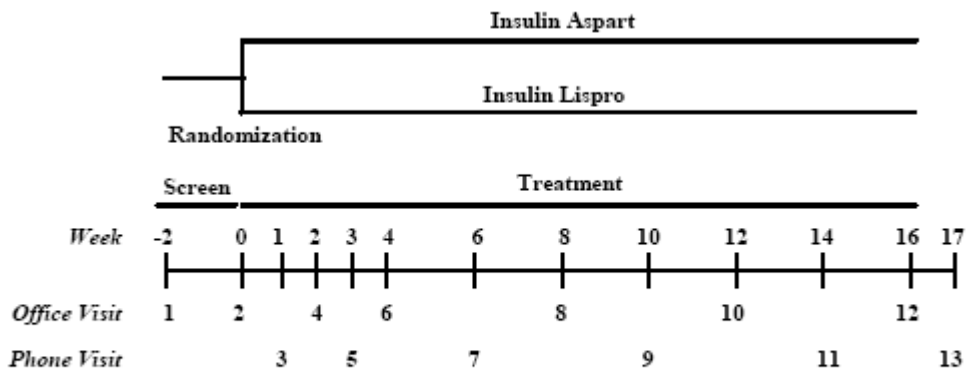


Figure 9-1 Trial Diagram

Timing of assessments:

Office Visits: Screening (-2 weeks), Baseline, Week 2, Week 4, Week 8, Week 12, Week 16
Phone Visits: Week 1, Week 3, Week 6, Week 10, Week 14, Week 17.

Children and adolescents with type 1 diabetes were randomized in a (2:1) manner to receive either aspart or insulin lispro as a continuous subcutaneous insulin infusion (CSII) in an external pump with changes in reservoir, infusion set, and infusion site at least once every 48 hours. Subjects were stratified by age (3 to 5 years, 6 to 11 years, and 12 to 18 years). This clinical trial was designed to test the non-inferiority of aspart compared with lispro for paediatric use in CSII pumps. This was designed as a multicenter study in order to observe the effect of aspart or lispro in a range of US clinical settings and in order to recruit sufficient subjects. At Visit 2, randomization was carried out centrally using a telephone randomization system (Interactive Voice Response System [IVRS]).

Treatments

Insulin aspart or insulin lispro was administered via continuous subcutaneous infusion using the patients’ own insulin pump. The following pumps were considered acceptable:

- MiniMed series 511, 512, 515, 712, 715 pumps (Medtronic Diabetes, Northridge, CA)
- Animas 1000 series pumps: IR1000, IR1200 and IR1250 (Animas Corporation, West Chester, PA)
- Deltec Cozmo pump (Smiths Medical MD, St. Paul, MN)

Pump supplies, including infusion sets and reservoirs, glucose meters, test strips, and topical anesthetic cream, were provided to the patients. The specific basal and pre-mealtime bolus doses

for each patient were ‘determined at the Investigator’s discretion’ to achieve the pre-specified glycemic targets. The glycemic targets were provided in Appendix D of the Study Protocol and are cited below.

Glycemic Targets			
	Plasma BG Range (mg/dL)		
Time	Ages 3-5	Ages 6 – 11	Ages 12 - 18
Preprandial	80-180	80 – 180	80 – 150
2hrPP	<180	< 180	<160
hs	120-180	120 – 180	110 –160

Insulin adjustments were aided by daily self-monitoring of blood glucose (SMBG) profiles (minimum four times daily) and 8-point profiles. Infusion insertion sites included the abdomen, lower back, hips, and thighs. In fusion sites and reservoirs were to be changed every 48 hours.

Study population

The entry criteria are summarized below.

Entry Criteria

- Pediatric patients (ages 3-18) with type 1 diabetes mellitus of at least one-year duration and treated continuously with continuous subcutaneous insulin infusion(CSII) pump therapy with lispro or aspart for the previous 3 months;
- Current CSII insulin analog basal rate > 0.05 units per hour
- HbA1c ≤ 10%
- Absence of active proliferative retinopathy, serum creatinine elevation, recurrent severe hypoglycemia, hypoglycemia unawareness, abnormal thyroid function, pregnancy, lactation or failure to use approved contraceptive measure in sexually active females of child bearing potential, chronic use of steroids in adrenal-suppressive doses
- Parental or guardian consent and ability and willingness to record self-monitoring of glucose and continue CSII pump therapy with child

The inclusion and exclusion criteria cited by the sponsor are quoted below.

Inclusion Criteria

- The subject’s parent/legal guardian gave signed informed consent including HIPAA requirements and child assent (if applicable) before beginning any trial-related activities. Trial related activities were defined as any procedures that would not have been

performed during normal management of the subject. Subjects who were 18 years of age signed the Informed Consent Form and did not require parental consent.

- Pediatric subjects (ages 3-18) diagnosed with type 1 diabetes for a duration of at least 1 year; and treated continuously for the previous 3 months with CSII therapy using either aspart or lispro.
- HbA1c $\leq 10\%$ (one retest within 1 week was permitted)
- Subjects had to be using one the following pumps: MiniMed® 511, 512, 515, 712, 715; Animas 1000 series pumps by Animas Corporation (IR1000, IR1200 and IR1250 pumps), the Deltec Cozmo® pump by Smiths Medical MD, Inc.
- Subject, parent/guardian willing to continue CSII for 16 weeks and accept the randomized insulin assigned.
- Subject, parent/guardian willing and able to perform and record in the subject's diary the SMBG profile at least 4 times daily.
- Subject, parent/guardian willing and able to perform and record in the subject's diary the SMBG profile at least 8 times daily for two days within 72 hours prior to Visit 2 (Week 0) and Visit 12 (Week 16).
- Parent/guardian willing and able to observe (when appropriate) subject performing SMBG and changing reservoirs and inserting infusion sets.

