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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	208751
Supplement #:	S-10 and S-11
Drug Name:	FIASP (insulin aspart injection)
Indication(s):	Pediatric patients with diabetes mellitus
Applicant:	Novo Nordisk
Date(s):	Submission Date: February 27, 2019
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Review Priority:	Standard
Biometrics Division:	DB2
Statistical Reviewer:	Jennifer Clark, PhD
Concurring Reviewers:	Yun Wang (Team Lead), PhD
	Mark Rothmann (Division Director), PhD
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Keywords: Pediatric Study, non-inferiority

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EXECUTIVE SUMMARY

The current submission is a supplemental new drug application (sNDA, supplement 10) to support expanding an indication of faster aspart (FIASP) for improved glycemic control to children with diabetes mellitus. Data from a single pediatric study which was a post-marketing requirement required under the Pediatric Research Equity Act was included in the submission. A total of 777 pediatric patients, ages ranging from 2 to 17, with type 1 diabetes mellitus (T1DM) were randomized to either mealtime FIASP, post-meal FIASP, or a NovoLog/NovoRapid control. The study met all its prespecified primary and secondary objectives of demonstrating non-inferiority of both mealtime FIASP and post-meal FIASP to control arm with a non-inferiority margin of 0.4 and superiority of mealtime FIASP over the control arm in HbA1c.

	Mealtime FIASP	**Post-meal FIASP**	**NovoLog/NovoRapid**
N	260	259	258
Week 26 Change (Week 26 – Baseline)	0.06 (0.05)	0.35 (0.05)	0.22 (0.05)
Trt vs NovoLog (95% CI)	-0.17 (-0.3, -0.03)	0.13 (-0.01, 0.26)	.

In a separate supplement (supplement 11), the applicant requested results from this pediatric study along with results from an adult device study in different supplement (supplement 8) be used to extrapolate use of the device in the pediatric population without a separate pediatric device study.

Statistical Issues and Findings

Issues from this submission include:

- Baseline measurements were taken after randomization for some patients (section 3.2.3)
- HbA1c increased from baseline at Week 26 (section 3.3.6)
- There was a slightly higher dosing of mealtime FIASP when compared to NovoLog/NovoRapid (Figure 10)
- Some patients experienced a much higher number of hypoglycemic events in the mealtime FIASP arm (Figure 12)
- There were some differences between the comparable adult and pediatric studies (section 3.3.8). Whether we can extrapolate results from this study and adult device study to support use of Fiasp in device for pediatric patients (Section 5.2)

Overall, the study did show a benefit in HbA1c for pediatric patients on mealtime FIASP when compared to NovoLog/NovoRapid. Most major issues were resolved upon further analysis with the benefit-risk assessment indicating that the large number of hypoglycemic events that a few patients experienced in the mealtime FIASP arm could outweigh the glycemic benefits they receive. This small group of patients may be better served with a different treatment (section 3.5). Patients in the NovoLog/NovoRapid arm, on average, had lower HbA1c at baseline which is likely why they also tended to have lower basal insulin doses throughout the study. It is possible that this could be due to unblinded randomization which would nullify any results seen in this study; however, it is more likely due to chance randomization. Generally, results from

this study do appear adequate to support expansion of labeling to include children in the indication.

The adult device study (Supplement 8) was reviewed by Dr. Kiya Hamilton. The Agency approved FIASP for use in insulin infusion pump for adults with Type 1 and 2 diabetes on October 22, 2019, based on this adult device study. (b) (4)

1 INTRODUCTION

The applicant, Novo Nordisk, submitted supplement 10, a Prior Approval Efficacy Supplement (sNDA), on 21 February 2019 to support the use of faster insulin aspart (FIASP) in pediatric patients with diabetes mellitus. FIASP was originally approved to improve glycemic control in adults with diabetes mellitus on 29 September 2017. The submitted phase 3b confirmatory efficacy and safety trial in T1DM pediatric subjects (NN1218-4101) was required under the Pediatric Research Equity Act (PREA) and a Post-Marketing Requirement (PMR) study described in the original approval. The initial Pediatric Study Plan (iPSP) for study NN1218-4101, an efficacy and safety study of faster-acting insulin aspart compared to NovoLog both in combination with insulin degludec in children and adolescents with type 1 diabetes, was agreed on 28 August 2015. Proposed labeling changes for section 1 include adding the term "and (b) (4)" to the current indication (italics have been added to the changes) to become, "FIASP is (b) (4) indicated to improve glycemic control in adults *and* (b) (4) with diabetes mellitus." Additionally, study results are proposed to be added to sections 6 and 14 of the label.

Currently, the active comparator insulin aspart is a fast-acting insulin analogue which is marketed as NovoRapid (NovoLog in the US) and indicated for the treatment of diabetes and approved for children as young as 1. FIASP is insulin aspart in a different formulation which can lead to greater early glucose-lowering effects when compared to NovoLog. Currently, the pediatric program for FIASP consists of 2 clinical pharmacology trials and one therapeutic confirmatory trial in pediatric subjects with T1DM. Only the confirmatory trial will be considered in this statistical review.

The applicant also concurrently submitted supplement 11 for this same NDA. This submission is meant to extrapolate efficacy results from the adult pump trial in T1DM to pediatric T1DM based on study NN1218-3854, a Phase 3b pump study currently under review in the Agency, study NN1218-4349, a completed adult single dose pump PK/PD study, and Study NN1218-4101, the current study that is reviewed here. Considerations regarding extrapolation of the adult study to the pediatric population based on results from study 4101 and the comparable adult study 3852 for supplement 11 will be included in this review. Please see the review by Dr. Kiya Hamilton for further discussions regarding extrapolation using analyses from study 3854, the adult pump study.

2 Overview

Study 4101 was a therapeutic confirmatory, 26-week, multicenter, partly double-blind, randomized, active controlled, treat-to-target, 3-armed parallel trial to compare the efficacy and safety of faster aspart with NovoRapid/NovoLog, both in combination with insulin degludec, in children and adolescents ages 1 to <18 with T1DM. The overall aim of the trial was to confirm the treatment effect and compare safety of mealtime FIASP with mealtime NovoLog in a basal-bolus regimen. A post-meal dosing arm was also included to confirm that post-meal administration of FIASP could be effective in achieving glucose control and could therefore

offer a clinically acceptable treatment option. Due to the timing of when the dose was administered, this arm was not blinded while the other two meal-time arms were blinded.

Two other studies under this NDA which have been or are currently under review are included in Table 1. References will be made in this review to study 3852 for discussions regarding extrapolation and results from the completed statistical review by Dr. Alex Cambon; analysis results cited in the statistical review signed on 2 September 2016 are used here and no new analyses were performed. Any discussions regarding extrapolation for study 3854, currently under review by Dr. Hamilton, will be included in the completed statistical review for supplement 8 under this NDA.

Table 1: Studies Referenced in this Review

Study	Design*	Treatment Arms	Study Population	Endpoint/Analysis	Supp	Statistical Reviewer	Stamp Date
4101	MC, R, PDB, PG, AC trial (26 wks)	Mealtime FIASP/ N=260 NovoLog/ N=259 Post-meal FIASP/ N=258	Children and adolescent (1-17 yrs) with T1DM	Primary Endpoint: Change in HbA1c from baseline to week 26	10 and 11	Clark	CUR*
3854	R, MC, DB, AC, treat-to-target, PG trial (26 wks)	FIASP / N=236 NovoLog / N=236	Adults with T1DM	Primary Endpoint: Change in HbA1c from baseline to week 16	8 and 11	Hamilton	CUR*
3852	R, DB, MC, AC trial (26 wks)	Mealtime FIASP/ N=381 NovoLog / N=380 Post-meal FIASP/ N=380	Adults with T1DM	Primary Endpoint: Change in HbA1c from baseline to week 26	Orig	Cambon	9/2/2016

*CUR: currently under review, MC: multi-center, R: randomized, PDB: partially double-blind, PG: parallel group, AC: active controlled, DB: double blind

2.1 History of the Submission

The original approval for FIASP included three safety and efficacy trials, one of which had an adult T1DM population (Trial 3852) and is similar to the current pediatric study. Table 6 includes results for this adult study as given in the current label. Although not explicitly stated in the label, looking at the statistical review of this study, it seems like these adult study results are taken from the pre-specified mixed model repeated measures (MMRM) analysis and not the statistical reviewer recommendation of using results from the sensitivity analysis. Methods used to derive study results should be included in the label in order to facilitate appropriate interpretation and comparability with results from similar treatments.

During the IND phase of the pediatric study, the applicant submitted the protocol and revisions three different times for which they received statistical comments for each submission. One comment which was sent for the protocol review dated 24 July 2015 requested that the applicant justify the proposed non-inferiority margin (NIM) of 0.4%. Previous studies for this product, including the adult studies, used the same NIM without appropriate justification; comments regarding this, including a request that they justify the margin, were included in the statistical review of the adult studies.

3 STATISTICAL EVALUATION

3.1 Data Sources

Material for this statistical review, including the data and clinical study report (CSR) were submitted electronically under the network path location <\\CDSESUB1\evsprod\NDA208751\0072>. The information necessary for this review was contained in Module 1 (Cover Letters, Previous Meeting Minutes, Labeling) and Module 5 (Clinical Study Report, Protocol, Amendments, Statistical Analysis Plan, Data, and Data Dictionary). Independent coding for the statistical analyses and plots was run for this review.

3.2 Data and Analysis Quality

3.2.1 Filing Issues

The initial submission had incomplete datasets wherein analysis results could not be reproduced with the incomplete data. The poor quality of the initial data submission had the potential to lead to a refuse-to-file. However, the following IR was sent to the applicant on 3 April 2019 to have them fix the filing issues before the filing deadline:

There seems to be a problem with your "adlb.xpt" dataset for Trial 4101, all data starting on row 29741 appears to be missing or set to 0. Please resend this dataset, along with any others that may have this same affliction, with all the data ASAP. If a dataset is too big to be properly submitted within one data file, you may consider split it into several files. Failure to have all the relevant data for the study endpoints and label outcomes could result in us being unable to file this submission.

