CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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#:	NDA 208751
Drug Name:	Insulin aspart injection
Indication(s):	To improve glycemic control in adults with diabetes mellitus
Applicant:	Novo Nordisk
Date(s):	PDUFA: 10/08/2016; Primary Review Due Date: 9/2/2016 Submitted 12/08/2015
Review Priority:	Standard
Biometrics Division:	II
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Keywords: active control/non-inferiority, analysis of covariance, sensitivity analyses, missing data, drop-outs, replication

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1 EXECUTIVE SUMMARY

Novo Nordisk is seeking approval for efficacy and safety of FIAsp (insulin aspart injection). The proposed indication for FIAsp is to improve glycemic control in adults with diabetes mellitus. The existing indication for NovoLog is to improve glycemic control in adults and children with diabetes mellitus. The sponsor submitted the new drug application (NDA) on December 9, 2015.

1.1 Conclusions and Recommendations

The primary efficacy endpoint is change from baseline in HbA1c after 26 weeks of randomized treatment. In both the Type 1 and the Type 2 diabetes randomized active-control studies, the FIAsp Mealtime group was statistically non-inferior to the NovoLog Mealtime group. This finding was consistent using the sponsor's primary analysis, and also across their sensitivity analyses which addressed possible shortcomings in the primary analyses. For the open-label study comparing FIAsp plus basal to basal, superiority for 18 Week Reduction in % HbA1c was pre-specified and achieved.

1.2 Brief Overview of Clinical Studies

This submission included one randomized double-blind 26 week study for Type 1 diabetes (Study 3852) comparing both meal time FIAsp and post-meal FIAsp with meal time NovoLog, one randomized double-blind 26 week study for Type 2 diabetes (Study 3853) comparing meal time FIAsp with meal time NovoLog, and one randomized open-label 18 week study comparing FIAsp-plus-basal to basal alone. Table 1 and Table 2 give further details of study treatment arms, study designs. Tables 3, 4 and 5 provide study results for each of the three studies. Emphasis in this review is on the first two studies (the randomized, double-blind, 26-Week studies).

Table 1: Description of Study Treatment Arms

3852 (T1DM)	3853 (T2DM)	4049 (T2DM)
Meal-T FIAsp + ins. det. Post-Meal FIAsp + ins. det.	Meal Time FIAsp + insulin glargine + metformin	Meal time FIAsp and basal insulin + metformin
Meal-Time NovoLog* + ins. det.	Meal-time NovoLog* + insulin glargine + metformin	Basal insulin + metformin

*Insulin aspart trade name; Abbreviations: Ins. Aspart-insulin aspart; ins. det.- insulin detemir; T1DM Type 1 Diabetes Mellitus; T2DM –Type 2 Diabetes Mellitus.

Table 2: Description of Study Design

Study	Study Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
3852	R,AC, DT, PG, DB*, MC, MN	26 weeks	26 weeks	FIAsp M : 381 FIAsp PM: 382 NovoLog M: 380	M/F ≥ 18 years, T1DM
3853	R, DB,AC, DT, PG, DB, MC, MN	26 weeks	4 weeks	FIAsp M: 386. NovoLog M: 379	M/F ≥ 18 years with T2DM
4049	R, AC, DT, PG, OL, MC, MN	18 weeks	4 weeks	FIAsp Meal : 123 placebo: 124	M/F ≥ 18 years, T2DM

* The FIAsp Meal and NovoLog Meal arms were double-blind; the FIAsp Post Meal arm was open label; Abbreviations: R-Randomized ; PC- Placebo controlled; DT-Dose titration; DB-double-blind; OL – Open-Label; DD-Double-dummy; PG-Parallel Group; AC-Active controlled; MC-Multi-center; MN-Multi-national; M/F –Male and Female subjects; FIAsp M- FIAsp Meal; FIAsp PM – FIAsp Post Meal; NovoLog M – NovoLog Meal; T1DM-Type 1 Diabetes Mellitus, T2DM – Type 2 Diabetes Mellitus; note – study 4049 was open label because "blinding would have required a large number of injections with the bolus vehicle in the basal treatment arm" (from section 9.4.6 of Report Body). The FIAsp PM arm on study 3852 was open label for the same reason.

Table 3: Description of Primary and Sensitivity Analysis Results Study 3852

Endpoint	Arms	Analysis* Method	Difference Between Arms	UCL	LCL	P-Value
26-Week Red. HbA1c (NI)	FIAsp-M – Novo M	MMRM	-0.15	-0.23	-0.07	<.0001 (for NI Margin of 0.4)
26-Week Red. HbA1c (NI)	FIAsp-M – Novo M	Switch to NovoLog after WD	-0.14	-0.22	-0.06	<.0001 (NI margin of 0.4

* Models other than MMRM are ANCOVA; Abbreviations: MMRM-Mixed Effects Repeated Measures Model; Red.- reduction; Novo M.-NovoLog Mealtime; FIAsp M. Faster acting Insulin Apart - Mealtime; FIAsp PM- FIAsp Post Meal; WD-Withdrawal