Exclusion criteria

- Chronic use of steroids in adrenal-suppressive doses. Stable doses of inhaled steroids prior to screening were permitted at the discretion of the Medical Monitor (Principal Investigator, or Sub-Principal Investigator) and were approved prior to entry. The use of topical steroids was acceptable.
- History of active proliferative retinopathy
- Subjects with a current basal rate ≤ 0.05 units per hour.
- Subjects on diluted insulin
- Basal dose was not stable for two weeks prior to screening visit
- Impaired hepatic function (alanine aminotransferase [ALT] > 2.0 times the upper reference limit for age and gender [one retest within one week was permitted])
- Impaired renal function (serum creatinine > the upper reference limit for age [one retest within one week was permitted])
- Abnormal thyroid function (thyroid stimulating hormone [TSH] > 2.0 times the upper reference limit for age and gender [one retest within one week was permitted]).
- Known or suspected allergy to insulin or any component of the study drug
- Recurrent severe hypoglycemia or hypoglycemic unawareness, as judged by the Investigator
- Mental incapacity, unwillingness to follow all study procedures, or language barriers precluding adequate understanding or cooperation
- Any condition that either the Investigator or Sponsor felt would interfere with study participation or evaluation of the results

- Pregnancy, lactation, or failure to use an approved contraceptive measure in sexually-active females of child bearing potential
- The receipt of any investigational drug within one month prior to the trial
- Previous participation in the randomization phase of this trial
- Subjects/caregivers had been unsuccessful in the past 3 months with using CSII and in changing reservoir and infusion sets.

Withdrawal criteria

- Pregnancy or intention of becoming pregnant
- Breastfeeding
- Withdrawal of consent
- An unexplained episode of DKA in the opinion of the Investigator
- Frequent unexplained episodes of minor hypoglycemia, defined by a plasma glucose ≤ 56 mg/dL or 3.1 mmol/L or symptomatic hypoglycemia with no recorded plasma glucose
- More than one episode of unexplained severe hypoglycemia, defined by a plasma glucose ≤ 56 mg/dL or 3.1 mmol/L requiring assistance by a 3rd party
- Failure to perform 4-point SMBG profiles or 8-point SMBG profiles per specifications in the protocol
- Failure to accurately record all hypoglycemic or hyperglycemic episodes
- Initiation of concomitant medication that influences glucose homeostasis, e.g., chronic use of steroids in adrenal suppressive doses
- Non-compliance with any of the study procedures
- Failure to dose insulin based on Investigator's and/or site staff's recommendations

Statistics

The Sponsor estimated that 156 patients with type 1 diabetes receiving insulin aspart and 78 patients receiving insulin lispro (2:1 ratio) as a continuous subcutaneous insulin infusion (CSII) in an external pump will have 80% power to establish non-inferiority of insulin aspart vs. insulin lispro in HbA_{1c} change from baseline to week 16 using a non-inferiority margin of 0.4% and assuming a standard deviation of 1.025%. The sponsor planned to enroll 282 patients to account for an estimated drop-out rate of 17%.

To show insulin aspart used in CSII pumps is non-inferior to lispro use in CSII pumps in HbA_{1c} change from baseline after 16 weeks of treatment, the primary analysis is analysis of covariance (ANCOVA) with treatment and age groups (3 to 5, 6 to 11 and 12 to 18 years old) as fixed effects and baseline HbA_{1c} as a covariate. The non-inferiority margin is 0.4%. The intent-to-treat (ITT) population using the last observation carried forward (LOCF) method was used for the primary analysis population.

Demographics

The baseline demographics were similar for the two treatment groups and are summarized in the table below;

Table 11-1 Demographics – All Randomised Subjects

	Aspart	Lispro	All
Number of Subjects	198	100	298
Sex (n (%))			
Male	95 (48.0%)	48 (48.0%)	143 (48.0%)
Female	103 (52.0%)	52 (52.0%)	155 (52.0%)
Race (n (%))			
White	180 (90.9%)	94 (94.0%)	274 (91.9%)
Hispanic	11 (5.6%)	3 (3.0%)	14 (4.7%)
Non-Hispanic	169 (85.4%)	91 (91.0%)	260 (87.2%)
Black	11 (5.6%)	2 (2.0%)	13 (4.4%)
Non-Hispanic	11 (5.6%)	2 (2.0%)	13 (4.4%)
Asian/Pacific Islander	1 (0.5%)	1 (1.0%)	2 (0.7%)
Non-Hispanic	1 (0.5%)	1 (1.0%)	2 (0.7%)
Other	6 (3.0%)	3 (3.0%)	9 (3.0%)
Hispanic	3 (1.5%)	3 (3.0%)	6 (2.0%)
Non-Hispanic	3 (1.5%)	0 (0.0%)	3 (1.0%)
Ethnicity (n (%))			
Hispanic	14 (7.1%)	6 (6.0%)	20 (6.7%)
Non-Hispanic	184 (92.9%)	94 (94.0%)	278 (93.3%)
Age (yrs)			
n	198	100	298
Mean	13.0	13.1	13.0
SD	3.30	3.02	3.21
Median	13.5	13.6	13.6
Min	4.2	4.7	4.2
Max	18.7	18.8	18.8

n = number of subjects.

Cross reference [EOT Table 14.2.1](#).

The baseline metabolic information and diabetes history were also similar for the two treatment groups:

Table 11-2 Baseline Prognostic Information – All Randomised Subjects

	Aspart	Lispro	All
Number of Subjects	198	100	298
Weight (kg)			
n	198	100	298
Mean	54.3	55.8	54.8
SD	19.89	19.13	19.62
Height (m)			
n	198	100	298
Mean	1.6	1.6	1.6
SD	0.18	0.17	0.18
BMI (kg/(m ²))			
n	198	100	298
Mean	21.7	21.8	21.7
SD	4.35	4.37	4.35
FPG (mg/dL)			
n	197	98	295
Mean	170.7	176.1	172.5
SD	77.80	67.47	74.46
HbA _{1c} (%)			
n	198	100	298
Mean	8.0	8.1	8.1
SD	0.94	0.84	0.91

BMI = body-mass index; FPG = fasting plasma glucose.
 Cross reference [EOT Table 14.2.2](#).