The applicant response sent on 5 April 2019, included corrections to 13 datasets for Trial 4101, as well as corrections to datasets in Trials 4371 and 4265, also presumably affected by this error. Corrections to the datasets before the filing deadline meant the submission could be filed from a statistical perspective.

3.2.2 Stratification Age Groups

There were 21 instances where the age variable did not match the calculated age at baseline. In fourteen of these cases, the differences change the stratification group for the patient. All fourteen cases had an analysis age of 11 (strata group 6-11) and descriptive age as 12 (strata

group would be 12-18). All analyses run by the applicant appear to use the calculated age. As calculated age is typically more reliable, this was used in the FDA analyses.

3.2.3 Baseline Measurements

One subject in the post-meal FIASP arm had HbA1c measurements taken two weeks before randomization and at randomization. The applicant used the two-week measurement (HbA1c = 7.8) for baseline, all FDA analyses used the randomization measurement (HbA1c = 8.1) for baseline. This difference does not numerically change any analysis results.

Some subjects did not have measurements at randomization, so baseline was set as the measurements taken at visits closest to randomization; these ranged anywhere from one to nineteen days after randomization. This could potentially lead to problems if there are many patients with baseline measurements taken post study treatment exposure; however, since everyone was exposed to NovoLog in the run-in phase, it may not impact results in this study. There were eight patients in the NovoLog arm, three in the mealtime FIASP arm, and none in the post-meal FIASP arm with HbA1c baseline measurements taken after randomization. These measurements were in line with other baseline measurements taken at randomization. Sensitivity analyses pertaining to this issue indicated that these subjects were not influential in changing the results for this study.

3.2.4 Visit Windows

Visits were supposed to occur within ±3 days of the specified visit week. While most were within this range, there were some that were taken well beyond this window for the primary Week 26 visit. There were 14 subjects that were more than 2 weeks outside of the target day (±2 weeks is approximately a 1-month window). Given that HbA1c tended to increase over time after randomization, it could be that these subjects may show bigger increases in HbA1c. Sensitivity analyses looking at the 14 subjects indicated that they were not highly influential on the treatment effect.

Table 2: Number of Days Outside Visit Target Day

	Within ±3 Days	±3 to 7 Days	±7 to 14 Days	±14 to 21 Days	±21 Days or more
FIASP (meal)	196 (76.6%)	41 (16.0%)	15 (5.9%)	2 (0.8%)	2 (0.8%)
FIASP (post)	185 (72.8%)	51 (20.1%)	12 (4.7%)	3 (1.2%)	3 (1.2%)
NovoLog (meal)	202 (79.5%)	31 (12.2%)	17 (6.7%)	3 (1.2%)	1 (0.4%)

Source: Statistical reviewer's analysis

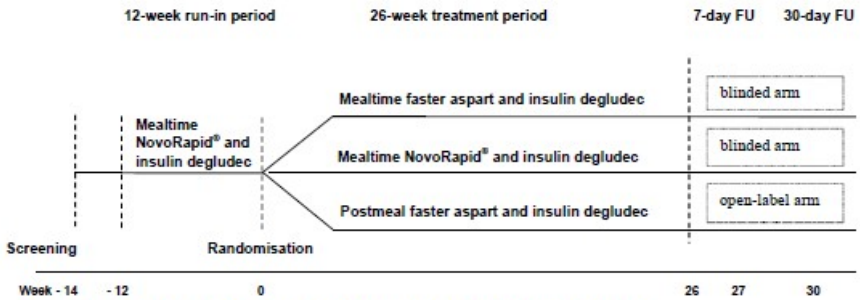
3.3 Evaluation of Efficacy

3.3.1 Study Design and Endpoints

Trial 4101 was a 26 week, randomized, partly double-blind, multicenter, multinational, active controlled, treat-to-target, 3-armed parallel-group trial with a 12-week run-in period. Treatment arms included mealtime FIASP, post-meal FIASP, and NovoLog in combination with insulin

degludec once daily in a basal-bolus regimen. The total trial duration was approximately 45 weeks with a 2-week screening period, 12-week run-in to optimize the insulin degludec dose, a 26-week treatment period, and a 7-day and 30-day follow-up period. Subjects were given NovoRapid/NovoLog during the run-in period and then switched to mealtime or post-meal FIASP or continued with NovoRapid/NovoLog in a 1:1:1 randomization. An applicant created schematic is shown in Figure 1 below. Both mealtime arms were blinded, and the post-meal arm was open-label due to the difference in timing for taking the study treatment.

Figure 1: Applicant Created Study Schematic



Source: CSR Page 55

During the 12-week run-in period, patients switched from their previous insulin treatment to insulin degludec once daily, titrated by investigators weekly to the fasting plasma glucose (FPG) pre-breakfast glycaemic target, and mealtime NovoLog. This period was focused on optimizing the basal insulin dose on a weekly basis to individual FPG targets. Much of change from week -12 to baseline, which tended to show an improvement in HbA1c (Figure 5), may be attributable to this. Patients with HbA1c at or below 9.5% who had shown ability and willingness to adhere to the trial protocol (investigator's judgement) were randomized at week 0. This entry criteria ensures that most subjects will be more likely to adhere to the study treatment during the 26-week treatment period. Adjustment of the basal insulin dose could be made if needed after randomization, but the focus after randomization was on titrating the bolus insulin. All three arms used insulin degludec in combination with the randomized study treatment. Titration during each phase was conducted using a treat-to-target principle with the target varying depending on which part of the trial the subject was in. The run-in period titrated the basal insulin towards a pre-breakfast self-measured plasma glucose (SMPG) glycemic target of 71-145 mg/dL. After randomization, bolus insulin had a pre-breakfast and pre-lunch target of 71-145 mg/dL, and a pre-dinner target of 120-180 mg/dL.

Mealtime dosing was defined as injecting 0-2 minutes before the meal; post-meal dosing was defined as injecting 20 minutes after the start of the meal. The study bolus insulin was administered for each of the 3 main meals (i.e., breakfast, lunch, and main evening meal) with additional bolus dosing allowed at the discretion of the investigator. Titration was based on the SMPG profiles recorded by the patients.

During the treatment period, adjustment of basal insulin dose was minimized, but could be adjusted if needed based on the investigator's discretion. The bolus insulin was titrated in a treat-to-target fashion to reach glycaemic pre-meal and bedtime targets. There was a high frequency of contacts in order to ensure optimal titration of FIASP and NovoLog.

Randomization was done 1:1:1 to each of the three arms after the 12-week run-in period. Randomization was stratified by age group based on the subject's age at randomization ($1 \leq age < 3$, $3 \leq age < 6$, $6 \leq age < 12$, $12 \leq age < 18$). Mealtime FIASP and NovoLog treatment groups were blinded, and the post-meal FIASP group was open-label due to the timing of the treatment administration.

3.3.2 Estimands

The primary estimand for this study was defined as the treatment difference between subjects randomized to FIASP and NovoRapid/NovoLog both in combination with insulin degludec assessed by change from baseline in HbA1c at week 26 of the study for all randomized subjects, regardless of treatment discontinuation or use of ancillary therapies. A secondary estimand was also defined for a hypothetical treatment effect assuming all subjects adhered to treatment.

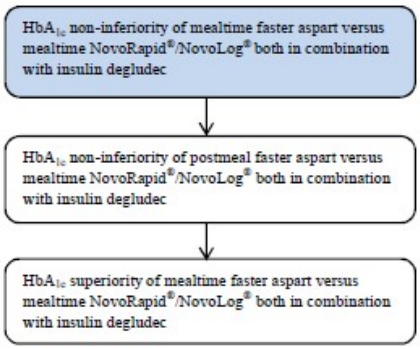
3.3.3 Statistical Methodologies

The applicant's pre-specified primary analysis used a multiple imputation (MI) regression with a missing at random (MAR) assumption for all patients missing Week 26 HbA1c measurements. The analysis was run for 100 imputed datasets using an ANCOVA model with baseline HbA1c, treatment, age strata, and region. The imputation regression used a model similar to the primary endpoint but also included week 12 HbA1c measurements within each treatment arm.

The MAR assumption with the MI analysis makes strong assumptions that those who are not followed-up at Week 26 have outcomes similar to those in the same treatment arm who are measured. Since HbA1c increased in each of the treatment arms after baseline, typically conservative sensitivity analyses such as return to baseline become anti-conservative. However, since missing data were minimal in this study (Table 4), it had little impact on their results. A sensitivity analysis applying a penalty equivalent to the NIM was run comparing mealtime FIASP to NovoLog.

Multiplicity for primary and secondary endpoints was controlled using a stepwise hierarchical testing procedure for the primary estimand. The primary non-inferiority hypothesis using a NIM of 0.4% was first in the sequence, followed by non-inferiority for post-meal FIASP vs. NovoLog, the last hypothesis in the hierarchy was for superiority of mealtime FIASP vs. NovoLog. Figure 2 shows an applicant created schematic of the hierarchy.

Figure 2: Applicant created schematic of the testing hierarchy



Source: Clinical Summary p.18

The sponsor provided a post-hoc rationale for the choice of the NIM in the study report. The sponsor cites an FDA guidance document for the NIM of 0.4%. The justification for this comes from a previous study in an adult T2DM population where the treatment effect of NovoLog vs. placebo is somewhere around -0.94% (-1.17, -0.72). The lower bound is typically used when looking to preserve treatment effect, using this lower bound of -0.72, we could expect a preserved treatment effect closer to -0.32 assuming that the T1DM treatment effect is similar to what is seen with the T2DM population.

3.3.4 Patient Disposition, Demographic and Baseline Characteristics

Baseline characteristics were generally well-balanced between the three treatment arms. Patients in Europe made up a majority of the study population, and nearly one quarter of the population from North America.