Table 4: Description of Primary and Sensitivity Analysis Results Study 3853

Endpoint	Arms	Analysis* Method	Difference Between Arms	UCL	LCL	P-Value
26-Week Red. HbA1c -NI	FIAsp-M – Novo M	MMRM	-0.02	-0.15	0.10	<.0001 (NI margin of 0.4)
26-Week Red. HbA1c -NI	FIAsp-M – Novo M	Switch to NovoLog after WD	-0.02	-0.15	0.11	<.0001 (NI margin of 0.4)

* Models other than MMRM are ANCOVA; Abbreviations: MMRM-Mixed Effects Repeated Measures Model; Red.- reduction; Novo M.-NovoLog Mealtime; FIAsp M. Faster acting Insulin Apart - Mealtime; FIAsp PM- FIAsp Post Meal; WD-Withdrawal

Table 5: Description of Primary and Sensitivity Analysis Results-Study 4049

Endpoint	Arms	Analysis* Method	Difference Between Arms	UCL	LCL	P-Value
18-Week Red HbA1c	FIAsp + Basal - Basal	MMRM	-0.94	-1.17	-0.72	<.0001 (Superiority)
18-Week Red HbA1c	FIAsp + Basal - Basal	Switch to Basal after WD	-0.92	-1.15	-0.70	<.0001

* Models other than MMRM are ANCOVA; Abbreviations: MMRM-Mixed Effects Repeated Measures Model; Red.- reduction; IT-inferior treatment (treatment inferior to NovoLog, using a non-inferiority margin of 0.4); Novo M.-NovoLog Mealtime; FIAsp M. Faster acting Insulin Apart - Mealtime; FIAsp PM- FIAsp Post Meal; WD-Withdrawal

1.3 Statistical Issues and Findings

This section addresses missing data and treatment dropouts. For further details concerning missing data and treatment dropouts, see Section 3.2.2.2 and Tables 5 and 6.

Study 3852 (T1DM) Missing 26-Week Assessment (HbA1c):

- For the 381 subjects randomized to the FIAsp Meal arm, 29 (8%) had missing data.
- For the 382 subjects randomized to the FIAsp Post Meal arm, 29 (8%) had missing data.
- For the 380 subjects randomized to the NovoLog Meal arm, 20 (5%) had missing data.

Study 3853 (T2DM) Missing 26-Week Assessment (HbA1c):

- For the 345 subjects randomized to the FIAsp Meal arm, 41 (12%) had missing data.
- For the 344 subjects randomized to the NovoLog Meal arm, 35 (10%) had missing data.

Study 3852 (T1DM) Treatment Dropouts:

- On the FIAsp Meal arm, 28 (7%) of subjects discontinued treatment before week 25.
- Only 2 of these 28 subjects had a non-missing 26-Week Assessment.
- On the FIAsp Post Meal arm, 32 (8%) of subjects discontinued treatment before week 25.
- Only 5 of these 32 subjects had a non-missing 26-Week Assessment.
- On the NovoLog Meal arm, 18 (5%) of subjects discontinued treatment before week 25.
- Only 2 of these 18 subjects had a non-missing 26-Week Assessment.

Study 3853 (T2DM) Treatment Dropouts:

- On the FIAsp Meal arm, 45 (13%) of subjects discontinued treatment before week 25.
- Only 6 of these 45 subjects had a non-missing 26-Week Assessment.
- On the NovoLog Meal arm, 39 (10%) of subjects discontinued treatment before week 25.
- Only 7 of these 39 subjects had a non-missing 26-Week Assessment.

2 INTRODUCTION

2.1 Overview

This submission included three confirmatory safety and efficacy trials: studies 3852, 3853, and 4049. The sponsor is seeking approval for efficacy and safety of FIAsp (insulin aspart injection) to improve glycemic control in adults with diabetes mellitus.

Trial 3852 was a 26 +26 week parallel three-arm randomized double-blind basal-bolus treat-to-target active-control study with an 8 week run-in period for basal insulin titration.

- Type 1 diabetes mellitus patients.
- Patients randomized in a 1:1:1 fashion to mealtime FIAsp, post meal FIAsp, or to insulin aspart (NovoLog).
- All three arms in combination with insulin detemir.
- Open-label post-meal FIAsp arm.