Table 11-3 Diabetic History – All Randomised Subjects

	Aspart	Lispro	All
Number of Subjects	198	100	298
Diabetes History ^a (yrs)			
Mean	6.1	6.0	6.1
SD	3.36	2.80	3.18
Current Diabetes Therapy (n (%))			
Aspart	97 (43.9%)	44 (44.0%)	131 (44.0%)
Lispro	111 (56.1%)	56 (56.0%)	167 (56.0%)
Type of Insulin Pump (n (%))			
MiniMed 511	52 (26.3%)	26 (26.0%)	78 (26.2%)
MiniMed 512	59 (29.8%)	36 (36.0%)	95 (31.9%)
MiniMed 712	43 (21.7%)	17 (17.0%)	60 (20.1%)
Other	44 (22.2%)	21 (21.0%)	65 (21.8%)
Use of CSII ^b (weeks)			
Mean	121.3	132.7	125.2
SD	80.28	69.99	77.05
Average Total Daily Insulin Dose Before Randomisation (Units)			
Mean	49.5	52.8	50.6
SD	24.17	24.01	24.13
Average Adjusted Total Daily Insulin Dose Before Randomisation (Units/kg)			
Mean	0.89	0.93	0.91
SD	0.258	0.246	0.254

^a Diabetic History is calculated from date diabetes was diagnosed to the screening date.

^b From the start of CSII to screening date.

Cross reference [EOT Table 14.2.3](#).

6.2.3 Efficacy Findings

The primary efficacy comparison was non-inferiority of CSII of aspart to insulin lispro in HbA_{1c} change from baseline to Week 16 using a margin of 0.4%.

The data for the primary efficacy comparison were reviewed by the FDA statistician, Lee Piang, Ph.D.

Table 2 displays the mean HbA_{1c} at baseline and week 16 and mean HbA_{1c} change from baseline.

Table 3 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 with insulin aspart is non inferior to insulin 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.

Table 2. Mean change (SD) from baseline in HbA_{1c} (%) at Week 16

full analysis set, last observation carried forward

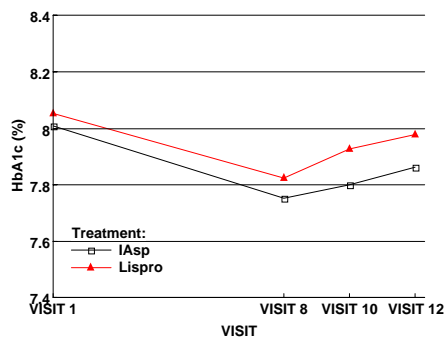
Treatment	N	Baseline	Week 16	Change
aspart	192	8.02 (0.94)	7.88 (0.93)	-0.13 (0.79)
lispro	96	8.14 (0.85)	8.07 (0.85)	-0.08 (0.70)

Table 3. Least squared mean change from baseline in HbA_{1c} (%) at Week 16 – ANCOVA* (LOCF)

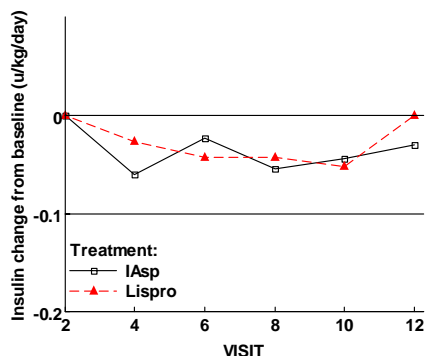
Treatment	LSMean	StdErr	Lower CL	Upper CL
aspart	-0.24	0.08	-0.40	-0.07
lispro	-0.13	0.10	-0.33	0.06
Aspart minus lispro	-0.10	(0.09)	[-0.27	0.07]

*ANCOVA (analysis of covariance) model included treatment group and age group as fixed effect and Baseline HbA_{1c} as covariate

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



The deterioration of glycemic control after the greatest decline in HbA_{1c} at visit 8 or 8 weeks is frequently observed in clinical trials of diabetes mellitus. Both treatment groups showed similar deterioration.



The applicant also analyzed the HbA1c data by age subgroups (ages 3-5, ages 6-11, and ages 12-18 years). Only ten patients participated in the youngest subgroup, and the remaining patients were distributed between the two other age groups. No significant differences were observed in the two older age groups or in the different treatments (aspart vs. lispro).

Daily Insulin Dose

The total daily insulin doses were not statistically significantly different in the two treatment groups, as indicated in the table below.

Table 11–23 Daily Insulin Dose (U)^a at Each Visit – ITT Population

Week	Aspart			Lispro			p-Value ^b
	n	Mean	SD	n	Mean	SD	
0	197	49.3	24.15	99	52.7	24.07	0.532
2	192	47.5	22.42	99	51.8	22.76	0.244
4	190	48.6	25.52	98	51.3	23.51	0.793
8	186	47.0	22.51	97	52.4	24.07	0.128
12	186	48.6	24.13	93	50.6	22.57	0.996
16	187	49.4	24.58	92	54.4	25.29	0.225

n = number of subjects.

^a 2-day average.

^b p-value is based on the model: average daily insulin dose (U) = treatment.

Cross references: [EOT Table 14.3.1.1.](#) and [EOT Table 14.3.2.1.](#)

Statistical differences were observed when the insulin dose was adjusted for weight. The applicant notes that “*aspart-treated subjects had a significantly lower mean daily adjusted insulin dose than lispro-treated subjects at Week 8 (p = 0.039) and Week 16 (p = 0.018). Despite a lower adjusted daily insulin dose, aspart-treated subjects had greater reductions in mean*

HbA1c (%) change from baseline at Weeks 8 and 16 than lispro-treated subjects (-0.26% vs. -0.22% at Week 8, -0.13% vs. -0.07% at Week 16, aspart vs lispro respectively).” Given the large standard deviations of the daily doses, the differences in adjusted insulin doses are not likely to be clinically significant.

Table 11–24 Adjusted Insulin Dose (U/kg)^a at Each Visit – ITT Population

Week	Aspart			Lispro			p-Value ^b
	n	Mean	SD	n	Mean	SD	
0	197	0.89	0.259	99	0.93	0.247	0.344
2	192	0.84	0.230	99	0.91	0.226	0.031*
4	188	0.86	0.251	98	0.90	0.247	0.620
8	185	0.84	0.224	97	0.90	0.219	0.039*
12	186	0.85	0.227	93	0.89	0.200	0.424
16	187	0.86	0.237	92	0.94	0.233	0.018*

n = number of subjects.

