CLINICAL REVIEW

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Established Name	Insulin aspart
(Proposed) Trade Name	NovoRapid®, NovoLog®
Therapeutic Class	Rapid Acting Insulin Analog
Applicant	Novo Nordisk
Priority Designation	S
Formulation	Aqueous Solution
Dosing Regimen	SC Injection
Indication	Type 1 Diabetes
Intended Population	Children 2-18 years

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1 EXECUTIVE SUMMARY

Insulin aspart is a rapid acting human insulin analog approved on June 7, 2000 for the treatment of insulin requiring diabetes mellitus in adults. IAsp is produced by recombinant DNA technology. IAsp has the same amino acid sequence as human insulin, with the exception of the substitution of proline with aspartic acid at position 28 of the B-chain. This substitution produces intermolecular repulsion and thereby reduces the tendency of the insulin molecules to self associate to dimers and hexamers. Thus, IAsp is absorbed more rapidly than regular human insulin (HI) when given subcutaneously, thereby leading to a more physiological pharmacokinetic profile. This rapid absorption and onset of action makes IAsp suitable for injection immediately before meals.

The Agency issued a Written Request for a pediatric study on December 14, 1999. A number of Written Request amendments were issued, the last of which was dated October 5, 2004. The sponsor submitted this supplement (S-033) on March 14, 2005 in accordance with Written Request amendment #6. It provides for the use of insulin aspart for treatment of type 1 diabetes in children and adolescents ages 2-18 years. The Pediatric Exclusivity Board met on May 24, 2005 and granted Pediatric Exclusivity to the Sponsor based on this submission.

1.1 RECOMMENDATION ON REGULATORY ACTION

The recommended regulatory action for this supplement and its attached label changes is APPROVAL. Please see attachment #1 for the proposed label changes.

The pharmacokinetics and pharmacodynamics of insulin aspart (IAsp) in children were addressed in the original NDA submission (study ANA/DCD/043). This current submission provides the complete study report of ANA-2126 trial (Trial 2126) that meet the terms of the issued Written Request. Supportive data from two exploratory trials ANA/DCD/060 (Trial 060) and ANA-1200 (Trial 1200) are included in this submission. Additionally, the Sponsor evaluated the use of insulin aspart in young children (2 to 6 years of age) in trial ANA-1415 which is discussed in the "Special Population" section of this review.

As per the Agency's Written Request, Trial 2126 was a 24-week, randomized, open-label, active-control study in children (6-18 years) with type 1 diabetes (n = 377) to assess the safety and efficacy of insulin aspart (IAsp) compared to regular human insulin (HI) and to insulin lispro when administered subcutaneously as the short/rapid acting insulin in a basal bolus regimen in which NPH provided the basal insulin component. IAsp and lispro were injected subcutaneously immediately before the meal while HI was injected 30 minutes prior to the meal.

IAsp was noninferior to HI in terms of HbA1c change from baseline, based on a noninferiority margin of 0.4%. IAsp failed to demonstrate noninferiority to lispro, but the mean HbA1c change from baseline for the IAsp arm was not significantly different from that of the lispro arm. No notable differences in the occurrence of adverse events were

observed between treatment arms. The rates of hypoglycemia (minor, major, nocturnal, or requiring intervention from a third party) were comparable for the three treatment arms.

1.2 RECOMMENDATION ON POSTMARKETING ACTIONS

Not applicable.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

This supplement was submitted electronically. This Reviewer accessed the submission via the electronic documents room (EDR) at: \\CDSESUB1\N20986\S_033\2005-03-14. The study reports were first reviewed, followed by the summary of clinical safety, then the summary of clinical efficacy. Select case report forms from study 2126 were evaluated. Study report 2126 was emphasized in the review process. All trials were used in the integrated safety analysis. The submitted data appeared to be of sufficient quality and integrity. No DSI audits were requested. The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. These arrangements do not raise questions about the integrity of the clinical data.

Data from four pediatric clinical trials are submitted. ANA-2126 trial (Trial 2126) is a therapeutic confirmatory trial and is the pivotal trial for this application. It is the focus of this review. It included children and adolescents from 6 to 18 years of age. Trials ANA/DCD/060 (Trial 060) and ANA-1200 (Trial 1200) enrolled subjects 6 to 17 years of age and are considered exploratory, providing supportive data. Trial 1200 is mainly discussed in the "Dosing Regimen and Administration" section (b) (4) The ANA-1415 trial (Trial 1415) included young children (2 to 6 years of age) and is the only trial in this age group. It is mainly discussed in the "Special Population" section of this review.