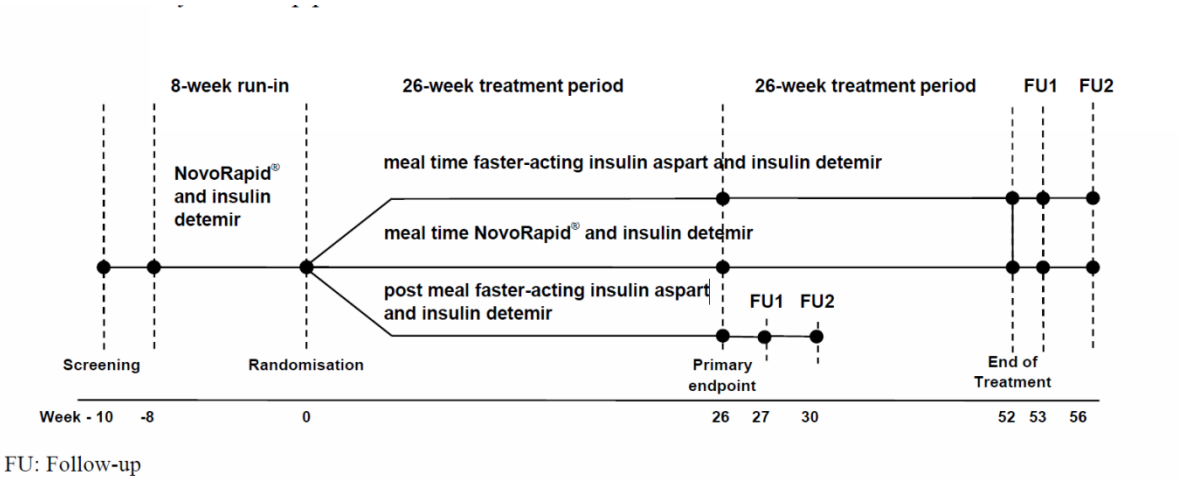
Study 3853 was a 26-week parallel two-arm randomized double-blind basal-bolus treat-to-target active-control study with an 8 week run-in period for basal insulin titration.

- Type 2 diabetes mellitus patients.
- Patients randomized in a 1:1 fashion to mealtime FIAsp or insulin aspart.
- Both arms in combination with insulin glargine and metformin.

Study 4049 was an 18-week two-arm, randomized, basal-bolus vs. basal, treat-to-target, active-control study with an 8 week run-in period for basal insulin titration.

- Type 2 diabetes mellitus patients.
- Open-label.
- Patients randomized in a 1:1 fashion to mealtime FIAsp plus basal insulin or basal insulin.
- Both arms in combination with metformin.

Figures 1-3 below give further details of study design for each of the three studies.



FU: Follow-up

Figure 1: Design for Study 3852
(Taken from sponsor Statistical Analysis Plan for Study 3852, Figure 1.1, Page 6)

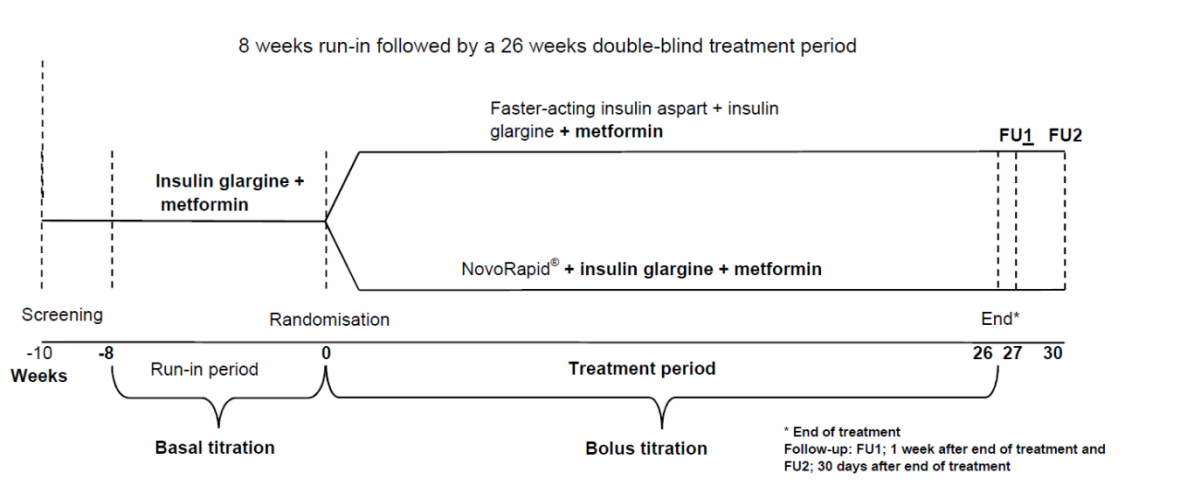


Figure 2: Design for Study 3853
(Taken from sponsor Statistical Analysis Plan for Study 3853, Figure 2.1, Page 8)