Table 3: Demographics and Baseline Characteristics

Characteristic	Category	Faster aspart (meal) N=260	Faster aspart (post) N=259	NovoLog(meal) N=258
Age	N	260	259	258
	Mean (SD)	11.7 (3.8)	11.7 (3.6)	11.7 (3.4)
	Median (Min, Max)	12.0 (2.0, 17.0)	12.0 (2.0, 17.0)	12.0 (4.0, 17.0)
Race	White	206 (79.2%)	217 (83.8%)	209 (81.0%)
	Asian	46 (17.7%)	37 (14.3%)	43 (16.7%)
	Black	6 (2.3%)	4 (1.5%)	5 (1.9%)
	Am Indian or Alaska	0 (0.0%)	1 (0.4%)	1 (0.4%)
	Other	2 (0.8%)	0 (0.0%)	0 (0.0%)
Ethnicity	Not Hispanic or Latino	244 (93.8%)	242 (93.4%)	246 (95.3%)

	Hispanic or Latino	16 (6.2%)	17 (6.6%)	12 (4.7%)
Sex	Male	134 (51.5%)	137 (52.9%)	148 (57.4%)
	Female	126 (48.5%)	122 (47.1%)	110 (42.6%)
Country	USA	67 (25.8%)	62 (23.9%)	66 (25.6%)
	Russia	32 (12.3%)	35 (13.5%)	37 (14.3%)
	Japan	24 (9.2%)	19 (7.3%)	23 (8.9%)
	Ukraine	20 (7.7%)	20 (7.7%)	20 (7.8%)
	India	22 (8.5%)	18 (6.9%)	19 (7.4%)
	Bulgaria	15 (5.8%)	15 (5.8%)	18 (7.0%)
	Czech Republic	6 (2.3%)	15 (5.8%)	15 (5.8%)
	Turkey	13 (5.0%)	15 (5.8%)	8 (3.1%)
	Israel	11 (4.2%)	9 (3.5%)	11 (4.3%)
	Italy	9 (3.5%)	10 (3.9%)	10 (3.9%)
	Poland	7 (2.7%)	9 (3.5%)	6 (2.3%)
	Serbia	5 (1.9%)	9 (3.5%)	6 (2.3%)
	Germany	8 (3.1%)	8 (3.1%)	2 (0.8%)
	Estonia	8 (3.1%)	5 (1.9%)	4 (1.6%)
	Latvia	6 (2.3%)	2 (0.8%)	5 (1.9%)
	Finland	5 (1.9%)	4 (1.5%)	4 (1.6%)
	Lithuania	2 (0.8%)	4 (1.5%)	4 (1.6%)
Region	Europe	147 (56.5%)	160 (61.8%)	150 (58.1%)
	North America	67 (25.8%)	62 (23.9%)	66 (25.6%)
	Asia (not Japan)	22 (8.5%)	18 (6.9%)	19 (7.4%)
	Japan	24 (9.2%)	19 (7.3%)	23 (8.9%)
HbA1c	N	260	259	258
	Mean (SD)	7.6 (0.8)	7.6 (0.8)	7.5 (0.8)
	Median (Min, Max)	7.6 (4.9, 10.0)	7.6 (5.6, 9.6)	7.5 (5.3, 10.6)
BMI	N	260	259	258
	Mean (SD)	19.7 (3.8)	19.7 (4.0)	19.6 (3.8)
	Median (Min, Max)	18.9 (11.8, 32.7)	18.5 (12.9, 33.5)	18.9 (12.9, 31.6)
Duration Diabetes	N	260	259	258
	Mean (SD)	4.5 (3.5)	4.4 (3.2)	4.3 (3.1)
	Median (Min, Max)	3.3 (0.5, 15.0)	3.8 (0.5, 15.3)	3.4 (0.5, 16.3)

Source: Statistical reviewer's analysis

Patient disposition, as done by the sponsor, was based on meeting certain milestone marker dates relative to the randomization date. Follow-up and treatment status, shown in Table 4, is based on when the actual week 26 visit occurred and whether the patient was on treatment at least 30 days before the primary week 26 measurement occurred.

Table 4: Treatment and HbA1c at Week 26 Status

	On Treatment	Off Treatment	Missing HbA1c
FIASP (meal)	252 (96.9%)	2 (0.8%)	6 (2.3%)
FIASP (post)	250 (96.5%)	1 (0.4%)	8 (3.1%)
NovoLog	253 (98.1%)	1 (0.4%)	4 (1.6%)

Source: Statistical reviewer's analysis

There are some differences between disposition and follow-up due to the differing criteria using dates relative to randomization vs. dates based on when the actual week 26 visit occurred.

Two patients which the applicant classified as completed the study on treatment had their week 26 HbA1c measurements taken more than 30 days after the target week 26 day, so these are considered missing in the table above but were classified by the sponsor as part of the week 26 assessment; data were not imputed in the applicant's primary analysis for these two patients. Both also had their last exposure to study treatment more than 30 days before their week 26 assessment.

One patient who completed the study on treatment did not have a week 26 HbA1c measurement, so they are also considered missing in the table even though they are also classified as someone who completed on treatment for disposition; imputation was used for this subject in the primary analysis.

Of the eighteen patients who are missing a week 26 measurement in Table 4, four had an end of study treatment date that was within 30 days of the week 26 goal date, so they could be considered missing on treatment. The MAR assumption for missing data would be more applicable for these patients than for the other patients missing a week 26 HbA1c measurement.

Two patients who were considered early discontinuers of both the study and study treatment were discontinued less than 30 days before the week 26 primary endpoint target day, so these measurements were still counted as part of the primary endpoint. Even though these patients are classified as prematurely discontinuing for the sponsor disposition, they are considered observed on treatment in Table 4; measurements for these subjects were used in the primary analysis and no imputation was done.

Three patients which are considered early discontinuers and missing for both sponsor disposition and Table 4 had measurements taken between 42 and 82 days before the week 26 primary endpoint which were used in the primary endpoint analysis. No imputation was used for these three subjects (all in post-meal FIASP) in the applicant's primary analysis. No imputation was run for the two subjects who had week 26 measurements taken more than 30 days after the week 26 target day (both in mealtime FIASP).

So, of the 18 patients considered missing in Table 4, 13 were imputed for the applicant's primary endpoint analysis. A sensitivity analysis imputing for all 18 patients in Table 4 was run for the primary analysis.

3.3.5 Results and Conclusions

The study results using the same ANCOVA model as the sponsor with a MAR MI on the 13 subjects discussed in section 3.3.4were the same as was described in the study report. Table 5 shows the average baseline HbA1c for each arm, which was similar, as well as model results for change from baseline in each arm and the treatment effect comparing both FIASP arms to NovoLog.

Table 5: HbA1c Results

	Mealtime FIASP	Post-meal FIASP	NovoLog
N	260	259	258
Mean Baseline (Std. Dev.)	7.57 (0.80)	7.58 (0.84)	7.53 (0.83)
Week 26 Change from Baseline	0.06 (0.05)	0.35 (0.05)	0.22 (0.05)
Treatment Diff vs NovoLog (95% CI)	-0.17 (-0.3, -0.03)	0.13 (-0.01, 0.26)	.

Source: Statistical reviewer's analysis

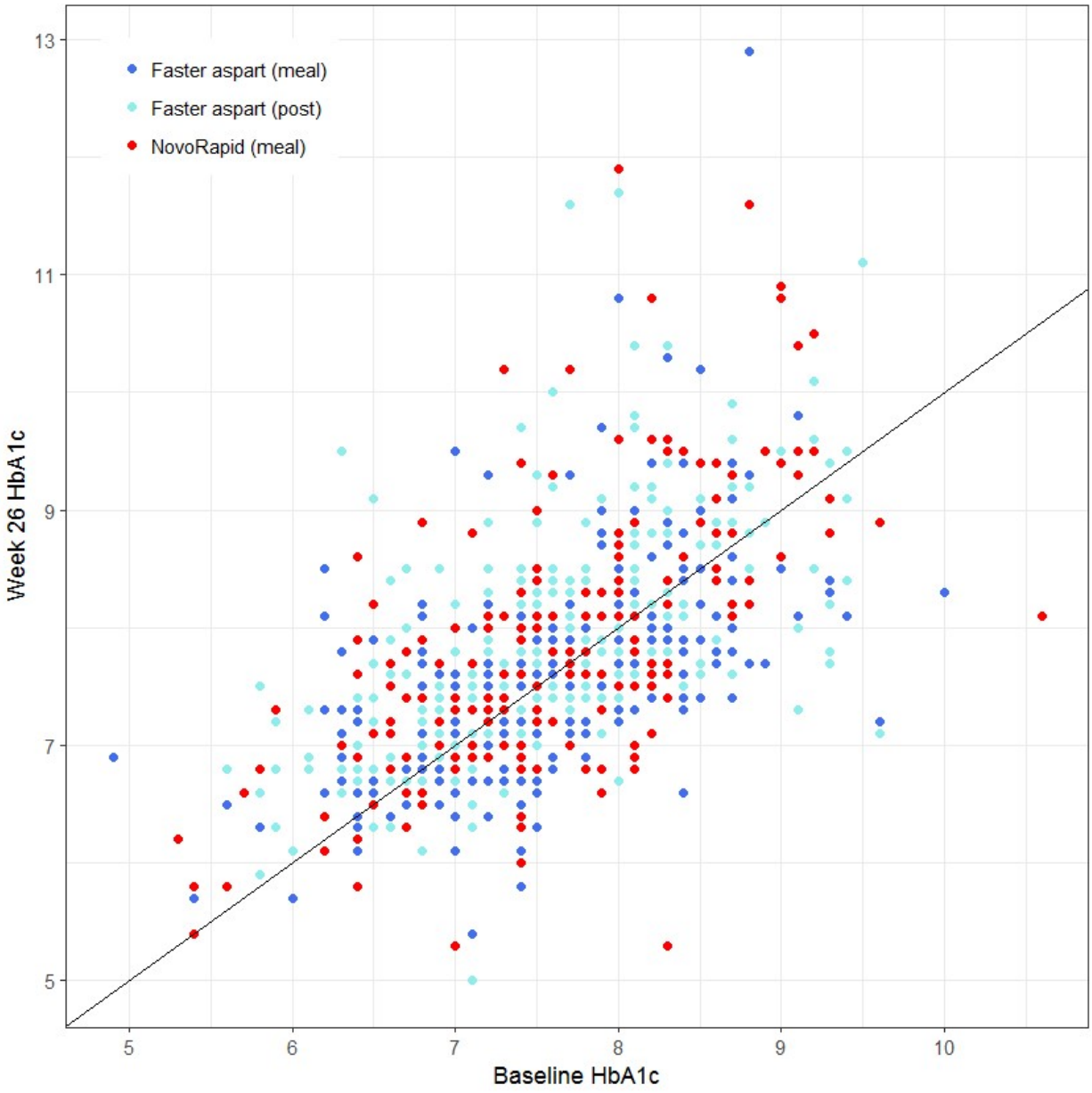
It is worth noting that change from baseline in all three treatment arms increased with higher HbA1c at week 26 than was seen at baseline. To better understand these results, further analyses were run looking at HbA1c and insulin doses over the run-in and treatment periods of the study.