Table 1: The main characteristics of the pediatric clinical trials

Trial	Treatment	Design	Primary Endpoint(s)	Subjects
Trial 2126	IAsp+NPH HI+NPH Lispro+NPH	Multi-center, randomized, open-label, parallel group. 24 weeks	HbA1c	377 subjects 6-18 years Type 1 diabetes.
Trial 060	IAsp+NPH HI+NPH	Multi-center, randomized, open-label, parallel group. 12 weeks	Adverse events HbA1c Serum fructosamine	123 subjects 6-17 years Type 1 diabetes.
Trial 1200	Preprandial IAsp Postprandial IAsp	Multi-center, randomized, open-label,	Serum fructosamine	76 subjects 6-17 years

		crossover. 6 weeks on each treatment.		Type 1 diabetes.
Trial 1415	IAsp+NPH (IAsp was injected preprandially and postprandially) HI+NPH	Multi-center, randomized, open-label crossover., 12 weeks on each treatment	Postprandial glucose increment Hypoglycemic episodes	26 subjects 2-6 years of age Type 1 diabetes

Trial 2126 was the most comprehensive of the three trials performed in the 6 to 18 year age group with respect to number of subjects and the duration of exposure (24 weeks). It was designed to evaluate efficacy and safety of insulin aspart (IAsp) as mealtime bolus insulin in a basal-bolus treatment regimen, where Neutral Protamine Hagedorn (NPH) insulin was used as the basal treatment. The design of the pivotal trial and the use of comparators were agreed with the FDA prior to trial initiation. The IAsp+NPH regimen was compared with two other basal-bolus regimens: regular human insulin (HI) (bolus) plus NPH (basal) and insulin lispro (Lispro) (bolus) plus NPH (basal). The bolus comparators were chosen as they were both widely used and their use well documented for this population and Lispro in particular for being a rapid-acting analogue with a similar mode of action as insulin aspart. NPH was used as basal insulin because it is widely used and has a documented record of safety and efficacy in this age group. The primary endpoint was HbA1c, which is the most widely accepted measure of chronic hyperglycemia.

Trial 060 was designed to evaluate the safety and applicability of IAsp as the mealtime bolus insulin in a basal-bolus treatment regimen with NPH as basal insulin. As in the pivotal trial the comparator was a basal bolus treatment regimen with HI and NPH. The duration of the trial was 12 weeks, which is sufficient for evaluating HbA1c. However, this trial was designed primarily as a safety trial. Trial 060 is discussed briefly as a secondary evidence of safety and efficacy.

Trial 1200 was designed to compare preprandial and postprandial administration of IAsp as the mealtime bolus insulin in a basal-bolus treatment regimen, where NPH was used as basal insulin. Each treatment period in this cross-over trial was 6 weeks. Therefore, the primary endpoint was serum fructosamine, which is an acceptable endpoint in short term trials. Trial 1200 is discussed (b) (4)

Trial 1415 was conducted in subjects 2 to 6 years of age. (b) (4) It was designed as a cross-over efficacy and safety trial with 12 weeks of treatment in each treatment arm (IAsp plus NPH *versus* HI plus NPH). The primary endpoints were the prandial blood glucose increment and incidence of hypoglycemic episodes. Trial 1415 is discussed mainly in the "Special Population" sections of this review.

In all four therapeutic trials the safety endpoints included adverse events and hypoglycemic episodes. In Trials 2126 and 060 insulin antibodies were also measured.

All trials were open-label because it was considered unacceptable to require pediatric subjects to take dummy injections. In Trials 2126, 060 and 1415 the recommended time of injection of the bolus insulin differed for the treatment regimens and in Trial 1200 IAsp was to be injected either preprandially or postprandially

1.3.2 Efficacy

1.3.2.1 Main Evidence; Trial 2126

This was a 24-week, randomized, multi-center, open-label, active-controlled, parallel-group study to investigate the efficacy and safety of basal/bolus IAsp+NPH as compared to Novolin R+NPH or lispro+NPH. The Trial enrolled pediatric patients (ages 6-18) with type 1 diabetes for a duration of at least 1 year, with HbA1c ≤12%. The patients were free of renal or hepatic impairment, hypoglycemia unawareness, and able to perform self-monitored blood glucose up to 4 times daily.

Insulin doses were adjusted by the investigator to achieve the following blood glucose ranges for preprandial, 2 hours postprandial, at bedtime, respectively: age 6 – 11 years: 80 – 180, <180, 120 – 180; age 12 – 18 years: 80 – 150, <160, 110 – 160;. Insulin aspart and insulin lispro were to be administered subcutaneously immediately before meals. Novolin R was to be administered 20 to 30 minutes before meals. NPH was administered before dinner or at bedtime at the investigator's discretion, and before breakfast (mixed with insulin aspart) as needed. The subjects received 24 weeks of treatment.