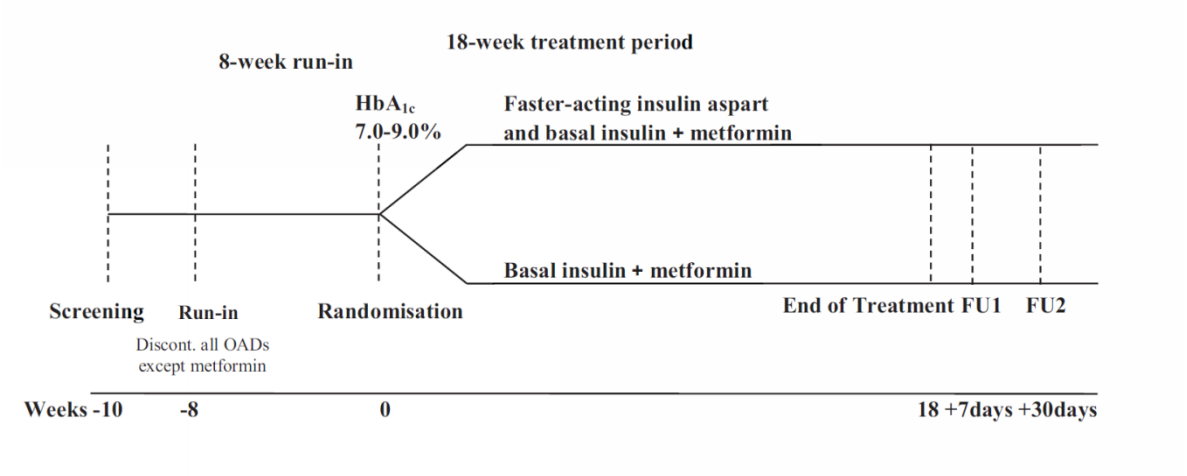


Figure 3: Design for Study 4049
(Taken from sponsor Statistical Analysis Plan for Study 4049, Figure 1.1, Page 4)

2.1.1 Class and Indication

FIAsp has the same active ingredient as NovoLog (Insulin aspart). However FIAsp has a new formulation which results in a faster initial absorption of insulin aspart following subcutaneous injection. Insulin aspart is homologous to human insulin, with the exception of the substitution of aspartic acid for proline. This substitution is related to faster absorption.

The proposed indication for FIAsp is to improve glycemic control in adults with diabetes mellitus. The existing indication for NovoLog is to improve glycemic control in adults and children with diabetes.

2.1.2 History of Drug Development

On February 1, 2010, Novo Nordisk submitted IND 106878, NN1218, for faster-acting insulin aspart (FIAsp). On June 7, 2000, NDA 020986 for NovoLog was approved. The End-of-Phase 2 meeting for this NDA was held on March 2, 2011. NovoLog is the active-control used for studies 3852 (T1DM) and 3853 (T2DM). NovoLog has the name NovoRapid in Europe. The NDA 208751 currently under consideration was submitted on 12/09/2015.

2.2 Data Sources

The data and final study report for NDA 208751 were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link.

\\CDSESUB1\evsprod\NDA208751\208751.enx

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The SDTM and ADaM data sets are located in the proper sections of the submission, and analysis reviewer guides are provided which defined variables and their locations.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary and secondary endpoints for the three studies are shown in Table 6 below. Note that steps 1, 2, and 4 for Study 3852 are similar to steps 1, 2 and 3 for Study 3853. Step 3 in Study 3852 includes the FIAsp Post Meal arm, which is not included in Study 3853.

Table 6: Primary and Secondary Endpoints

Study	Endpoint Type	Description
3852	Primary	Change from baseline in HbA1c after 26 weeks ORT (FIAsp M vs Nov. M, NI)
3852	Key Secondary	Change from baseline in 2-hour PPG increment after 26 weeks ORT (FIAsp M vs. Nov. M, Sup.)
3852	Key Secondary	Change from baseline in HbA1c after 26 weeks ORT (FIAsp PM vs. Nov. M, NI)
3852	Key Secondary	Number of treatment emergent severe or BG confirmed hypoglycemic events from baseline until week 26 (FIAsp M vs Novo M, Sup.)
3852	Key Secondary	Change from baseline in body weight after 26 weeks ORT (FIASP M vs. Nov. M, Sup.)
3852	Key Secondary	Number of treatment emergent severe or BG confirmed hypoglycemic events from baseline until week 26 (FIAsp PM vs Novo M, Sup.)
3852	Key Secondary	Change from baseline in body weight after 26 weeks ORT (FIAsp PM vs. Nov. M, Sup.)
3853	Primary	Change from baseline in HbA1c after 26 weeks ORT (NI)
3853	Key Secondary	Change from baseline in 2-hour PPG increment after 26 weeks ORT (Sup.)
3853	Key Secondary	Number of severe or BG confirmed hypoglycemic episodes from baseline to week 26 (Sup.)
3853	Key Secondary	Change from baseline in body weight after 26 weeks ORT
4049	Primary	Change from baseline in HbA1c after 18 weeks of treatment (Sup.)

Abbreviations: ORT-Of Randomized Treatment; NI – Non-Inferiority; Sup.-Superiority; M – Mealtime; PM-Post Meal; Novo-NovoLog; PPG - Post Prandial Glucose

3.2.1.1 Multiple Testing Procedure

Hierarchical testing is used for each of the three studies. For each study, endpoints are tested in the order given in Table 6, and only if significance is achieved (alpha<0.025, one-sided) does testing continue on to the next endpoint in the hierarchy.

3.2.1.2 Non-Inferiority Margin

It should be noted that, for the primary endpoints in studies 3852 and 3853 (26-week reduction in HbA1c – FIAsp Meal vs. NovoLog Meal) justification for the non-inferiority margin of 0.4% has not (yet) been provided by the sponsor (see the draft Guidance for Industry – Non-inferiority Clinical Trials: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.). However, the upper confidence bounds for the treatment difference in Study 3852 is negative, and in Study 3853 it is estimated at 0.10% using the sponsor's primary analysis, and 0.15% using the sponsor's sensitivity analyses which assumes that subjects who withdraw are switched to a treatment inferior (by the non-inferiority margin of 0.4%) to NovoLog.