Missing data were not an issue in the primary endpoint analysis. Sensitivity analysis results imputing for all 18 subjects specified in Table 4 did not change results seen in Table 5. More conservative sensitivity analyses applying a NIM penalty of 0.4% to the FIASP arms were also relatively robust with an overall treatment effect for mealtime FIASP vs. NovoLog of -0.16 (-0.3, -0.2) and post-meal FIASP vs. NovoLog as 0.14 (0.005, 0.27). Overall conclusions on non-inferiority and superiority remain the same, and nominal significance on whether post meal FIASP is worse than NovoLog remains something that should be investigated further if a unambiguous interpretation is needed.

3.3.6 HbA1c

The scatter plot below shows patients' baseline HbA1c measurements plotted against their Week 26 measurements. The diagonal line shows where baseline measurements are equal to Week 26. Patients plotted above the line have HbA1c measurements that worsened at Week 26. There does seem to be slightly more patients with measurements showing a worse HbA1c at Week 26 when compared to baseline, although they are generally scattered around the line.

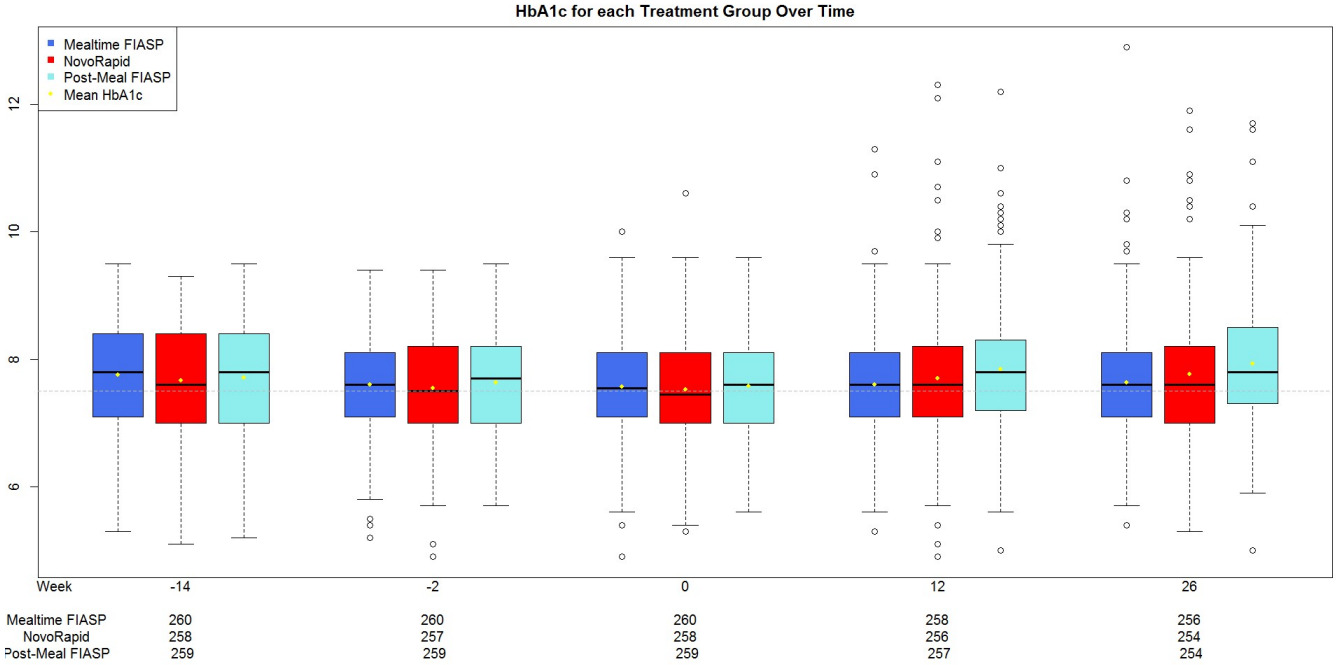
Figure 3: Baseline by Week 26 HbA1c



Source: Statistical reviewer's analysis

To better understand why these measurements are bigger after randomization we first examined the distribution of Hba1c measurements throughout the study periods. The boxplots in Figure 4 show HbA1c results for each treatment arm along with the average HbA1c and a line drawn at the target HbA1c of 7.5%. As we would expect, the distribution of HbA1c appears fairly comparable for all three arms up through baseline (week 0). Variability of HbA1c measurements seems to increase within each of the treatment arms after randomization with some increase in the mean for the post-meal FIASP and NovoLog arms. While the mealtime FIASP seems to have the least amount of increase, it also seems to have an increased variability seen in all three treatment arms.

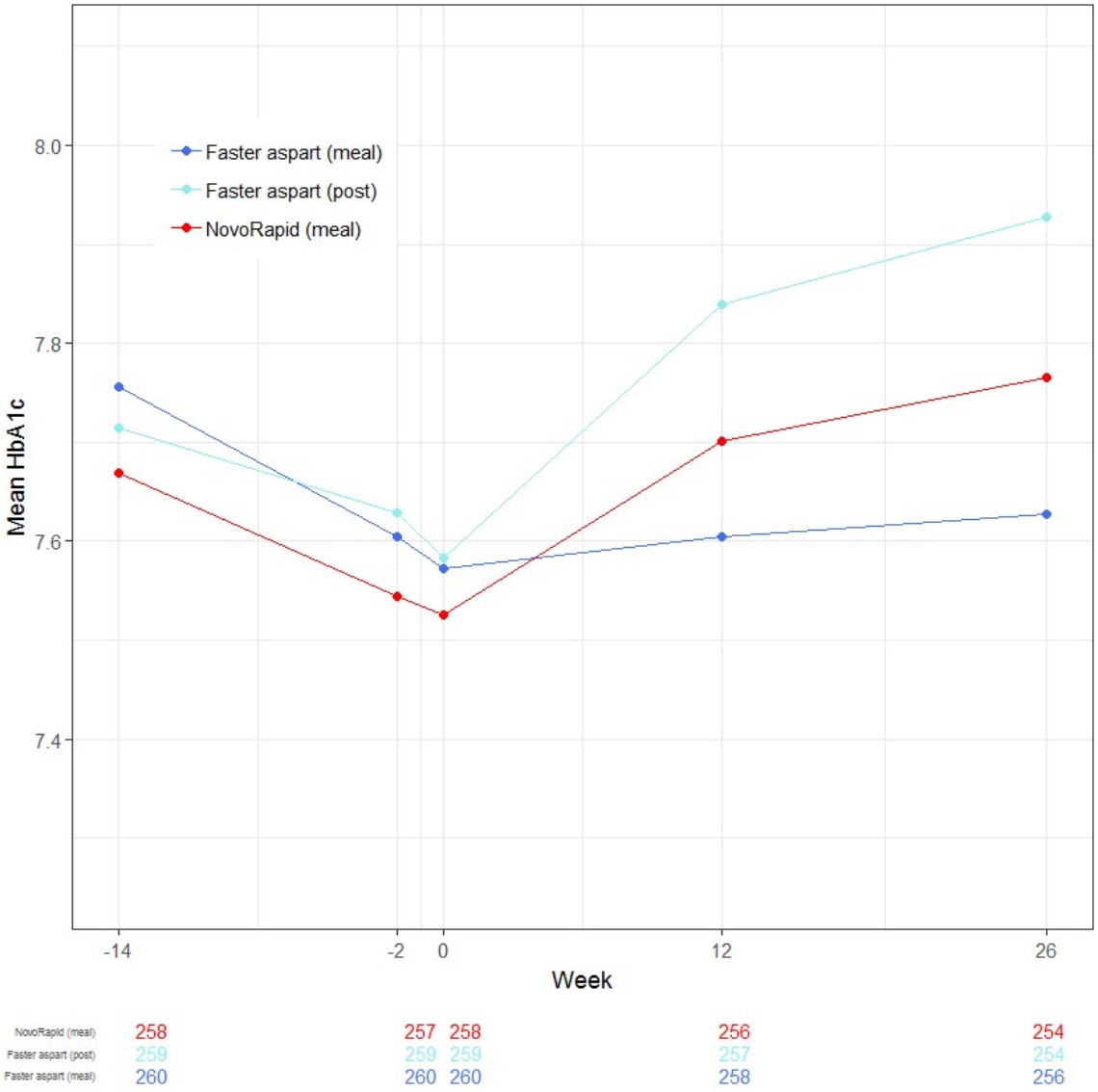
Figure 4: HbA1c over Time



Source: Statistical reviewer's analysis

The trend of HbA1c over time can more easily be seen in Figure 5 with the mean HbA1c at each visit. HbA1c was lowest at randomization. Post-randomization mealtime FIASP had the least amount of increase while post-meal FIASP had the greatest increase. The increase in NovoLog is surprising as this was what was used during the run-in period for all patients up to randomization at Week 0. Such an increase from baseline was not seen in similar adult studies for T1DM and could be indicative of a lack in adherence to treatment in the juvenile population or a consequence of the different treatment targets. This issue appears to be an issue in all three treatment arms, so it is likely not due to any specific study treatment.