Demography of trial population:

Values are mean (SD) unless otherwise noted	**IAsp+NPH**	**Novolin R+NPH**	**Lispro+NPH**
Number Randomized	187	96	95
Age, (years)	11.8 (3.1)	11.5 (2.7)	11.4 (2.9)
Age Group, n, (%), 6–11 /12–18	91 (49) / 96 (51)	49 (51) / 47 (49)	48 (51) / 47 (49)
Sex, male/female, (n, (%))	86 (46) / 101 (54)	54 (56) / 42 (44)	52 (55) / 43 (45)
Weight (kg)	50.8 (19.6)	48.8 (15.7)	51.0 (22.1)
Height (cm)	151.2 (16.6)	150.8 (15.6)	150.8 (17.4)
BMI (kg/m^2)	21.4 (4.8)	20.8 (3.6)	21.4 (5.3)
Duration of Diabetes (yrs)	4.8 (3.3)	4.6 (3.1)	4.4 (3.1)
HbA_{1c}	8.3 (1.2)	8.3 (1.3)	8.4 (1.2)

Subject disposition, n (%), is tabulated below:

	All	**IAsp+ NPH**	**Novolin R+NPH**	**Lispro+NPH**
Randomized	378	187	96	95

Completed	300 (79)	146 (78)	74 (77)	80 (84)
Withdrawals (total)	78 (21)	41 (22)	22(23)	15(16)
Adverse events	5	2	3	0
Ineffective therapy	6	4	1	1
Non-compliance	49	26	12	11
Other	18	9	6	3

For the change in HbA1c from baseline, treatment with IAsp+NPH was demonstrated to be non-inferior to treatment with Novolin R+NPH since the upper limit of the 97.5% confidence interval calculated for the difference between groups [-0.506%, 0.119%] was less than the non-inferiority criteria of 0.4%. Treatment with IAsp+NPH was not found to be non-inferior to treatment with lispro+NPH since the upper limit of the 97.5% confidence interval [-0.058%, 0.542%] exceeded the non-inferiority criteria of 0.4%. However, the mean change from baseline HbA1c value for the IAsp+NPH group (0.1%±1.0) was not significantly different from that of the lispro+NPH group. (-0.1%±1.0).

Table 2: HbA1c values (%) during Trial 2126

	IAsp + NPH		Novolin R + NPH		Lispro + NPH		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	97.5% CI
Baseline	187	8.3 (1.2)	95	8.3 (1.3)	95	8.4 (1.2)	
Week 12	170	8.3 (1.3)	80	8.5 (1.4)	88	8.0 (1.0)	
Week 24	150	8.3 (1.3)	72	8.4 (1.4)	81	8.2 (1.3)	
End of Study	170	8.4 (1.4)	82	8.5 (1.4)	89	8.2 (1.2)	
Change from Baseline	170	0.1 (1.0)	82	0.1 (1.1)	89	-0.1 (1.0)	[-0.506, 0.119][a] [-0.058, 0.542][b]

a: Confidence interval for comparison of IAsp+NPH group to Novolin R+NPH group at the end of study.
b: Confidence interval for comparison of IAsp+NPH group to lispro+NPH group at the end of study.
a: ANCOVA analysis on HbA_{1c} after 24 weeks of treatment includes treatment, center, HbA_{1c} at screening and age as fixed effects, and baseline HbA_{1c} as covariate. Cross-reference: End-of-text Table 7.

Bolus insulin doses were similar across treatment groups at baseline and increased slightly by the end of the study. Basal insulin doses were also similar across treatment groups at baseline and increase slightly by the end of the study.

Table 3: Mean ±SD daily basal and bolus insulin doses in pivotal trial (U/kg)

	-----IAsp+NPH-----				-----HI+NPH-----				-----Lispro+NPH-----			
Visit	N	Basal	N	Bolus	n	Basal	n	Bolus	n	Basal	n	Bolus
Week 0[a]	170	0.66 (0.22)	178	0.36 (0.23)	90	0.69 (0.27)	91	0.35 (0.22)	89	0.61 (0.24)	93	0.38 (0.20)
Week 4	166	0.64 (0.22)	166	0.40 (0.21)	87	0.63 (0.27)	86	0.42 (0.25)	89	0.59 (0.24)	89	0.43 (0.22)
Week 8	157	0.65 (0.21)	158	0.42 (0.25)	83	0.65 (0.27)	83	0.45 (0.29)	83	0.61 (0.24)	83	0.42 (0.21)
Week 12	154	0.67 (0.22)	153	0.43 (0.22)	77	0.68 (0.31)	77	0.45 (0.28)	83	0.62 (0.25)	83	0.45 (0.26)
Week 24	140	0.70 (0.23)	140	0.45 (0.24)	74	0.72 (0.32)	74	0.46 (0.26)	77	0.67 (0.26)	77	0.43 (0.27)
End of Trial	149	0.70 (0.25)	150	0.45 (0.25)	78	0.71 (0.31)	76	0.45 (0.26)	82	0.67 (0.26)	83	0.43 (0.27)