3.2.2 Statistical Methodologies

3.2.2.1 Sponsor Statistical Methodology

For studies 3852 and 3853, the sponsor's defined primary analysis was Mixed Effects Repeated Measures (MMRM). The response variable was 26-week reduction in HbA1c. From Section 9.7.5.1 and 9.7 of the Report Body:

> This model included treatment, region and stratification as fixed effects, subject as random effect, HbA1c at baseline as covariate and interactions between all fixed effects and visit and between the covariate and visit. An unstructured covariance matrix was used to describe the variability for the repeated measurements for a subject.
>
> Stratification included eight strata: combination of method for adjusting bolus insulin [carbohydrate counting or bolus algorithm], basal treatment regimen [once or twice daily], CGM and frequently sampled meal test subgroup [yes or no]).

However the sponsor also incorporated sensitivity analyses which used ANCOVA models and pattern mixtures for missing data. These patterns assume that subjects who have a missing 26-Week assessment are switched to NovoLog or an inferior treatment after withdrawal. This may be reasonable in situations where rescue medication is used. Switching to NovoLog or an inferior treatment is accomplished as follows: missing data are imputed sequentially (by visit) based on non-missing data on the NovoLog arm only, using stratification factors and region. In this way, the "switch" to NovoLog or an inferior treatment occurs at the first missing visit for each subject.

One possible shortcoming in this approach may be that only subjects with non-missing data on the NovoLog arm (the completers) are used to impute missing data. For Study 3852, the impact of this shortcoming is somewhat lessened by the fact that the missing rate on the NovoLog arm is only 5%. For Study 3853 the missing rate is 10% on the NovoLog arm. The sponsor's sensitivity analyses which assume subjects are switched to NovoLog or an inferior treatment attenuates somewhat the treatment difference found in the primary analysis. However findings are still consistent with those in the primary analysis. Table 4 shows results for primary analysis as well as the Switch-to-NovoLog sensitivity analysis for Study 3853. As well, I performed a Return-to-Baseline (or "wash-out") analysis for this study. Results from this analysis were similar to the

sponsor's Switch-to-NovoLog approach. The Return-to-Baseline approach may not be reasonable in situations where rescue medication is used, but here I use it to show that treatment difference estimates and confidence intervals do not change much if assumptions using the Switch-to-NovoLog approach are violated in this manner.

Primary Analysis Population

The primary analysis population was defined as all randomized subjects.

3.2.2.2 Characterization of Missing Data

Missing Measurements

The rate of missing primary efficacy data was 7% for Study 3852 (Table 7). The primary endpoint is regarded as missing for a subject if there is no HbA1c measurement during the week 26 visit. The control group (NovoLog) had less missing data than the other two arms (5% for control group, compared to 8% for each of the other two arms), and fewer subjects that discontinued treatment before 25 weeks (5% for the control group, compared to 7% for the FIAsp Meal arm and 8% for the FIAsp Post Meal Arm). For Study 3853 (Table 8), the proportion of subjects with missing data was 11% (12% on the FIAsp arm and 10% on the NovoLog arm).

Few Retrieved Dropouts

For Study 3852, only 2 of 28 subjects on the FIAsp Meal arm who discontinued treatment before 25 weeks had a primary endpoint measurement (Table 7). As well, only 5 of 32 on the FIAsp Post Meal arm and 2 of 18 on the NovoLog Meal arm had a primary endpoint measurement. For Study 3853 (Table 9), only 6 of 45 subjects on the FIAsp Meal arm and 7 of 39 subjects on the NovoLog Meal Arm who discontinued treatment before 25 weeks had a primary endpoint assessment (Table 8). Because of the sparsity of retrieved dropouts, there was limited information to conduct an analysis which incorporated this information.

Finally, from Tables 7 and 8, it does not appear that treatment discontinuation is associated with baseline HbA1c values.

Table 7: Study 3852 (T1DM) Treatment and Discontinuation Status for Week 26 %HbA1c