^a Two-day average.

^b p-value is based on the model adjusted daily insulin dose (U) = treatment.

* Statistically significant difference (p < 0.05) aspart vs. lispro.

Cross references: [EOT Table 14.3.1.2](#), [EOT Table 14.3.2.2](#).

6.2.4 Efficacy Conclusion

This reviewer agrees with the applicant that treatment of children and adolescents with type 1 diabetes mellitus with continuous subcutaneous insulin infusion (CSII) by external pump appears to be similar whether insulin aspart or insulin lispro is used. The major limitation of this study, from a regulatory perspective, is the absence of an approved comparator. Because of the intensity and practice requirements of continuous subcutaneous insulin (CSII) infusion by external pump therapy, and in view of the improved glycemic control that can be achieved with pump therapy versus multiple insulin injections, a randomized comparison of pump therapy and multiple insulin injections would not have been practicable. Near-normal glycemic control is often difficult to achieve in children and adolescents. Given the constraints of the age group, the HbA1c of ~8% in both treatment groups suggests a reasonable treatment success.

7 INTEGRATED REVIEW OF SAFETY

Safety assessments included reports of adverse events and episodes of hypoglycemia, hyperglycemia, and diabetic ketoacidosis; physical examination findings; laboratory test results for hematology, blood chemistry, and insulin antibody binding.

7.1 Methods and Findings

7.1.1 Deaths

No deaths were reported in Study ANA-2181 or Study ANA-1507.

7.1.2 Other Serious Adverse Events

Seven patients reported serious adverse events (SAEs) in Study ANA-2181 and SAEs were reported for four patients in Study ANA-1507. No patients withdrew from the studies as a result of the SAEs. Three patients reported episodes of hypoglycemia (one each) as SAEs in Study ANA-2181 and one patient had an episode of hypoglycemia in Study ANA-1507. One patient reported an episode of diabetic ketoacidosis (after a missed breakfast, disconnection of pump, and injection of a bolus insulin dose). All of the patients recovered from SAEs. The table below summarizes the serious adverse events.

Table 5–2 List of Subjects Reporting SAEs in Trials ANA-2181 and ANA-1507

Subject	Age (Gender)	Treatment	AE (Onset Day)	Outcome	Relationship
<i>Trial ANA-2181</i>					
103	12 (F)	CSII Aspart	Hypoglycaemic seizure (73)	Recovered	Unlikely
1010	13 (F)	CSII Aspart	Diabetic ketoacidosis (30)	Recovered	Unlikely
2006	12 (M)	CSII Aspart	Hypoglycaemia (25) Accidental overdose (of insulin) (25)	Recovered Recovered	Probable Probable
3705	12 (M)	CSII Aspart	Hyperglycaemia (21)	Recovered	Unlikely
5507	15 (M)	CSII Aspart	Skin laceration (23)	Recovered	Unlikely
703	14 (M)	CSII Lispro	Hypoglycaemia (46)	Recovered	Possible
3612 ^a	16 (F)	Prior to study drug	Hypoglycaemia (-11), headache (-11), pyrexia (-11)	Recovered	Unlikely
<i>Trial ANA-1507</i>					
27	7 (M)	MIT Aspart	Severe hypoglycaemia (143)	Recovered	Probably
34	5 (F)	MIT Aspart	Acute gastroenterocolitis (166)	Recovered	Unlikely
182 ^b	4 (M)	CSII Aspart	Acute tonsillitis (-14)	Recovered	Unlikely
180 ^b	5 (M)	CSII Aspart	Gastrointestinal infection (-5)	Recovered	Unlikely

Age is given in years. M = male. F = Female.

a: Subject had an SAE prior to the treatment period but went on to be randomised to CSII insulin lispro and completed the study.

b: Subjects had an SAEs during the run-in period but went on to be allocated to CSII insulin aspart and completed the study.

Cross reference [Section 12.3, CTR for ANA-2181](#) and [Section 10.2, CTR for ANA-1507](#).

7.1.3 Dropouts

One patient treated with insulin lispro withdrew from Study ANA-2181 on Day 13 because of persistent hyperglycemia due to an infusion set problem. No patient withdrew from study ANA-1507.

7.1.3.1 Other significant adverse events

Hypoglycemia

In Study ANA-2181, episodes of hypoglycemia were classified as follows:

- **Major hypoglycemic episode:** An episode with severe central nervous system symptoms consistent with hypoglycemia in which the patient is unable to treat himself/herself, and which had one or both of the following characteristics: Plasma glucose < 56 mg/dL (3.1 mmol/L), or reversal of symptoms after either food intake or glucagon/IV glucose administration.
- **Minor hypoglycemic episode -** An episode with or without symptoms consistent with hypoglycemia with a plasma glucose measurement < 56 mg/dL (< 3.1 mmol/L), which was handled by the patient him/herself;
- **Hypoglycemic symptoms:** Symptoms that were considered to be related to hypoglycaemia but not confirmed by a plasma glucose measurement or a plasma glucose measurement \geq 56 mg/dL (\geq 3.1 mmol/L) but were rated by the subject/caregiver as symptomatic.

The table below summarizes the episodes of hypoglycemia:

Table 5-4 Analysis of Hypoglycaemic Episodes Reported in Trial ANA-2181

Type of Episode	CSII Aspart (N=198)			CSII Lispro (N=100)			Aspart/Lispro	
	n (%)	E	R	n (%)	E	R	Rate Ratio	95% CI
Total:								
All	190 (96%)	5547	92.2	97 (97%)	2418	81.3	1.13	0.93; 1.38
Major	19 (10%)	25	0.42	8 (8%)	9	0.3	1.37	0.57; 3.32
Minor	188 (95%)	4643	77.2	94 (94%)	1961	66.0	1.17	0.96; 1.43
Symptoms Only	149 (75%)	722	12.0	82 (82%)	394	13.3	0.91	0.62; 1.31
Unclassified	24 (12%)	157	2.6	18 (18%)	54	1.8	1.44	0.39; 5.29
PG ≤36 mg/dL	94 (48%)	301	5.0	41 (41%)	117	3.9	1.27	0.80; 2.02
Nocturnal ^a:								
All	118 (60%)	340	5.7	56 (56%)	184	6.2	0.91	0.62; 1.34
Major	3 (2%)	4	0.1	1 (1%)	1	0.0	1.98	0.17; 23.60
Minor	112 (57%)	293	4.9	47 (47%)	157	5.3	0.92	0.62; 1.38
Symptoms Only	25 (13%)	33	0.6	19 (19%)	23	0.8	0.71	0.38; 1.34
Unclassified	6 (3%)	10	0.2	1 (1%)	3	0.1	1.65	0.18; 15.12
PG ≤36 mg/dL	18 (9%)	25	0.4	8 (8%)	19	0.6	0.65	0.25; 1.69
Daytime:								
All	188 (95%)	5170	85.9	97 (97%)	2206	74.2	1.16	0.95; 1.41
Major	17 (9%)	21	0.4	7 (7%)	8	0.3	1.30	0.52; 3.25
Minor	185 (93%)	4326	71.9	94 (94%)	1780	59.9	1.20	0.98; 1.48
Symptoms Only	148 (75%)	684	11.4	79 (79%)	369	12.4	0.92	0.63; 1.34
Unclassified	24 (12%)	139	2.3	18 (18%)	49	1.7	1.40	0.40; 4.94
PG ≤36 mg/dL	91 (46%)	275	4.6	36 (36%)	96	3.2	1.42	0.88; 2.28

E = number of episodes. R = rate (number of events/subject/year).

a: Events with missing times excluded from Nocturnal (24:00 through 0.5:59).

Cross reference: [EOT Table 14.5.5](#), [CTR for ANA-2181](#).

The percentage of patients with major hypoglycemia was similar for the insulin aspart and insulin lispro treatment groups – for the total, nocturnal, and daytime episodes. Similarly, the frequency of hypoglycemia did not significantly differ between the pump patients and the patients treated with multiple dose insulin regimens in Study ANA-1507.

Table 5-5 Hypoglycaemic Episodes Reported in Trial ANA-1507

Hypoglycaemic Episode	CSII Aspart		MIT Aspart		MIT HI	
	N (%)	E (Rate)	N (%)	E (Rate)	N (%)	E (Rate)
N exposed	20		20		21	
Major Episode	1 (5%)	3 (0.3)	1 (5%)	1 (0.1)	0	0
Minor Episode	17 (85%)	235 (21)	18 (90%)	189 (18)	19 (90%)	242 (20)
Symptoms Only	7 (35%)	14 (1.2)	5 (25%)	12 (1.1)	9 (43%)	17 (1.4)

E=number of episodes. Rate=number of episodes/year of exposure.

Cross Reference: [Table 4-4](#), [Module 2.7.4](#).

Diabetic ketoacidosis (DKA)

Four patients met the criteria for DKA (as outlined in the 2002 ADA Clinical Practice Guidelines) [3 insulin aspart, 1 insulin lispro] in Study ANA-2181. No episodes of DKA were reported in Study ANA-1507.

Hyperglycemia

In Study ANA-2181, hyperglycemia, defined as plasma glucose > 300 mg/dL, was reported by investigators if they considered the hyperglycemia an adverse event. An adverse event of hyperglycemia was reported in 21 (11%) of patients treated with insulin aspart and in 17 (17%) of the patients treated with insulin lispro. Hyperglycemia was not reported as an adverse event in Study ANA-1507.

Infusion Site Reactions

An adverse event of infusion site reaction was reported in 34 (17%) of patients treated with insulin aspart and in 21 (21%) of the patients treated with insulin lispro (p=0.432, Fisher's Exact Test). The most frequently reported infusion site adverse events (i.e., preferred terms) were infusion site erythema and infusion site reaction. The table below summarizes these adverse events.

Table 5-3 Subjects with Infusion Site Reactions in Trial ANA-2181

Preferred Term	CSII Aspart		CSII Lispro	
	N (%)	No. Events	N (%)	No. Events
N treated	198		100	
N w/ infusion site reaction	34 (17%)		21 (21%)	
Catheter site related reaction	1 (<1%)	1	3 (3%)	4
Infusion site erythema	11 (6%)	16	6 (6%)	8
Infusion site induration	5 (3%)	7	2 (2%)	2
Infusion site inflammation	1 (<1%)	1	0	0
Infusion site irritation	1 (<1%)	1	3 (3%)	4
Infusion site pruritus	2 (1%)	2	0	0
Infusion site rash	3 (2%)	3	1 (1%)	1
Infusion site reaction	12 (6%)	15	7 (7%)	10
Infusion site swelling	1 (<1%)	1	0	0
Infusion site vesicles	0	0	1 (1%)	1

Cross reference [EOT Table 14.5.17](#) and [EOT Table 14.5.6a](#), CTR for ANA-2181.

7.1.4 Laboratory Findings

No significant differences in mean values for hematology, biochemistry, or urinalysis parameters were observed at the beginning or end of Study ANA-2181. Only baseline screening hematology and chemistry parameters were measured in Study ANA-1507, and these did not differ among the three groups.

7.1.5 Vital Signs

Vital sign assessments were similar for the different treatment groups at all timepoints in both studies.

7.1.6 Immunogenicity

Prior to enrollment in Study ANA-2181, all of the patients were treated with continuous subcutaneous insulin infusion pump therapy. Forty-four percent (44%) were treated with insulin aspart, and 54% were treated with insulin lispro. Not surprisingly, many patients had baseline cross-reacting antibodies.

Table 5. Cross-reacting Antibodies in Study ANA-2181

<i>Treatment Group</i>	Insulin Aspart	Insulin Lispro
Antibodies cross-reacting with regular HI and insulin aspart	% binding, mean (SD) values	% binding, mean (SD) values
• Baseline	30.4 (18.5)	29.6 (20.8)
• Week 16	35.2 (19.6)	28.6 (19.8)
Antibodies cross-reacting with regular HI and insulin lispro		
• Baseline	30.0 (18.3)	29.1 (20.3)
• Week 16	34.6 (19.3)	27.9 (19.3)

The cross-reacting antibodies were not associated with a deterioration in HbA1c or an increased insulin dose requirement.