Lunchtime insulin injections were taken by approximately 60% of the subjects in each treatment group. When the inclusion of a lunchtime insulin bolus was used as a fixed effect in the ANCOVA model, the calculated confidence intervals (97.5%CI: [-0.488%,

0.139%] and [-0.065%, 0.538%] for IAsp+NPH compared to Novolin R+NPH and lispro+NPH, respectively) were consistent with those of the primary endpoint suggesting that the lunchtime bolus injection did not appear to influence the result of the overall HbA1c analysis.

Mean FPG levels were high at baseline (11.9 to 13.6 mmol/l, 214 to 245 mg/dL) across all treatments and remained high at the end of the study (12.8 to 14.7 mmol/L, 230 to 265 mg/dL). The end-of-study mean FPG values in the IAsp+NPH group (14.0 ± 5.6 mmol/L) were not significantly different than those in the Novolin R+NPH group (13.1 ± 5.7 mmol/L; treatment comparison: 97.5% CI: -1.186 mmol/L, 2.50 mmol/L); or those in the lispro+NPH group (12.9 ± 5.3 mmol/L; treatment comparison 97.5% CI: -0.69 mmol/L, 2.87 mmol/L). In general, FPG values were relatively high at baseline and remained so during the trial.

8-Point SMBG profiles showed that BG values after lunch and dinner were significantly lower after treatment with IAsp than after treatment with regular human insulin. IAsp and lispro had similar results after lunch and dinner.

Continuous glucose monitoring systems (CGMS) were worn by only a few subjects during the study. For the IAsp+NPH group (6 subjects) and lispro+NPH group (3 subjects) at the end of the study, most of the CGMS measurements (75% to 85%, respectively) were in the range >140 mg/dL. The percentage of CGMS readings in the range >140 mg/dL (78%) for the Novolin R+NPH group (4 subjects) at Week 12 was similar to that of the other treatment groups at the end of the study.

When timing of the evening NPH dose (supper or bedtime) was used as a fixed effect in the ANCOVA model, the calculated confidence intervals (97.5%CI: [-0.533%, 0.099%] and [-0.044%, 0.563%] for IAsp+NPH compared to NovolinR+NPH and lispro+NPH, respectively) were consistent with those of the primary endpoint suggesting that evening NPH timing did not appear to influence the result of the overall HbA1c analysis.

1.3.2.2 Supportive Evidence

Table 4: A summary of Trial 060 efficacy findings

Objectives	Design	Subjects Exposed (M/F)	Treatment and Dose	Results and Conclusions
Primary objective: Evaluate, in pediatric diabetes patients, the safety and applicability of IAsp, in comparison with regular human insulin **Primary endpoints:** Adverse events HbA1c and serum fructosamine	Parallel group open-label trial Patients were randomized 1:1 to receive either IAsp or HI, in combination with NPH for a period of 12 weeks	**Age group:** 6 to 17 years of age **IAsp+NPH:** 65 subjects (M: 37; F: 28) **HI+NPH:** 58 subjects (M: 39; F: 19)	IAsp and HI were injected immediately and 30 minutes before the meal, respectively NPH insulin was used for basal insulin needs Dosage of the trial drugs was adjusted throughout the trial	• Mean (SD) change in HbA1c from baseline to Week 12 was 0.41 (1.20)% in the IAsp+NPH group and 0.27 (1.00)% in the HI+NPH group. • Mean (SD) change in fructosamine from baseline to end of trial was 53 (108) ⌈mol/L for IAsp+NPH and 30 (81) ⌈mol/L for HI+NPH. • IAsp administered immediately before meals provided glycemic control comparable to that of HI administered 30 minutes prior to meals (HbA1c: p=0.128; fructosamine: p=0.106). IAsp was effective for both pediatric and adolescent patients.

1.3.3 Safety

1.3.3.1 Main Evidence, Trial 2126

No notable differences in the occurrence of adverse events were observed between treatments. Approximately 96% of the adverse events in any treatment group were mild or moderate in severity. The number of treatment emergent adverse events (TEAEs) with probable or possible study drug relatedness and the number of subjects with those TEAEs were similar across treatment groups.

