CLINICAL REVIEW
NDA 20986-S33
EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendation on Regulatory Action

The recommended regulatory action for this supplement and its attached label changes is APPROVAL.

1.2 Recommendation on Postmarketing Actions

Not applicable.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

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. The objective of Trial 1200 was to validate postprandial administration of insulin aspart (IAsp). The ANA-1415 trial (Trial 1415) included young children (2 to 6 years of age) and is the only trial in this age group.

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, crossover. 6 weeks on each	Serum fructosamine	76 subjects 6-17 years Type 1 diabetes.

		treatment.		
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.

2.2 Efficacy

Trial 2126 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.

For the change in HbA1c from baseline, treatment with IAsp+NPH was 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)

2.3 Safety

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.

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