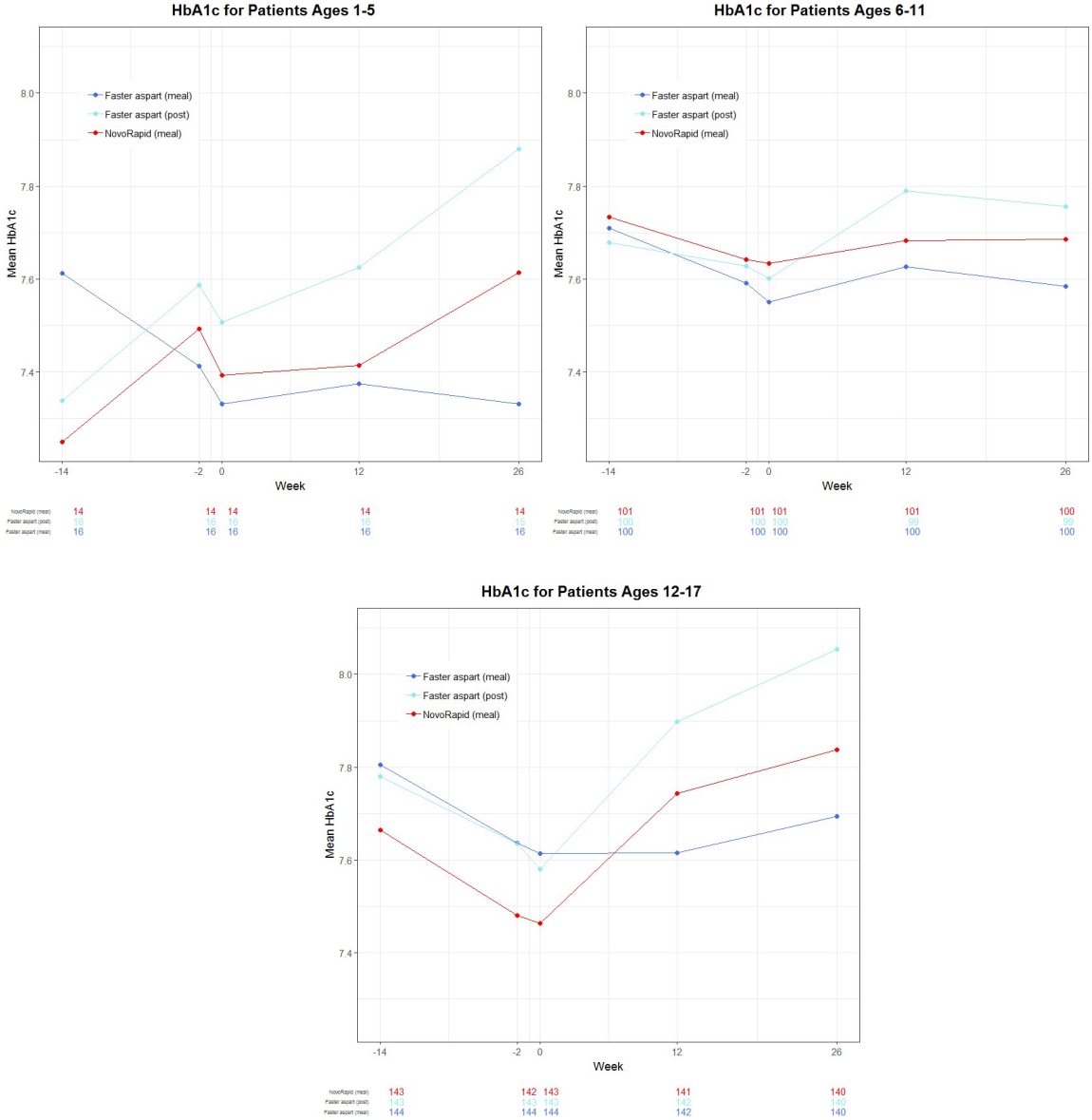
Figure 5: Mean HbA1c Over Time



Source: Statistical reviewer's analysis

Figure 6 shows mean HbA1c for each age stratification group. The patterns of HbA1c post-randomization remains similar between each of the groups with mealtime FIASP showing the smallest amount of increase and post-meal FIASP showing the greatest increase amongst the treatment arms. The biggest increases from baseline, no matter what the treatment, tend to be in the oldest age group. Interpretation for the youngest age group should be done with great caution due to the small sample size.

Figure 6: Mean HbA1c Over Time by Age Stratification



Source: Statistical reviewer's analysis

3.3.7 Study Dosing and Titration Targets

The pediatric protocol for this study specified a treat-to-target principle wherein doses were adjusted for each subject to achieve prespecified glycaemic targets. Basal insulin was titrated towards a pre-breakfast self-measured plasma glucose (SMPG) target of 4.0-8.0 mmol/L (71-145 mg/dL) during the 12 week run-in period. After randomization, titration focused on bolus insulin using the treat-to-target principle, with adjustments to basal insulin dose made if needed. The bolus insulin was titrated to a pre-breakfast and pre-lunch target of 4.0-8.0 mmol/L (71-145 mg/dL), and a pre-dinner target of 6.7-10.0 mmol/L (120-180 mg/dL).

Daily Bolus Doses

Split violin plots in Figure 7 and Figure 8 below show the distribution of daily bolus doses taken throughout the study. A kernel density estimation is used to show the distribution shape of the data. Wider sections of the plot indicate a higher probability of that particular dose. A line is drawn at the median dose for each distribution. The distribution for mealtime FIASP is shown in darker blue, post-meal FIASP in lighter blue, and NovoLog in red. Doses comparing mealtime and post-meal FIASP to NovoLog seem well matched throughout the study.

Figure 7: Bolus Dose Over Time, Mealtime FIASP and NovoLog

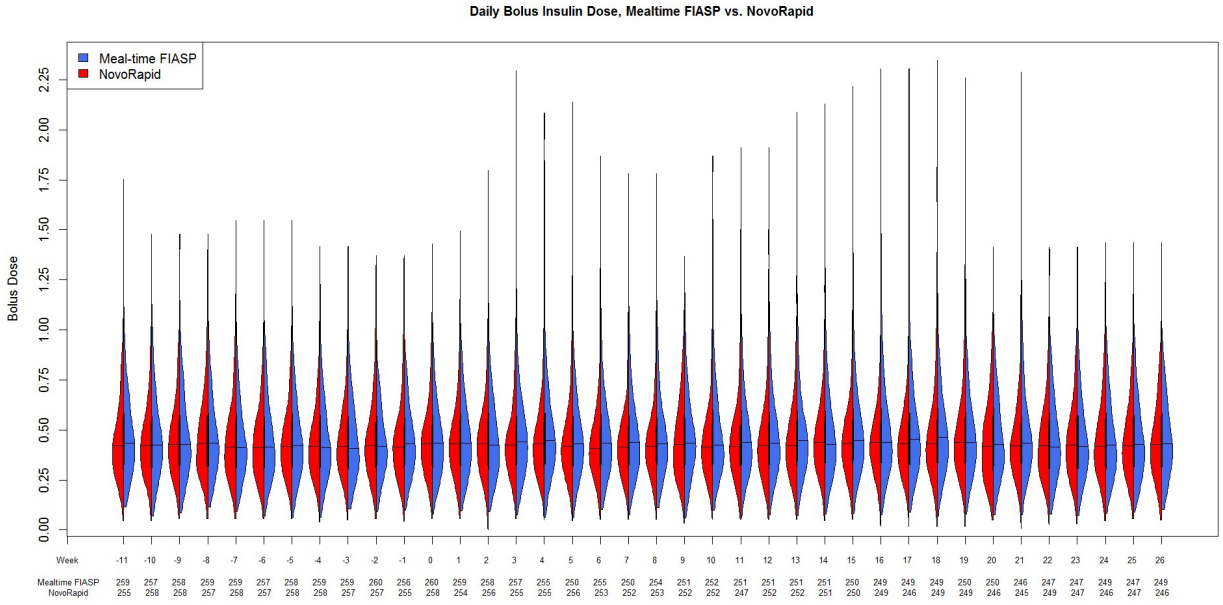
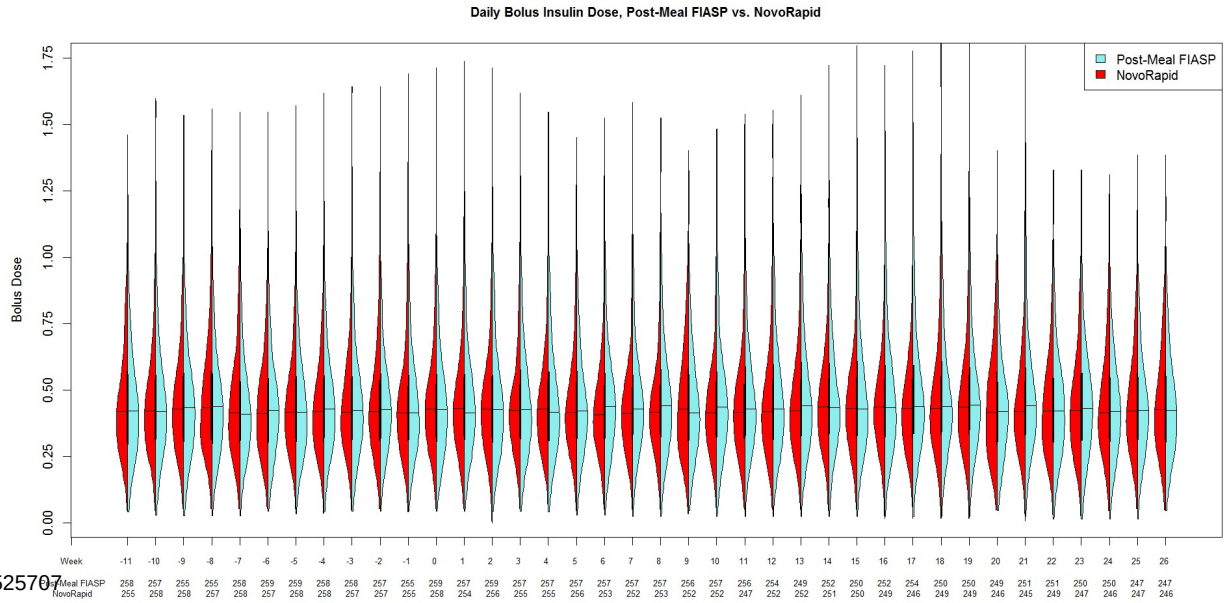