Five subjects were withdrawn from the study because of adverse events: 2 subjects in the IAsp+NPH group (diabetic ketoacidosis and grand mal convulsion) and in 3 subjects in the Novolin R+NPH group (urticaria, increased blood glucose, and diabetic ketoacidosis). Serious adverse events were reported by 14 (7.5%) subjects in the IAsp+NPH group, 7 (7.3%) subjects in the Novolin R+NPH group, and 5 (5.3%) subjects in the lispro+NPH group. Three subjects withdrew because of their serious adverse event: 1 subjects in the IAsp+NPH group (diabetic ketoacidosis) and in 2 subjects in the Novolin R+NPH group (increased blood glucose, and diabetic ketoacidosis).

Minor hypoglycemia (confirmed by BG <50 mg/dL) was reported by a similar percentage (80 to 87%) of the subjects in each treatment group at a rate of 26.4, 31.8, and 26.0 episodes per subject year, for the IAsp+NPH, Novolin R+NPH, and lispro+NPH, respectively. Major hypoglycemia was reported by 6, 9, and 8% of the subjects in the IAsp+NPH, Novolin R+NPH, and lispro+NPH groups, respectively and had a similar overall rate of 0.2, 0.3, and 0.2 episodes per subject year in the respective treatment groups. Hypoglycemic episodes with blood glucose values <36 mg/dL and/or requiring intervention from a third party were reported by 40, 43, and 34% of the subjects in the IAsp+NPH, Novolin R+NPH, and lispro+NPH groups, respectively, and had similar overall rates of 2.9, 2.6, and 3.1 episodes per subject year for the respective treatment groups. Nocturnal minor hypoglycemia (23:00 to 6:00) was reported by 44, 45, and 36% of the subjects in the IAsp+NPH, Novolin R+NPH, and lispro+NPH groups, respectively and had similar overall rates of 2.6, 3.2, and 2.4 episodes per subject year for the respective treatment groups.

Diabetic ketoacidosis was reported for 5% of the subjects in the IAsp+NPH group, 2% of the subjects in the Novolin R+NPH group, and 3% of the subjects in the lispro+NPH group. Two subjects were withdrawn from the trial because of DKA, one subject in the IAsp+NPH group and one subject in the Novolin R+NPH group.

Treatment with insulin aspart +NPH, Novolin R+NPH, or lispro+NPH did not have an adverse effect upon physical examination findings, vital signs, weight, or hematology, blood chemistry, or lipid laboratory values.

Cross-reacting insulin antibody binding values were similar at baseline between treatment groups and increase slightly (~3% absolute units) by the end of the study for the IAsp+NPH and lispro+NPH groups. Mean cross reacting insulin antibody binding for the Novolin R+NPH group did not increase during the study.

1.3.3.2 Supportive Evidence; Trial 060

No deaths occurred during the study. One serious AE occurred during the trial. A patient in the regular insulin group was hospitalized with moderate hyperglycemia. The trial drug was adjusted and the patient continued in the study. The incidence of AEs was similar between treatment groups; 55 (85%) IAsp treated patients and 45 (78%) regular human insulin-treated patients experienced an AE. A similar number of AEs were reported in both treatment groups (IAsp, 168 events; regular insulin, 174 events). All adverse events were mild to moderate in severity. The most common adverse events were respiratory tract disorders, headaches, and nausea. There were no significant or relevant differences between treatment groups in clinical laboratory findings, vital signs, physical examinations, IGF-1 values, cross-reacting insulin antibodies and antibodies specific to IAsp or regular insulin.

Hypoglycemic episodes occurred with similar frequency in both treatment groups. During the entire trial, 5 major hypoglycemic episodes were reported (3 in the IAsp group; 2 in the regular human insulin group. The overall rates of minor and major hypoglycemia were comparable for IAsp and HI treatment arms.

Table 5: The overall rates of minor and major hypoglycemia in Trial 060

	IAsp (n=65)	HI (n=58)
Hypoglycemia (weeks 4-12)	Episode/patient	Episode/patient
Minor	13.6	15.3
Major	0.03	0.03

1.3.4 Dosing Regimen and Administration

1.3.4.1 Dosing and Administration for Efficacy and Safety

All four clinical trials used IAsp as a meal time insulin in a basal-bolus regimen supplemented with an intermediate-acting or long-acting insulin (in most cases NPH). In the Trials 2126 and 060, subjects were instructed to inject IAsp/Lispro immediately before meals and to inject HI 20-30 minutes before meals. In Trials 1200 and 1415 IAsp was administered preprandially and postprandially.

The protocols for Trials 2126 and 060 stated that subjects were to take their bolus insulin dose before meals. However, administration of lunchtime bolus insulin may be problematic for school children for several reasons. Difficulties during school include zero-tolerance policies that prevent children from administering any drug to themselves while in school, unavailability of nursing staff to supervise a lunchtime injection, and fear of afternoon hypoglycemia. The percentage of subjects taking a lunch time bolus

injection was recorded in both the pivotal trial and in Trial 060 and the effect of compliance to lunchtime dosing on glycemic control was analyzed.