Treatment Group	FIAsp M	FIAsp M	FIAsp Post	FIAsp Post	Novo M	Novo M
N per Group	**353**	**28**	**350**	**32**	**362**	**18**
Treatment Duration Group	>= 25 Weeks	< 25 Weeks	>= 25 Weeks	< 25 Weeks	>= 25 Weeks	< 25 Weeks
Change from Baseline						
N	350	2	348	5	358	2
Mean (95%CI)	-0.3 (-0.4 - -0.3)	-0.6 (-0.8 - -0.4)	-0.1 (-0.2 - -0.1)	-0.4 (-0.6 - -0.3)	-0.2 (-0.2 - -0.1)	-1.5 (-1.7 - -1.2)
Median (min - max)	-0.3 (-2.8 - 1.4)	-0.6 (-1.0 - -0.2)	-0.1 (-1.9 - 1.7)	-0.4 (-1.2 - 0.2)	-0.2 (-1.8 - 3.4)	-1.5 (-1.9 - -1.0)
Missing	3	26	2	27	4	16
Percent Change from Baseline						
N	350	2	348	5	358	2
Mean (95%CI)	-3.9 (-4.7 - -3.2)	-7.7 (-10.2 - -5.2)	-1.5 (-2.3 - -0.8)	-5.1 (-7.2 - -3.0)	-1.9 (-2.7 - -1.0)	-15.8 (-19.1 - -12.5)
Median (min - max)	-4.1 (-34.1 - 17.6)	-7.7 (-12.5 - -2.9)	-1.5 (-21.3 - 22.4)	-5.7 (-12.9 - 2.9)	-2.5 (-23.1 - 43.0)	-15.8 (-20.9 - -10.8)
Missing	3	26	2	27	4	16
Baseline Value (C)						
N	353	28	350	32	362	18
Mean (95%CI)	8 (8 - 8)	8 (8 - 8)	8 (8 - 8)	8 (8 - 8)	8 (7 - 8)	8 (8 - 8)
Median (min - max)	8 (6 - 10)	8 (7 - 10)	8 (6 - 9)	8 (7 - 10)	8 (6 - 10)	8 (7 - 9)
Treatment Duration (Weeks)						
N	353	28	350	32	362	18
Mean (95%CI)	26.3 (26.2 - 26.4)	11.0 (8.1 - 13.9)	26.4 (26.4 - 26.5)	13.4 (10.7 - 16.1)	26.3 (26.3 - 26.4)	17.7 (14.8 - 20.5)
Median (min - max)	26.1 (25.0 - 31.3)	9.6 (1.0 - 24.9)	26.1 (25.0 - 32.3)	13.0 (0.3 - 24.9)	26.1 (25.0 - 29.9)	18.1 (2.9 - 24.7)

Abbreviations: Novo-NovoLog; M-Meal; Post – Post Meal

Table 8: Study 3853 (T2DM) Treatment and Discontinuation Status for Week 26 %HbA1c

Treatment Group	**FIAsp M**	**FIAsp M**	**Novo M**	**Novo M**
N per group	**300**	**45**	**305**	**39**
Treatment Duration Group	>= 25 weeks	< 25 weeks	>= 25 weeks	< 25 weeks
Change from Baseline				
N	298	6	302	7
Mean (95%CI)	-1.4 (-1.5 - -1.3)	-1.4 (-1.6 - -1.2)	-1.4 (-1.5 - -1.3)	-1.1 (-1.6 - -0.7)
Median (min - max)	-1.5 (-4.2 - 1.3)	-1.2 (-2.4 - -0.6)	-1.4 (-3.8 - 2.6)	-1.4 (-2.8 - 1.5)
Missing	2	39	3	32
Percent Change from Baseline				
N	298	6	302	7
Mean (95%CI)	-17.7 (-18.9 - -16.5)	-16.7 (-19.1 - -14.4)	-16.9 (-18.2 - -15.7)	-13.0 (-18.3 - -7.8)
Median (min - max)	-18.7 (-47.2 - 16.7)	-14.7 (-27.0 - -8.6)	-17.6 (-46.3 - 31.3)	-18.5 (-30.8 - 19.2)
Missing	2	39	3	32
Baseline Value (C)				
N	300	45	305	39
Mean (95%CI)	8 (8 - 8)	8 (8 - 8)	8 (8 - 8)	8 (8 - 8)
Median (min - max)	8 (7 - 11)	8 (7 - 10)	8 (5 - 10)	8 (7 - 10)
Treatment Duration (Weeks)				
N	300	45	305	39
Mean (95%CI)	26.3 (26.2 - 26.4)	10.1 (8.0 - 12.1)	26.3 (26.2 - 26.4)	11.5 (9.1 - 14.0)
Median (min - max)	26.1 (25.0 - 32.3)	8.7 (0.0 - 23.4)	26.1 (25.0 - 30.0)	12.0 (0.0 - 24.7)

Abbreviations: FIAsp M-FIAsp Meal; Novo M- NovoLog Meal

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The distributions of baseline demographic characteristics for studies 3852 and 3853 are shown in Table 9 and Table 10 below. In general these characteristics seem evenly distributed between treatment arms for each of the two studies. In particular, baseline HbA1c levels are similar between arms for each study.