Figure 8: Bolus Dose Over Time, Post-meal FIASP and NovoLog

Source: Statistical reviewer's analysis

Daily Basal Doses Over Time

The figures below show the distribution of daily basal insulin doses throughout the run-in and treatment periods of the study. The doses of post-meal FIASP and NovoLog are relatively well matched in distribution with post-meal FIASP slightly higher at different time-points; at the



primary week 26 timepoint the distributions appear quite similar. Mealtime FIASP appears to have slightly higher median values throughout much of the study periods including at week 26. However, this trend also seems to hold during the run-in period, pre-randomization when everyone is on the same study treatment, so it is likely not due to purposeful dosing strategies to increase the study treatment effect. The patterns seen here and with HbA1c is likely due to imperfect randomization with more patients with lower HbA1c and lower basal doses randomized to NovoRapid. There is the possibility that randomization was done in an unblinded manner to have patients with lower HbA1c randomized to NovoLog, which would thereby compromise the integrity of the study and all results. However, given the amount of oversight for these types of trials, this seems an unlikely option and would be beyond the scope of this review to detect.

Figure 9: Basal Dose Over Time, Mealtime FIASP and NovoLog

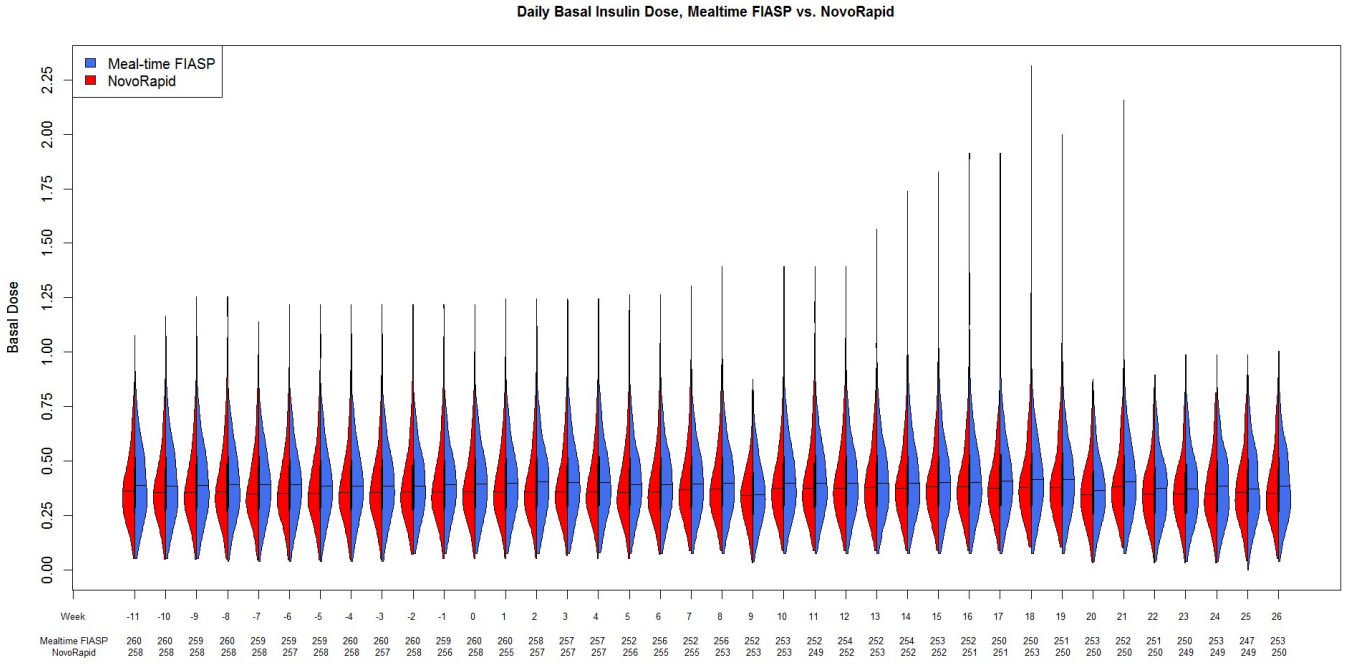
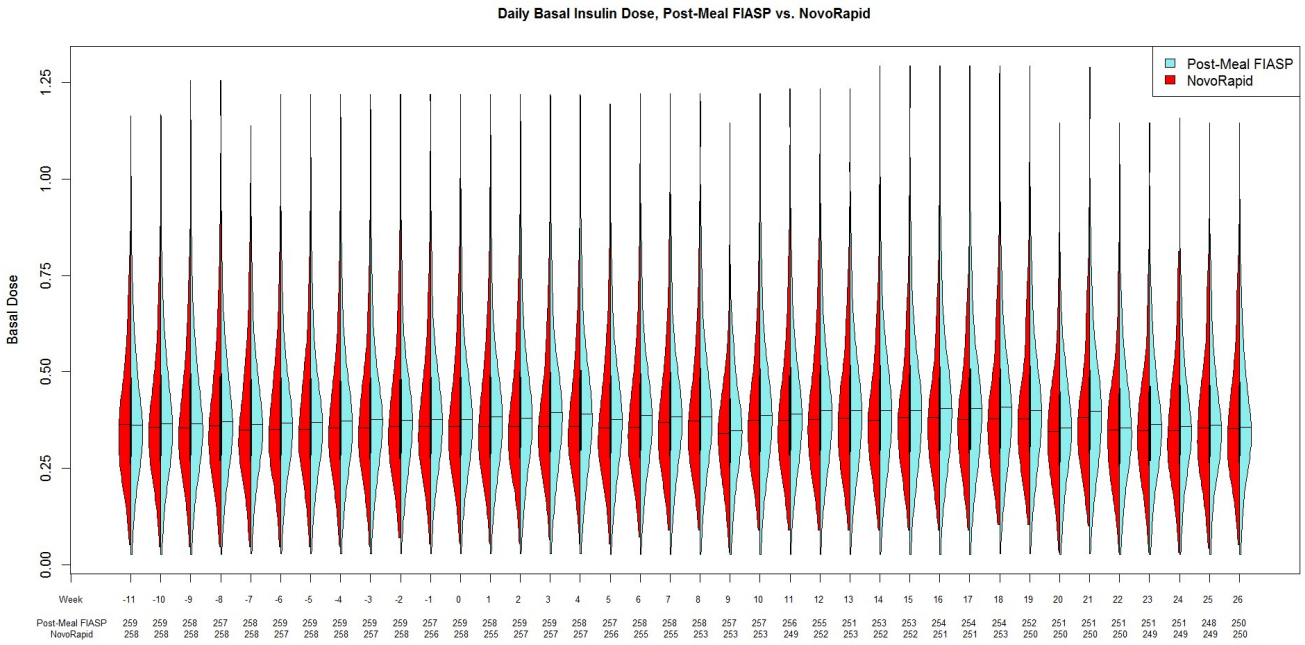


Figure 10: Basal Dose Over Time, Post-meal FIASP and NovoLog



Source: Statistical reviewer's analysis

3.3.8 Adult Study Device Extrapolation

Study 3852, T1DM Adult Study Results

Pediatric study results seen in Table 5 are different from what was seen in the adult studies where HbA1c decreased at week 26. Table 6 shows results for the adult study as they appear in the current FIASP label.

Table 6: Results from the Adult T1DM Study as they appear in the current label

	Mealtime FIASP + insulin detemir	**Post-meal FIASP + insulin detemir**	**Mealtime NovoLog + insulin detemir**
Number of subjects randomized (N)	381	382	380
HbA_{1c} (%)			
Baseline (mean)	7.6	7.6	7.6
Adjusted mean change from baseline	-0.32	-0.13	-0.17
Estimated treatment difference vs. mealtime NovoLog [95% CI]*	-0.15 [-0.23;-0.07]		
Estimated treatment difference vs. mealtime NovoLog [95% CI]*		0.04 [-0.04;0.12]	

Baseline is based on the mean of the observed last available values prior to randomization.
*Tested for non-inferiority
7.6% of subjects on the Mealtime FIASP arm, 7.6% of subjects on the Post-meal FIASP arm, and 5.3% of subjects on the Mealtime NovoLog arm were missing the final HbA_{1c} assessment.

Source: Current FIASP label, Section 14

Study 3852, an efficacy and safety study of FIASP compared to NovoLog both in combination with insulin detemir in adults with T1DM, is currently in the label from the original approval and is similarly designed to the current pediatric study but done in adults with ages ranging from 18 to 83. This used a similar treat-to-target approach throughout the study, but with different targets in the adult population than what are set for the pediatric population, please see the clinical review by Dr. Hyon Kwon for more information. The basal insulin dose was titrated during the run-in period, but with adult targets of 71-90 mg/dL for the pre-breakfast glycemic target, and a pre-dinner target of 71-108 mg/dL if a twice daily regimen was specified. The target for the pediatric study during the basal titration 12-week run-in period were specified for a pre-breakfast self-measured plasma glucose glycemic target of 71-145 mg/dL.

At randomization the bolus insulin was titrated in a treat-to-target approach to a preprandial or bedtime SMPG target of 71-108 mg/dL at the subsequent meal or bedtime for the adult study. In the pediatric study, the treatment period had pre-breakfast and pre-lunch glycemic targets of 71-145 mg/dL, and a pre-dinner target of 120-180 mg/dL for the bolus insulin titration. Although the treat-to-target approach in the study design is similar between the adult and pediatric study, the differences in the targets complicates comparabiltly between the study treatment effects. However, the studies do seperately suggest that there is a treatment effect within the adult and pediatric population. For more information on the adult studies and the results, please see the clinical review by Dr. Hyon Kwon, signed on 7 October 2016, and the statistical review by Dr. Cambon, signed on 2 September 2016.