In Trial 2126, NPH was to be administered before dinner or at bedtime at the investigator's discretion, and before breakfast (mixed with IAsp, HI or Lispro) as needed. The timing of the evening NPH injection was recorded so that an analysis of the influence of the timing of the evening NPH on HbA1c and FPG could be performed. In Trials 060 and 1200, the basal insulin was administered according to the pre-trial regimen used by the subjects. In Trial 1415, NPH was injected up to four times daily.

No insulin titration algorithms were provided in any of the trial protocols, but it was generally recommended to adjust the insulin doses according to BG measurements to meet predefined targets and according to local practice for treatment of children with diabetes.

1.3.4.2 Postprandial Administration of IAsp: Trial 1200

It has been shown that preprandial administration of IAsp provides the best glycemic control for diabetic patients. However, it is often hard to predict how much a child will eat at a particular meal. One advantage of postprandial administration of IAsp is the ability to adjust insulin dose according to the actual food intake. Therefore, the sponsor submitted Trial 1200, which compared the glycemic control and the safety profile of IAsp when administered postprandially and preprandially.

A random sequence, 6-week/6-week crossover study of children and adolescents, age 6-17 years, with type 1 diabetes (n=76; 37M, 39F) compared the blood glucose control of IAsp injected postprandially (within 30 minutes of starting the meal) with IAsp injected preprandially (immediately before the meal) using 3.0 ml Penfill. There was no wash-out period between the periods. IAsp was injected at least thrice daily. The dose of IAsp was adjusted to achieve prespecified blood glucose targets. Subjects continued with their long acting basal insulin at pre-trial doses and kept the basal insulin regimen constant throughout the trial.

A total number of 76 subjects (IAsp pre/post: 42 patients, IAsp post/pre: 34 patients) were evaluated for the efficacy parameters. The sequence groups were found to be well comparable regarding the demographic and baseline characteristics of the subjects.

For the primary endpoint, the change in fructosamine from baseline to Week 6, noninferiority was demonstrated for the postprandial use of IAsp when compared with preprandial use (upper 95% CI limit < 0.1). No significant differences between children and adolescents regarding fructosamine levels could be shown.

With preprandial use of IAsp, the HbA1c levels remained nearly unchanged at the baseline level of 8%, while with postprandial use a slight increase from 8.0% at baseline

to 8.3% at the end of the treatment period was observed. The difference between the two regimens of insulin aspart was not statistically significant (p= 0.14).

The average blood glucose concentration on the profile day after 6 weeks was 8.5 mmol/L under preprandial IAsp compared with 9.2 mmol/L under postprandial IAsp. The estimated difference between the treatment means (0.65 mmol/L) was found to be not statistically significant (p=0.08). Neither age groups (p=0.59) nor sequence groups (p=0.55) differed significantly regarding the average blood glucose levels.

In both treatment groups the mean daily doses of IAsp remained stable at 0.11 U per kilogram body weight throughout the trial. The mean doses of basal insulin were about 0.16 IU/kg BW at baseline in both treatment groups and revealed to be nearly unchanged at the end of each treatment sequence. No relevant changes from the dosing at baseline was observed in both treatment groups.

Table 6: Main efficacy outcomes of trial 1200

	IAsp pre n=76 Mean (SD)	IAsp post n=74 Mean (SD)
Fructosamine		
Baseline	366.8 (73.7)	383.5 (83.3)
Week 6	378.0 (89.7)	385.4 (77.3)
Change	11.1 (73.2)	1.84 (53.7)
HbA1c		
Baseline	7.9 (1.3)	8.0 (1.4)
12-week	8.0 (1.5)	8.3 (1.5)
Change	0.034 (0.086)	0.233 (0.798)
Blood Glucose at Wk 6	8.49 (0.31)	9.15 (0.36)

The overall rate of hypoglycemic episodes per month of treatment was found to be slightly higher under IAsp pre (5.2 episodes/month) as compared with IAsp post (4.4 episodes/month). The signed rank test revealed the treatment regimens to be not significantly different (p=0.29). The rate of major hypoglycemic episodes were very rare with both treatment regimens. A total number of 3 major episodes occurred throughout the whole trial period. No relevant differences between IAsp pre and IAsp post were found.