7.1.7 Assessment of Effect on Growth

The height and weight data for Study ANA-2181 are summarized in the Table below. Whereas weight data were carried forward, the height data are for completers only. For that reason, the population sizes may differ for some of the groups. Based on these data, the effect on growth appeared similar for the aspart and lispro treatment groups. The major reason for this analysis was to confirm that children in both treatment groups were growing during the study. The slight discrepancy in the numbers available for height and weight measurements does not affect the conclusion.

Table 6 . Height and Weight at Baseline and 16 Weeks in Study ANA-2181

<i>Mean (SD, range)</i>	Aspart	Lispro
N	190	97
Height (cm)		

• Baseline	156 (18, 100-196)	158 (17, 109-196)
• 16 weeks	157 (18, 103-196)	160 (17, 109 – 196)
• Change	1.6 (1.6, -1.8 -13.4)	1.7 (1.8, -1.3 – 10.0)
N	196	99
Weight (kg)		
• Baseline	54.2 (19.7, 17.2 – 142.5)	55.5 (18.9, 19.8 -121.4)
• 16 weeks	56.0 (20.1, 17.1 -149.0)	57.1 (19.2, 20.5-124.1)
• Change	1.8 (2.1, -4.3 – 8.2)	1.6 (2.1, -2.8-11.0)

Consistent with the height and weight data, a progression in pubertal status (assessed by Tanner staging) was observed in both treatment groups over the 16-week study period.

7.1.8 Postmarketing Experience

Since insulin aspart was granted pediatric exclusivity (5/24/05) and approved for pediatric use (NDA 20-986 S033, approved 9/13/05), the Division of Drug Risk Evaluation summarized the one-year post exclusivity post-marketing spontaneous adverse event reports in the Adverse Event Reporting System (AERS) database. There was a total of 1338 reports for aspart in the AERS database, including 154 (11.5%) pediatric reports. In the year following exclusivity, there was a total of 284 reports for aspart, including 28 (9.9%) pediatric reports. Of the 26 unduplicated pediatric reports, there were 3 deaths, 4 unlabeled events and 19 labeled events. Six events occurred during exposure via maternal use, including four unlabeled events. The post-exclusivity case characteristics summarized in the DDRE safety evaluator’s review are cited in the table below. (*Source: NDA 20-986 1-year Post-Pediatric Exclusivity Post-Marketing Adverse Event Review for NovoLog® (insulin aspart recombinant), J. Swann, 8/24/06, Accessed through the Division File System.*)

Table 26. Post-marketing Data – One year post exclusivity

Table 3: Characteristics of Pediatric Cases reported during the pediatric exclusivity approval through AERS cut-off date (May 24, 2005 through June 24, 2006) N=26	
<u>Gender</u>	n=25
Female	11
Male	14
<u>Age at time of event</u>	
0 < 1 month	6
1 month < 2 yrs	2
2-5 yrs	3
6-11 yrs	6
12-16 yrs	9
Mean	7.3 yrs
Median	8.0 yrs
Range	4 days-15 yrs
<u>Origin</u>	
US	17
Foreign	9
<u>Event date</u>	n=25
2003	2
2004	6
2005	16
2006	1
<u>Time to Event, (days)</u>	n=11
Mean	264
Median	122
Range	1-1214
<u>Indications</u>	
Type 1 diabetes mellitus	20
Exposure via Maternal Use	6
<u>Outcomes</u>	
Congenital Anomaly	3
Death	3
Disability	1
Hospitalization	14
Life-Threatening	5
Other	9
Required intervention	5

† Outcomes are not mutually exclusive; one case could contain more than one outcome.

Two fatal congenital malformations were described in infants exposed to maternal insulin aspart: a case of *truncus arteriosus communis*, and a case of hypoxic ischemic encephalopathy and fetal distress at birth. Non-fatal *in utero* exposure events were described in the following four cases: (1) neonatal hypoglycemia and a congenital anomaly (ankyloglossia); (2) urinary retention, neonatal asphyxia, and a hypoxic-ischemic lesion of the central nervous system; (3) dysmorphism of the right frontal lobe, increased frontal subarachnoid space, and asymmetry of the lateral ventricle; and (4) neonatal hypoglycemia. In a spontaneous reporting system such as AERS, it is not possible to distinguish whether the *in utero* exposure events, including congenital malformations and neonatal hypoglycemia, were secondary to insulin aspart or to the underlying maternal diabetic milieu, as these events occur relatively frequently (>5%) in controlled clinical trials. AERS data are better suited for signal detection of rare, serious, or life-threatening events. No recommendations for label changes were made on the basis of this post-marketing analysis.

For the conversion of the prescribing information to the PLR format, a consult regarding cases of anaphylaxis was requested from the Office of Surveillance and Epidemiology (J. Swann, January 17, 2008)⁷.

The following case definition for anaphylaxis was cited:

Case definition for anaphylaxis⁴:

1. Clinical diagnosis of anaphylaxis (reports submitted by a healthcare professional) OR
2. If skin or mucosal tissue involvement (e.g., urticaria, angioedema, pruritus, and flushing)
AND one of the following:
 - a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia),
or
 - b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotension, syncope, hypotonia [collapse]).

In a review of the FDA spontaneous Adverse Event Reporting System (AERS), 23 cases with hypersensitivity or anaphylaxis were identified with aspart (NovoLog®) treatment. Of these, thirteen were thought to meet the case definition for anaphylaxis by the safety evaluator. In reviewing these cases, the clinical reviewer noted that three of these thirteen cases did not discontinue treatment with aspart. The absence of discontinuation of aspart makes a clinical diagnosis of anaphylaxis less plausible. However, there were at least 3 cases (ID numbers 39, 40, 46 in J. Swan's review) that met the case definition for anaphylaxis, discontinued treatment with aspart, and were not treated with other confounding concurrent medications. On this basis, the inclusion of the term 'anaphylaxis' in the prescribing information appears justified, based on the post-marketing case reports.

8 OVERALL ASSESSMENT

8.1 Conclusions

The purpose of external insulin pump therapy is maximal improvement of glycemic control and not just a convenience factor. The data from the studies submitted by Novo Nordisk (Study ANA-2181 and Study ANA-1507) support the safety and effectiveness of insulin aspart continuous subcutaneous insulin infusion by external pump in the pediatric population. Insulin aspart and insulin lispro treatments by external pump resulted in similar efficacy, and the findings were similar to those observed in studies in adults.