Table 9: Demographics and Baseline Characteristics by Treatment Arm-Study 3852

Treatment Group	Faster Aspart M	Faster Aspart PM	Novo.
N per group	381	382	380
Sex			
F (%)	166 (44)	163 (43)	142 (37)
M (%)	215 (56)	219 (57)	238 (63)
Race			
Asian (%)	5 (1)	2 (1)	7 (2)
Black Or African American (%)	5 (1)	12 (3)	9 (2)
White (%)	363 (95)	355 (93)	348 (92)
Other (%)	0 (0)	3 (1)	3 (1)
NA (%)	7 (2)	9 (2)	11 (3)
Ethnicity			
Hispanic Or Latino (%)	33 (9)	30 (8)	16 (4)
Age			
Mean (95%CI)	46.1 (44.7 - 47.5)	43.5 (42.1 - 44.9)	43.7 (42.3 - 45.1)
Median (min - max)	47.0 (18.0 - 83.0)	44.0 (18.0 - 77.0)	43.0 (19.0 - 78.0)
Age>=65 Years (%)	35 (9)	23 (6)	28 (7)
HbA1c at Baseline			
Mean (95%CI)	7.6 (7.5 - 7.7)	7.6 (7.6 - 7.7)	7.6 (7.5 - 7.6)
Median (min - max)	7.6 (6.0 - 9.8)	7.6 (6.1 - 9.8)	7.5 (5.6 - 9.6)
Body Mass Index at Baseline			
Mean (95%CI)	26.4 (26.0 - 26.8)	26.9 (26.5 - 27.3)	26.7 (26.4 - 27.1)
Median (min - max)	26.2 (18.1 - 35.8)	26.6 (17.0 - 37.9)	26.4 (17.1 - 36.8)
Diabetes Duration			
Mean (95%CI)	20.9 (19.6 - 22.2)	19.5 (18.2 - 20.7)	19.3 (18.1 - 20.5)
Median (min - max)	19.6 (1.3 - 65.4)	17.3 (1.2 - 59.2)	16.7 (1.2 - 57.4)

Abbreviations: M-Mealtime; PM-Post-Meal; CI-confidence interval

Table 10: Demographics and Baseline Characteristics by Treatment Arm-Study 3853

Treatment Group	FIAsp Meal	NovoLog
N per Group	345	344
Sex		
F (%)	182 (53)	171 (50)
M (%)	163 (47)	173 (50)
Race		
Asian (%)	40 (12)	42 (12)
Black Or African American (%)	22 (6)	18 (5)
White (%)	277 (80)	281 (82)
Other (%)	1 (0)	3 (1)
Ethnicity		
Hispanic Or Latino (%)	26 (8)	18 (5)
Age		
Mean (95%CI)	59.6 (58.6 - 60.6)	59.4 (58.4 - 60.4)
Median (min - max)	60.0 (33.0 - 82.0)	61.0 (21.0 - 83.0)
Age>=65 Years	104 (30)	96 (28)
HbA1c at Baseline		
Mean (95%CI)	8.0 (7.9 - 8.0)	7.9 (7.8 - 8.0)
Median (min - max)	7.9 (6.7 - 10.6)	7.8 (5.3 - 10.0)
Body Mass Index at Baseline		
Mean (95%CI)	31.5 (31.0 - 32.0)	31.0 (30.5 - 31.5)
Median (min - max)	31.6 (20.6 - 42.4)	31.1 (20.6 - 40.9)
Diabetes Duration		
Mean (95%CI)	13.2 (12.5 - 13.9)	12.3 (11.6 - 12.9)
Median (min - max)	13.0 (2.0 - 39.0)	11.0 (1.0 - 38.0)

3.2.4 Results and Conclusions

The results for the primary analysis using the sponsor's MMRM demonstrated non-inferiority of FIAsp Meal with respect to NovoLog Meal, both in the 3852 T1DM trial (estimated difference in 26-Week reduction in HbA1c: -0.15, 95% CI: -0.23,-0.07) trial and in the 3853 T2DM trial: (-0.02, 95% CI: -0.15, 0.10). However this approach does not differentiate between subjects who have missing data and those who do not. As well, it does not take into account the non-inferiority null hypothesis for missing data. The sponsor's sensitivity analysis assumes that subjects who have missing data are switched to NovoLog or an inferior treatment after withdrawal. The non-inferiority method used a 0.4% penalty equal to the non-inferiority margin specified by the sponsor. Using either sensitivity analysis approach, the treatment difference is somewhat diminished, but conclusions remain the same. For example in Study 3852, using the switch-to-inferior-treatment approach, the estimated difference in 26-Week reduction in HbA1c is -0.11, (95% CI: -0.20, -0.03). In Study 3853, using the same approach, the estimated difference in 26-Week reduction in HbA1c is 0.03 (95% CI: -0.10, 0.15), but conclusions remain the same.

One possible shortcoming in the approach to missing data incorporated in the sponsor's sensitivity analysis is that only the non-missing subjects (the completers) on the NovoLog arm were used to impute missing data. For Study 3852, the fact that only 5% of subjects on the NovoLog arm had missing data lessens possible impact of missing data for that study. For Study 3853, the missing rate was 10% for the NovoLog arm. I conducted a return-to-baseline sensitivity analysis for this study which incorporated variation around the baseline mean. All subjects with a missing 26-Week assessment, regardless of treatment arm, were assumed to have their treatment effect completely "washed out" in this manner. Using this approach, the treatment difference was estimated as 0.00 (95% CI: -0.14, 0.14). The treatment difference using this approach is attenuated slightly compared the Switch-to-NovoLog results from the same study, and slightly larger compared to the Switch-to-Inferior-Treatment analysis. Results for the primary analysis and Switch-to-NovoLog analyses are shown in Table 3 for Study 3852 and in Table 4 for Study 3853. Conclusions remain the same.