1.3.5 Special Populations

1.3.5.1 Safety and Efficacy in Young Children (age 2-6 years); Trial 1415

A random sequence, 12-week/12-week crossover study of children, age 2-6 years, with type 1 diabetes (n=26; 17M, 9F) compared IAsp injected immediately after meals (unless the preprandial blood glucose was unacceptably high (> 250 mg/dL or the situation did not allow postprandial injection) with HI injected 30 minutes before the meals. There was no wash-out period between the periods. Extra injections of IAsp or HI were permitted in order to minimize the risk of hyperglycemia. For both treatments, NPH insulin was

administered as the basal insulin 1-4 times daily. After the first 2 weeks of each treatment period, it was recommended to continue with same daily doses and frequency for the rest of the period.

Table 7: Main efficacy outcomes of trial 1415

	IAsp	HI
Postprandial BG Increment (mmol/L)	2.02 (0.82)	1.63 (0.73)
HbA1c (%)	7.7 (0.23)	7.56 (0.25)
Fructosamine (µmol/L)	299.83 (11.04)	301.6 (11.83)
Hypoglycemia Rate (event/yr)	143.03	142.36

For the primary efficacy endpoint, the postprandial blood glucose increment after 12 weeks of treatment no significant difference was found between the IAsp and the HI treatment. The 7-point blood glucose profiles at end of treatment showed no significant differences between the IAsp and the HI treatment. Glycemic control as measured by end-of-trial levels of HbA1c and fructosamine showed no significant differences between treatments. The total dose of insulin (including NPH) was almost constant through the trial and the dose level (~0.7 U/kg) was almost the same in the two treatments; the HI dose tended to increase slightly towards the end of the treatment.

The frequency of hypoglycemic episodes was similar with the two treatments and the relative risk of episodes during HI and IAsp treatment was not significantly different from 1.0. The number and severity of adverse events was similar with the two treatments. Most events were categorized as mild and only 3 out of a total of 112 events were categorized as severe. Three serious adverse events were registered, none of which were considered related to the treatment. One non-serious skin disorder was labeled as possibly related to treatment. Almost all results from clinical laboratory tests, vital signs and physical examinations were within the reference ranges for these evaluations. None of the few 'outliers' were considered of clinical importance.

1.3.5.2 Differences between children (6-11 years) and adolescents (12-18 years)
It is a general experience that adolescence is a period of deteriorating glycemic control. Changes in lifestyle, hormonal changes and increasing responsibility for control of diabetes may all play a role in glycemic control. But an increase in insulin resistance is also found in adolescence, a finding which was also seen in the pivotal trial population, where the adolescents (12-18 years) had a higher HbA1c and needed a higher dose of insulin (U/kg) than the children (6-11 years).

HbA1c at the end of Trial 2126 was in the range 7.9%–8.2% for children (6-11 years of age) in the three treatment-groups and was in the range 8.5%-8.8% for adolescents (12-18 years of age). In children, HbA1c did not change from baseline in the IAsp+NPH and HI+NPH group but seemed to decrease slightly in the Lispro+NPH group. The lower HbA1c in children compared to adolescents was maintained throughout the trial, and was achieved with a lower insulin dose than used in adolescents.

In terms of safety, subjects in the 6 – 11 year age group had greater rates of minor hypoglycemia across all treatment groups than did subjects in the 12 – 18 year age group (6 – 11 years: 32.3, 42.4, and 41.8 episodes per subject year; 12 – 18: 19.9, 20.8, and 11.5 episodes per year for the aspart +NPH, Novolin R+NPH, or lispro+NPH groups respectively).

In Trial 060, Pediatric (age 6-11 years) and adolescent (age 12-17 years) patients in both treatment groups had comparable increases from baseline in HbA1c and fructosamine values.

Table 8: HbA1c levels stratified by age group

	IAsp (n=65)	HI (n=58)
Ages 6-11		
Baseline	8.4 (1.03)	8.5 (1.13)
12-week	9.0 (1.03)	8.8 (1.51)
Change	0.6 (0.91)	0.27 (1.51)
Ages 12-17		
Baseline	9.2 (1.45)	8.6 (1.12)
12-week	9.4 (1.42)	8.9 (0.99)
Change	0.29 (1.36)	0.27 (0.90)

Attachment #1
Recommended Label Changes

1) CLINICAL STUDIES

Delete the following statements (b) (4)

(b) (4)

2) INDICATIONS AND USAGE

Delete the word (b) (4) to become: "NovoLog is indicated for the treatment of patients with diabetes mellitus, for the control of hyperglycemia."