8.2 Recommendation on Regulatory Action

This clinical reviewer recommends approval of this efficacy supplement. Specifically, this reviewer recommends approval of the following:

⁷ NDA 20-986 047 Review of Serious Hypersensitivity Events, J. Swann, Pharm.D., January 17, 2008

- the pediatric indication of continuous subcutaneous insulin infusion (CSII) by external insulin pump for treatment of hyperglycemia in patients with type 1 diabetes mellitus;
- the prescribing information for NovoLog insulin analog (Insulin Aspart (Asp) [rDNA origin]) in the revised Physician Labeling Rule (PLR) format⁸, pending agreement with FDA modifications. a waiver for children ages three and younger, as there are inadequate number of children in this age group for study, and efficacy and safety data are not expected to differ from those observed in older children.

Additional Recommendation Regarding Pediatric Intravenous Administration of NovoLog®

The intravenous indication for NovoLog was based on an adult pharmacokinetic pharmacodynamic study and it was approved on October 21, 2005. The pediatric intravenous indication was not specifically mentioned in the approval letter for the intravenous indication. In fact, that letter stated the following:

“All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.”

Presumably the last sentence referred to the original pediatric subcutaneous indication for aspart, which was approved on September 13, 2004

Recommendation:

This reviewer recommends that we waive the requirement for the pediatric intravenous study. There is no physiologic reason to suspect intravenous insulin would act differently in the pediatric population. Intravenous insulin should be administered in a hospital setting by trained personnel, so the 'in use' aspect that is evaluated in clinical studies should also not differ. This topic was discussed with members of the FDA Pediatric Review Committee. They concurred that the product is already appropriately labeled in the pediatric population and further pediatric studies for the pediatric indication are not needed. The Pediatric Review Committee has proposed the following language:

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This drug product (NovoLog®) is fully labeled for use in all appropriate pediatric populations. Therefore, no additional pediatric studies are needed at this time.

⁸ 21CFR201.57, Revised as of April 1, 2006.

8.3 Recommendation on Postmarketing Actions

8.3.1 Risk Management Activity

Other than the modifications in the prescribing information, no other specific risk management activities are recommended.

8.3.2 Required Phase 4 Commitments

No new Phase 4 commitments are requested.

8.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

8.4 Labeling Review

A red-lined version of the label, with comments from CMC, clinical pharmacology, and statistics is attached to this review. Pharmacology/toxicology had no changes.

Because the submission of an efficacy supplement triggered conversion of labeling to the PLR format, Novo Nordisk was advised to submit a label with changes similar to the ones this reviewer and others in the team had made in the PLR version of the [REDACTED], [REDACTED]

This clinical reviewer has made additional changes to the label based on the following:

- a word-by-word comparison of the PLR label to the previously approved (4/07 non-PLR) version.
- changes we made to format the NovoLog [REDACTED] PLR label from the non-PLR format [REDACTED] 9
- review of current European Medicines Agency (EMA) aspart (NovoRapid®) label 10

10 EMA label for aspart (NovoRapid®) accessed electronically at
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/Novorapid/H-258-PI-en.pdf>

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- review of other US-approved insulin labels 11 (including the NovoLog [REDACTED])
- review of prior FDA medical officer and clinical pharmacology reviews of NovoLog submissions for subcutaneous, pump, and intravenous use 12
- review of prior FDA medical officer and clinical pharmacology reviews of lispro (Humalog®, Lilly) submissions for subcutaneous and pump use 13
- review of Office of Surveillance and Epidemiology consult and the cited 23 postmarketing cases of hypersensitivity and/or anaphylaxis¹⁴

Per FDA instructions (including specific table schemata), Novo Nordisk completed a number of tables, including the following:

- tables of emergent adverse events during Type 1 and Type 2 clinical trials (*Section 6*);
- tables summarizing the key efficacy and safety parameters for the various referenced clinical trials (*Section 14*).

The schemata for these tables are included. I have suggested the same table format for the various clinical trials cited, for easier readability. There are a number of additional questions for the company in the comments.

The current indication (with FDA changes) states :

NovoLog[®] is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus (1.1)

The DOSAGE AND ADMINISTRATION section outlines the three modes of administration (cited from the Highlights page):

- **The dosage of NovoLog[®] must be individualized.**

11 insulin labels accessed electronically at Drugs@FDA

12 NDA 20-986 Clinical Review of aspart, E. Koller, M.D., August 1999.

NDA 20-986 003 Clinical Review of aspart for external pump use in adults, E. Koller, M.D, December 21, 2001

NDA 20-986 003 Division Director Review of aspart for external pump use in adults, D. Orloff, M.D, December 21, 2001

NDA 20-986 033 Clinical Review of pediatric subcutaneous aspart use, E. Koller, M.D., September 2005

NDA 20-986 032 Clinical Review of intravenous aspart use, E. Gabry, M.D., October 11, 2005

NDA 20-986 040 Action Letter approval of diluent, October 27, 2006

13 NDA 20-563 Clinical Review of lispro, E. Koller, M.D., June 2004.

NDA 20-986 003 Clinical Review of aspart for external pump use in adults, E. Koller, M.D, December 21, 2001

NDA 20-986 003 Division Director Review of aspart for external pump use in adults, D. Orloff, M.D, December 21, 2001

NDA 20-986 033 Clinical Review of pediatric subcutaneous aspart use, E. Koller, M.D., September 2005

NDA 20-986 032 Clinical Review of intravenous aspart use, E. Gabry, M.D., October 11, 2005

NDA 20-986 040 Action Letter approval of diluent, October 27, 2006

14 NDA 20-986 047 Review of Serious Hypersensitivity Events, J. Swann, Pharm.D., January 17, 2008

- *Subcutaneous injection:* NovoLog[®] should generally be given immediately (within 5-10 minutes) prior to the start of a meal (2.1)
- *Use in pumps:* Change the NovoLog[®] in the reservoir, the infusion set, and the infusion set insertion site at least every 48 hours. NovoLog[®] should not be mixed with other insulins or with a diluent when it is used in the pump. (2. 3)
- *Intravenous use:* NovoLog[®] should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride. (2.3)

Of note, the Study Endpoints and label Development (SEALD) team had been consulted to review the PLR label for insulin aspart, after the Division had completed its revisions. On February 25, 2008, the SEALD team announced that it no longer reviews PLR labels for already approved drugs.