Differences seen in the change from baseline in each of the treatment arms could be due to the titration targets being different for the pediatric population. Since the increase is smallest in the mealtime FIASP arm, treatment effect is maintained when compared to NovoLog. Post-meal FIASP has the largest increase, however, since the upper limit is below the NIM of 0.4%, it is still considered non-inferior to NovoLog. Results show a noticeably deteriorating treatment effect with an increased effect towards the control arm relative to post-meal FIASP; the treatment effect is over three times favoring control from what was seen in the comparable adult study (0.04 [-0.04, 0.12] vs. 0.13 [-0.01, 0.26]).

Even though the change from baseline to week 26 was considerably different in the pediatric study when compared to results from the comparable adult study, the overall treatment effect was somewhat preserved and similar when comparing mealtime FIASP to NovoLog. Differences between the adult and pediatric populations in treatment targets and compliance make extrapolation of the actual treatment effect seen in the adult device study, currently under review under the same NDA, difficult to determine. However, the treatment effect seen in the current pediatric study is highly indicative that there would be a treatment effect for the pediatric population using a device with this treatment if the current adult device study shows a beneficial treatment effect. While I would not recommend that the actual treatment effect seen in the adult device study be extrapolated to the pediatric population, it would be reasonable, to extrapolate that there would be a beneficial effect for the pediatric population using this treatment with a device if there is a benefit seen in the adult population.

3.4 Evaluation of Safety

Hypoglycemia

Only events classified as treatment emergent (event had an onset date on or after the first day of exposure to randomized treatment, and no later than 7 days after the last day of randomized treatment) were used to determine the total number of hypoglycaemic episodes while subjects were on study treatment. Table 7 has the classifications for each hypoglycemic event. Patients can have none or multiple events, all of the events captured in the study were included in the table. A majority of these events could not be classified for all treatment arms. While the proportion of classifications for hypoglycemic events were similar between treatment arms, there were numerically more events in the mealtime faster aspart arm.

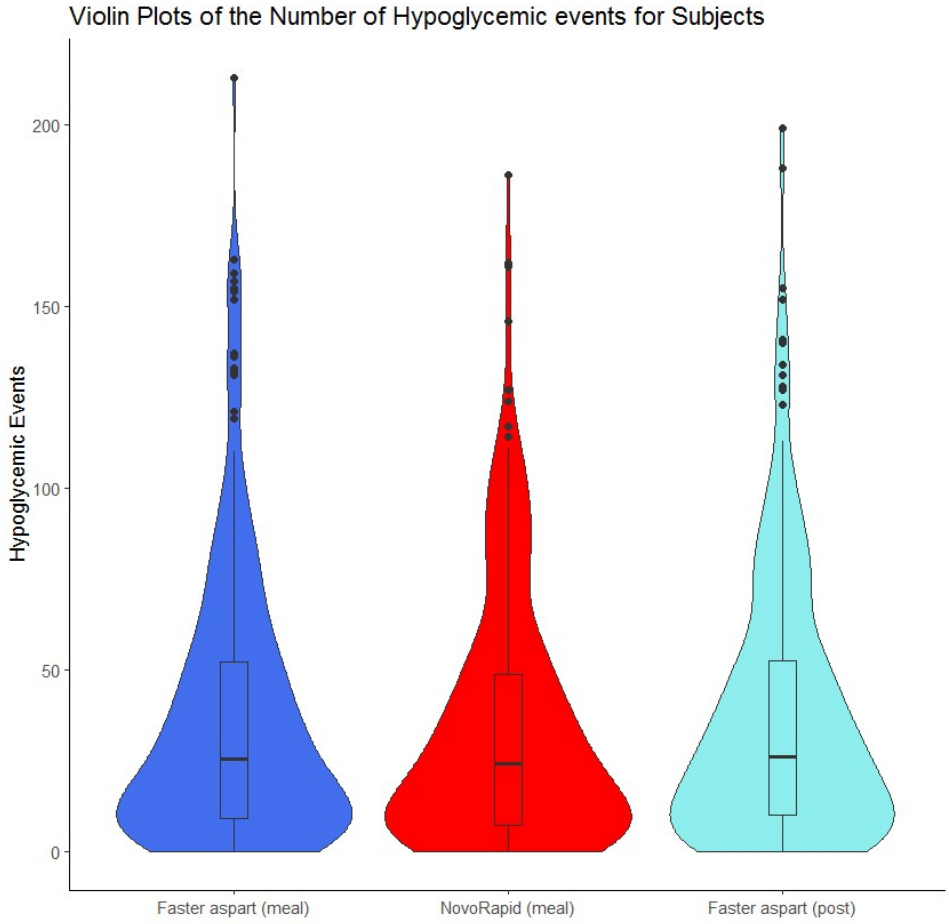
Table 7: Number of Hypoglycemic Events in each arm

	Faster Aspart (Meal)	Faster Aspart (Post)	NovoLog
Symptomatic BG Confirmed	2233 (23.08%)	2425 (25.33%)	2190 (24.6%)
Asymptomatic BG Confirmed	1338 (13.8%)	1170 (12.22%)	1082 (12.15%)
Severe	3 (0.03%)	8 (0.08%)	4 (0.04%)
Unclassifiable	6103 (63.07%)	5971 (62.37%)	5626 (63.2%)
	9677	9574	8902

Source: Statistical reviewer's analysis

Of the 777 patients in the study, only 27 did not experience a hypoglycemic event (10 (3.9%) mealtime FIASP, 8 (3.1%) post-meal FIASP, 9 (3.5%) NovoLog). Figure 11 shows violin plots which contain box plots in black for the distribution of the number of hypoglycemic events experienced by each patient in each treatment arm. So, while there were more events in the mealtime FIASP arm, the distributions for the number of events experienced by patients in the study were fairly similar, the numeric imbalance appears to be due to more outliers in the FIASP arm who also tended to have more events.

Figure 11: Violin Plots of the number of Hypoglycemic Events Experienced by Patients in each treatment arm



Source: Statistical reviewer's analysis

Most patients experiencing hypoglycemia during the study had 10 or fewer episodes in all arms. This can be seen in the overlaying histograms in Figure 12 and Figure 13 comparing each FIASP arm to NovoLog. The number of outliers, which can be seen in the tails of the histograms with the number of events (x-axis) experienced by patients within each treatment arm (y-axis), seems to be slightly higher for the mealtime FIASP arm. While there tended to be a few more outliers who tended to experience more hypoglycemic episodes in the mealtime FIASP arm which led to a numerically higher number of hypoglycemic episodes, the overall distribution patterns between the three arms are fairly similar.

Figure 12: Histogram of the number of Hypoglycemic Events Experienced by Patients, Mealtime FIASP and NovoLog

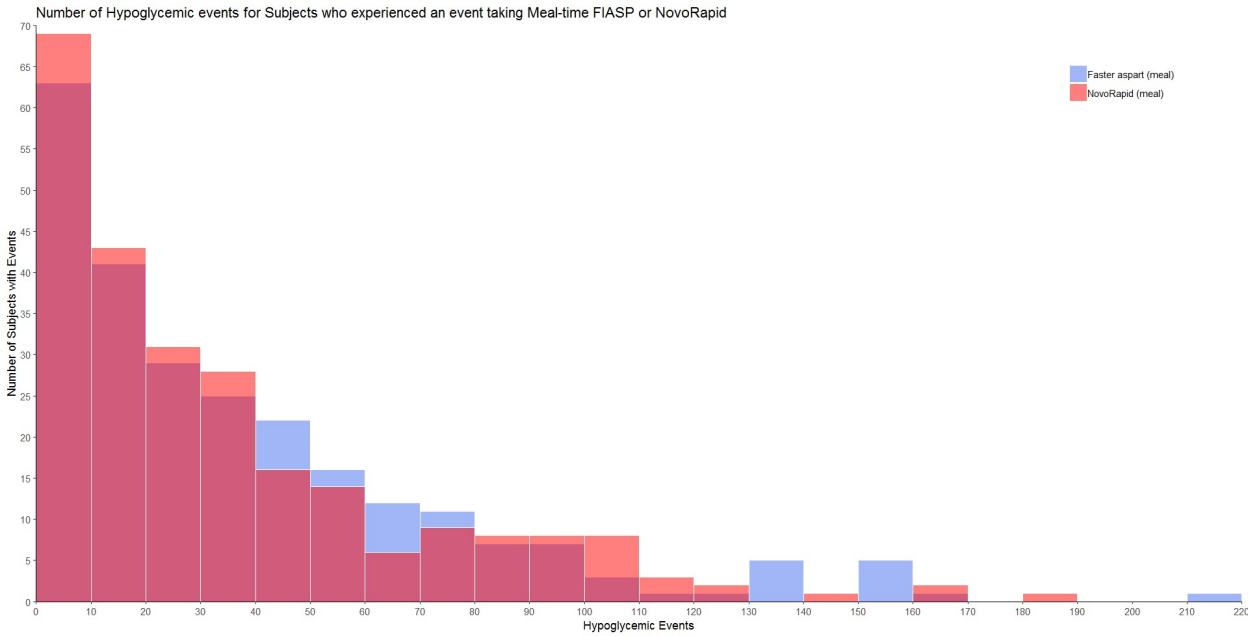
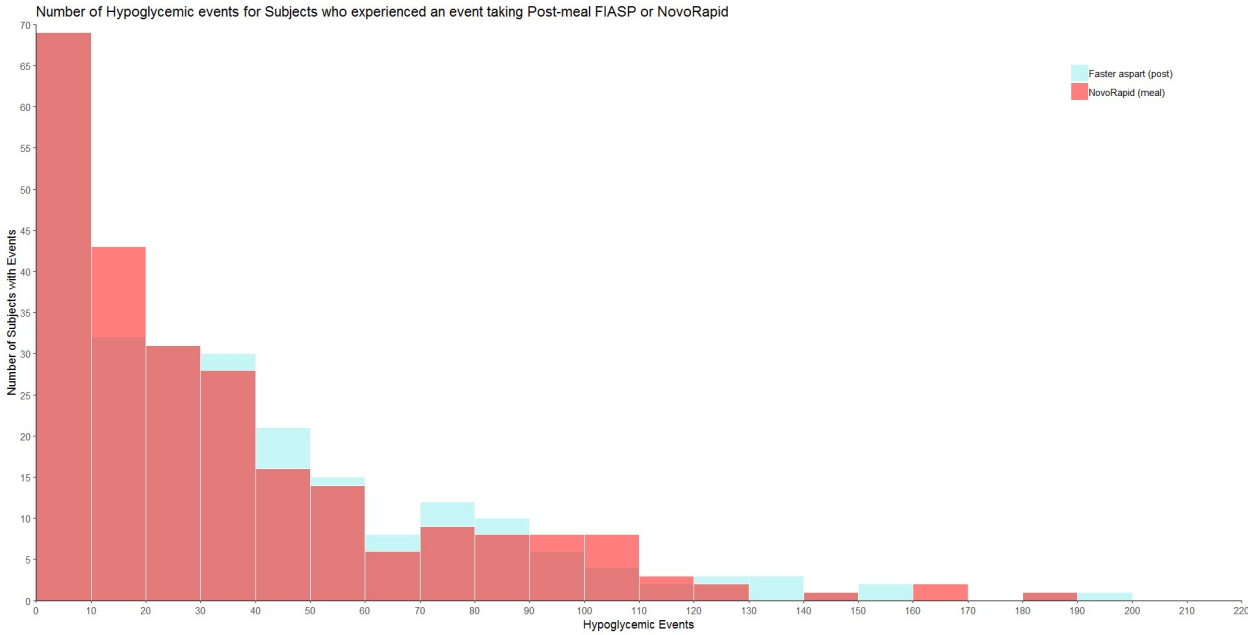