3) PRECAUTIONS--Pediatric Use

a) Add the following paragraph (Lines 456-465): "A 24-week, parallel-group study of children and adolescents with type 1 diabetes (n = 283) age 6-18 years compared the following treatment regimens: NovoLog (n = 187) or Novolin R (n = 96). NPH insulin was administered as the basal insulin. NovoLog achieved glycemic control comparable to Novolin R, as measured by change in HbA1c. The incidence of hypoglycemia was similar for both treatment groups. NovoLog and regular human insulin have also been compared in children with type 1 diabetes (n=26) age 2-6 years. As measured by end-of-treatment HbA1c and fructosamine, glycemic control with NovoLog was comparable to that obtained with regular human insulin. As observed in the 6 to 18 year old pediatric population, the rates of hypoglycemia were similar in both treatment groups."

b) Delete the following statement (b) (4)

4) DOSAGE AND ADMINISTRATION

a) Delete the word (b) (4) and add "may vary and" so it reads: "The total daily insulin requirement may vary and is usually between 0.5 to1.0 units/kg/day."

b) Move the following paragraph (b) (4) to Lines 508-510: "Because of NovoLog's comparatively rapid onset and short duration of glucose lowering activity, some patients may require more basal insulin and more total insulin to prevent pre-meal hyperglycemia when using NovoLog than when using human regular insulin."

Attachment #1
Summary of the Amended Pediatric Study Written Request

1. *Type of study*:
Six-month minimum, active-controlled, randomized, open-label clinical trial in children with type 1 diabetes.

2. *Objectives/Indication to be studied*:
Safety and effectiveness of NovoLog® treatment in pediatric patients with type 1 diabetes.
The objectives of the study are to determine (a) HgbA1c levels, hypoglycemia rates, and diabetic ketoacidosis rates in children with type 1 diabetes treated with NovoLog® insulin analogue before meals, and (b) whether children can be dosed with NovoLog® insulin before all meals. If alternative dosing regiments are used, these data should be captured. Alternate dosing regiments could include twice daily dosing, additional injections of basal or rapid-acting insulin, or different injection times, e.g. after meals.

3. *Age group in which study will be performed*:
Children ages 6 through 18 years old, stratified by age.

4. *Study design*:
Six-month minimum on NovoLog®, 3-arm, active-controlled (NovoLog® versus human regular insulin versus Humalog®), randomized, open-label clinical trial in children with type 1 diabetes. The comparisons in the analysis of the data should be between NovoLog®, human regular insulin, and Humalog®, dividing the alpha for each comparison.

5. *Number of patients to be studied*:
Approximately 150 patients should be randomized to NovoLog® and approximately 75 patients should be randomized to each of the control groups. All patients who have at least one post-randomization HbA1c measurement should be included in the statistical analysis.

6. *Entry criteria*:
i. Male and female patients with type 1 diabetes treated with insulin for at least one year.
ii. HgbA1c <12% at entry.
iii. Patients (parents, guardian) with the ability and willingness to perform glucose monitoring with a glucometer.

7. *Study endpoints*:
i. The primary endpoint will be change in HgbA1c from study baseline.
ii. Secondary endpoints will include the incidence and frequency of clinically significant hypoglycemia, the incidence and frequency of hyperglycemia-diabetic ketoacidosis, and fasting serum glucose values.
iii. Safety evaluation will include reporting of adverse events and evaluation for the development of anti-insulin (cross-reacting) antibodies.

8. Drug information:
dosage form*:* Injection
route of administration: Subcutaneous
regimen: Immediately before meals for NovoLog® and Humalog®; 20 to 30 minutes before meals for human regular insulin

formulation: Same as proposed for marketing in NDA 20-986

9. *Drug-specific safety concerns*:
i. The incidence, frequency, and severity of clinically significant hypoglycemia.
ii. The incidence, frequency, and severity of hyperglycemia-diabetic ketoacidosis.

10. *Statistical information, including power of study and statistical assessments*:
The analysis of the primary efficacy variable will use a statistical model with the change from baseline HgbA1c as the dependent variable, and treatment and randomization stratification factors as independent variables. Non-inferiority of the test drug compared to control will be assessed by constructing a 97.5% two sided confidence interval for the between-group difference in change from baseline HgbA1c using the least square means. The test drug will be considered non-inferior to each control if the appropriate confidence bound falls within a non-inferiority margin of 0.4%.

11. *Labeling that may result from the study*:
There may be changes to the following sections of the labeling: DOSAGE AND ADMINSITRATION, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, INDICATIONS AND USAGE, and CLINICAL PHARMACOLOGY.

12. *Format of reports to be submitted*:
Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation, with accompanying computer-based clinical and safety data listings. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

13. *Timeframe for submitting reports of the study*:
Reports of the studies that meet the terms of this Written Request must be submitted to the Agency on or before March 31, 2005, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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/s/

Kamal Gabry
9/7/2005 12:53:43 PM
MEDICAL OFFICER

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9/12/2005 03:11:08 PM
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