The patient label and the product information for vials, cartridges and pens were modified to match the physician PLR prescribing information after agreement between FDA and Novo Nordisk was reached.

Intravenous aspart use

The Dosage and Administration section of the Highlights page of the PLR reads as follows:

•DOSAGE AND ADMINISTRATION•.....

- The dosage of NovoLog[®] must be individualized.
- *Subcutaneous injection:* NovoLog[®] should generally be given immediately (within 5-10 minutes) prior to the start of a meal (2.1)
- *Use in pumps:* Change the NovoLog[®] in the reservoir, the infusion set, and the infusion set insertion site at least every 48 hours. NovoLog[®] should not be mixed with other insulins or with a diluent when it is used in the pump. (2.3)
- *Intravenous use:* NovoLog[®] should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags. (2.3)

Use of intravenous insulin aspart was previously approved with the wording cited above. The data for the three infusion fluids (0.9% sodium chloride, 5% dextrose, or 10% dextrose) was presented in an amendment to the intravenous insulin supplement.¹⁵ Note that potassium was added only to the 10% dextrose solution but not to the other solutions. The data are summarized in the table below:

15 Hennigan, BB. *White Paper: Intravenous Use of Insulin Aspart and Regular Human Insulin in the Acute Management of Hyperglycemia and its Complications in Patients in a Hospital Setting.* Submitted as amendment to NDA 20-986 032, August 1, 2005.

Table 2 Minimum and Average Recovery of Insulin (%) from Infusion Fluids

Insulin (U/mL)	Infusion Fluid	----- Insulin aspart -----		----- Human Insulin -----	
		Minimum Recovery (%)	Average Recovery (%)	Minimum Recovery (%)	Average Recovery (%)
0.05	0.9% NaCl	84.9	87.2	75.9	80.8
0.2	0.9% NaCl	91.2	94.2	89.8	94.2
1.0	0.9% NaCl	96.4	97.4	98.5	99.2
0.05	5% Glucose	81.3	83.9	70.3	76.2
0.2	5% Glucose	89.7	91.6	86.2	87.5
1.0	5% Glucose	97.7	98.6	88.4	92.6
0.05	10% Glucose, 40 mM KCl	85.7	88.2	68.0	76.4
0.2	10% Glucose, 40 mM KCl	91.1	93.1	87.6	91.1
1.0	10% Glucose, 40 mM KCl	96.8	97.8	94.2	96.8

Additional Recommendation Regarding Pediatric Intravenous Administration of NovoLog®

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“All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.”

Presumably the last sentence referred to the original pediatric subcutaneous indication for aspart, which was approved on September 13, 2004

Recommendation:

This reviewer recommends that we waive the requirement for the pediatric intravenous study. There is no physiologic reason to suspect intravenous insulin would act differently in the pediatric population. Intravenous insulin should be administered in a hospital setting by trained personnel, so the 'in use' aspect that is evaluated in clinical studies should also not differ. This topic was discussed with members of the FDA Pediatric Review Committee. They concurred that the product is already appropriately labeled in the pediatric population and further pediatric studies for the pediatric indication are not needed. The Pediatric Review Committee has proposed the following language:

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All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This drug product (NovoLog®) is fully labeled for use in all appropriate pediatric populations. Therefore, no additional pediatric studies are needed at this time.

Comments to Applicant

Comments have been conveyed to the applicant electronically in the multiple line-by-line red-lined labeling reviews discussed above.

9 APPENDICES

9.1 Line-by-Line Labeling Review

Please see attached label, which incorporates the changes described in the labeling review and the multiple negotiations described below. The following are attached to this review, but they are entered into the Division File System separately because of the tracked changes.

- Physician Labeling for NovoLog® in the Physician Labeling Rule format
- Patient Labeling for NovoLog®

There are three sets of Instructions for Use. These instructions were not significantly modified by the clinical reviewer and they are not included in this review *per se*.

- Instructions for Use for Vial
- Instructions for Use for cartridge
- Instructions for Use for pen

The label was revised by FDA and forwarded to Novo Nordisk on February 11, 2008. Novo Nordisk submitted a revised label on February 15, 2008, and additional FDA revisions were forwarded to Novo Nordisk on February 20, 2008. The patient label and Instructions for Use were reviewed by the Division of Risk, Office of Surveillance and Epidemiology. Additional changes in the physician label, patient label, and three sets of Instructions for Use (vial, cartridge, pen) were made and forwarded to the sponsor on March 7, 2008. Novo Nordisk responded with additional minor changes on March 11, 2008, which were discussed in a teleconference with Novo Nordisk on March 12, 2008. The attached label is the label that was finalized as of March 12, 2008. (Please note – others at FDA may recommend additional modifications; this labeling has not yet been deemed the final labeling for this supplement.)

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REFERENCES

1. NovoLog® (insulin aspart) package insert, Novo Nordisk. January 26, 2007.
2. Hyperglycaemic crises in patients with diabetes mellitus: Position statement from the American Diabetes Association. *Diabetes Care*. 2002;25(Suppl 1):S100-S108.
3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J of Med*. 1993;329(14):977-986
4. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F. Consensus statement on the use of insulin pump therapy in the pediatric age group. *Diabetes Care*. Available online March 19, 2007.
5. Tamborlane WV, Sikes KA, Steffen AT, Weinzimer SA. Continuous subcutaneous insulin infusion (CSII) in children with type 1 diabetes. *Diabetes Research and Clinical Practice*. 2006;74:S112-S115.

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Joanna Zawadzki
3/12/2008 07:08:10 PM
MEDICAL OFFICER

Hylton Joffe
3/12/2008 08:29:49 PM
MEDICAL OFFICER
Please see clinical team leader memo.

Mary Parks
3/13/2008 09:39:26 PM
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