Figure 13: Histogram of the number of Hypoglycemic Events Experienced by Patients, Post-meal FIASP and NovoLog



Source: Statistical reviewer's analysis

3.5 Benefit-Risk Assessment

While HbA1c did increase from baseline, it did so in all three treatment arms and is likely indicative of the unique titration treatment targets which tend to be higher for the pediatric population. The treatment effect in this randomized trial is still preserved when comparing

blinded mealtime FIASP to mealtime NovoLog, so this population does seem to derive a benefit from mealtime FIASP. There were a few more patients in this arm that had a larger number of hypoglycemic events which led to a higher number of overall events in this arm. The numerically higher number of patients experiencing more events could be due to natural variability. If, however, there is a certain subset of patients who tend to have more hypoglycemic episodes on mealtime FIASP, there are typically no long-term consequences to these AEs, and these patients can switch to a different treatment if the risk of hypoglycemia outweighs the glycemic benefits.

There did not seem to be any additional benefit in the post-meal FIASP when compared to Novolog. While the treatment was considered non-inferior, the magnitude and direction of the treatment effect warrants further investigation for less ambiguous results. The NI design with a margin of 0.4 indicates there is likely some treatment effect preserved when comparing post-meal FIASP to placebo. The number of hypoglycemic events is similar to NovoLog with some patients who are already experiencing a moderate to higher level of events experiencing a few more events. While additional hypoglycemia does not seem to be a concern with this arm, the possible decrease of glycemic benefit makes it reasonable to recommend either of the mealtime dosing arms over this one.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

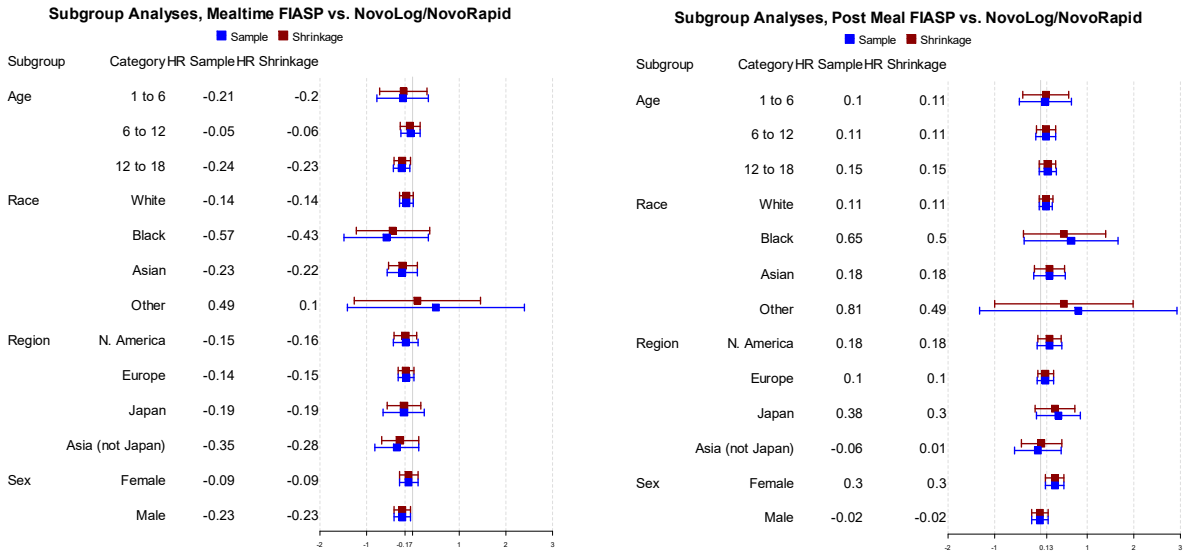
4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were done for age, race, sex, and geographic region. Analyses were first run using the same ANCOVA model with MAR MI for missing data for the primary endpoint with the subgroup and treatment by subgroup interaction added to the model and a contrast statement used to estimate the treatment effect for each subgroup. For subgroups which had some adjustment in the primary endpoint model (ie, age and region), the subgroup variable was used in lieu of the adjusting covariate if they were not the same. There are some random highs and random lows in sample estimates of subgroup treatment effects due to small sample sizes and large variability for some subgroups. To address this, shrinkage estimates of subgroup treatment effects were derived using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. We used the same flat prior to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:
For $i = 1, 2\ldots$ Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 16)$, $\tau^2 \sim$ *Half-Cauchy*(25)

Results with the sample and shrinkage estimates are shown below in Figure 14 with hazard ratios comparing mealtime FIASP and post-meal FIASP to NovoLog. In addition to reference lines, a line is drawn at the overall estimated treatment effect of -0.17 (mealtime FIASP vs. NovoLog) and 0.13 (post meal FIASP vs. NovoLog). Most results are similar between the sample and shrinkage estimates. Subgroups with the smallest sample sizes are the ones that are most affected by the shrinkage analysis as they will borrow more heavily from other subgroups. This can most easily be seen in the "Other" race subgroup which only has four patients, so the sample estimates may not be a very good estimate of the treatment effect. Subgroups with larger sample sizes and smaller variance had less shrinkage and were more like the sample estimates.

Figure 14: Forrest Plots of Subgroup Analysis Results



Source: Statistical reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

While there were a number of statistical issues analyzed and discussed throughout this review, none seemed to change the efficacy results for mealtime FIASP and post meal FIASP vs. NovoLog. The most impactful issues discussed were:

- An increase from baseline in HbA1c at Week 26
- Differences in HbA1c results when compared to the original adult study. Whether we can extrapolate results from this study and adult device study to support use of FIASP in device for pediatric patients

5.2 Collective Evidence

Evidence from the pediatric FIASP study indicates there is an improved treatment effect when comparing mealtime FIASP to NovoLog. Evidence is less conclusive comparing post meal FIASP to NovoLog, although it may be termed "non-inferior" to NovoLog with the pre-specified non-inferiority margin of 0.4%. Further exploration on this treatment effect is needed for any sort of conclusive interpretations. However, it is likely that there is some treatment effect preserved for mealtime FIASP if it were compared to placebo. There is also the possibility that a few patients may experience a higher number of hypoglycemic events on mealtime FIASP (section 3.4). It is possible that differences seen in basal doses could be due to non-blinded randomization with more subjects having lower HbA1c at baseline randomized to NovoLog. However, if we are confident in the randomization process and that the proper blinding procedures in the protocol were followed for randomization, then this is most likely due to arbitrary randomization.

The observed FIASP treatment effect in this pediatric study (Table 5) is qualitatively better than what was observed in adult device study reviewed in Supplement 8 (Table 9 in FIASP Label) and quantitively slightly better than what was observed in adult study (Table 6). While I would not recommend that the actual numeric treatment effect seen in the adult device study be extrapolated to the pediatric population, it would be reasonable to extrapolate that there is a beneficial effect of FIASP in a device for the pediatric population (Supplement 11), since the Agency approved FIASP for use in insulin infusion pump for adults with Type 1 and 2 diabetes on October 22, 2019, based on the adult device study (Supplement 8).

5.3 Conclusions and Recommendations

Statistical evidence of efficacy from this submission support approval for a pediatric indication for mealtime FIASP. While evidence is less conclusive concerning post meal FIASP, results from this arm should be included if this will be a viable option that patients may choose when prescribed this treatment (Supplement 10).

If extrapolation of benefit can be made without inferring extrapolation of the numeric treatment effect, then this study can be considered supportive for extrapolation for the pediatric population (Supplement 11).

5.4 Labeling Recommendations

Statistical methods and models used to calculate results (adjusted mean change, estimated treatment difference, etc.) should be included in the label. This can be added as a footnote in the table containing the results. This should be done for this (study 4101) and all other studies already included in the label. Currently, statistical methods and adjusting covariates and models are not included and I had to look back at previous reviews to infer what statistical methodology was used for the label (Supplement 10).

It is reasonable to infer that there is some benefit for the pediatric population if there is benefit for the adult population. However, it should not be inferred that the pediatric population will have a similar treatment trajectory as to what is seen in the adult population (Supplement 11).

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