It is noted that superiority was also achieved in Study 3852 for the primary endpoint. However, since superiority was not replicated across the two studies, a claim for superiority is not likely to be allowed for this endpoint for either study (see Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf).

Secondary Endpoints

As outlined in Section 3.2.2.1, the sponsor used a hierarchical testing procedure for primary and secondary endpoints for each study. Since the primary endpoints for studies 3852 and 3853 were both achieved, testing of secondary endpoints proceeded according to the order shown in Table 6.

For Study 3852, the second and third endpoints shown in Table 6 for that study were achieved, but the fourth one, number of treatment emergent severe or BG confirmed hypoglycemic events, was not achieved, so the testing for that study stopped, and the endpoints below this one are not included in the label as being achieved. For Study 3853, the second endpoint in Table 6 for this study (change from baseline in 2-hour PPG increment) was not achieved, and so endpoints further down in the hierarchy were not tested. The primary analysis for Study 4049 was achieved.

3.3 Evaluation of Safety

Please see the clinical review of Dr. Hyon Kwon for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analysis for gender, race, ethnicity, age, and geographic region is shown in Table 11 for Study 3852 and in Table 12 for Study 3853. Table 13 shows treatment-subgroup interaction p-values for both studies. For Study 3852, the treatment effect (treatment difference between FIAsp and NovoLog) was 0 for females, and -0.24 for males. The corresponding treatment-sex interaction p-value was 0.005. In Study 3853, the treatment difference was lower for females than for males (-0.10 vs. 0.09) and the p-value was 0.15.

In Study 3853, the treatment difference for the North American region was 0.22, vs. -0.17 for Europe, and the corresponding treatment-region interaction p-value was 0.005. Conversely, in Study 3852, the North American region had a larger negative treatment difference vs. Europe (-0.20 vs -0.07). The corresponding treatment-region interaction p-value for that study was 0.12.

It should be noted that, while there were low treatment-subgroup interaction p-values for Sex (in Study 3852) and Region (in Study 3853), these results were not replicated across both studies. Moreover, the direction of the treatment difference was in reverse order across the two studies for both subgroups.

Table 11: Treatment Difference in Change in HbA1c by Subgroup-Study 3852 (FIAsp Meal Vs NovoLog)

Subgroup	Estimate	Lower 95%	Upper 95%
Overall	-0.15	-0.23	-0.07
Female	0.00	-0.13	0.12
Male	-0.24	-0.35	-0.13
White	-0.14	-0.23	-0.06
Black	-0.15	-0.82	0.52
Hispanic/Latino	0.19	-0.16	0.54
Age ≥ 65	0.09	-0.25	0.43
Age < 65	-0.17	-0.25	-0.08
North America	-0.20	-0.31	-0.09
Europe	-0.07	-0.19	0.05

Based on sponsor's MMRM primary analysis

Table 12: Treatment Difference in Change in HbA1c by Subgroup-Study 3853 (FIAsp Meal Vs NovoLog)

Subgroup	Estimate	Lower 95%	Upper 95%
Overall	-0.02	-0.15	0.10
Female	-0.10	-0.26	0.06
Male	0.09	-0.11	0.28
White	0.03	-0.17	0.11
Black	0.35	-0.56	1.27
Asian	-0.22	-0.48	0.04
Hispanic/Latino	0.38	-0.25	1.00
Age ≥ 65	-0.09	-0.30	0.13
Age < 65	0.00	-0.15	0.16
North America	0.22	0.00	0.44
Europe	-0.17	-0.35	0.00

Based on sponsor's MMRM primary analysis

Table 13: Subgroup-Treatment Interaction P-Values

Study	Sex	Race*	Ethnicity	Age	Region
3852	0.005	0.98	0.05	0.12	0.12
3853	0.15	0.44	0.12	0.50	0.005

*Race p-values for black vs. white; for study 3853, Asian vs. White: p-value-0.23.

5 SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

The primary endpoint for studies 3852 and 3853 is 26-week reduction in HbA1c – FIAsp Meal vs. NovoLog Meal. Non-inferiority was pre-specified and achieved in both of these studies. This

finding was consistent using the sponsor's primary analysis, and sensitivity analyses conducted by the sponsor (as well as by me for Study 3853).

5.2 Labeling Recommendations

(b) (4)

The MMRM primary analysis does not adequately address missing data and should not be the analysis used for labeling purposes. The sensitivity analysis which most closely addresses missing data should be the one put in the label. Descriptive statistics for missing data by arm should be included in the label.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEXANDER CAMBON
09/02/2016

MARK D ROTHMANN
09/02/2016
I concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 208751 **Applicant: Novo Nordisk** **Stamp Date: Dec 08 2015**

Drug Name: faster acting insulin aspart **NDA/BLA Type: Standard Review**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	*			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	*			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	*			Results of subgroup analysis are presented in ISE Appendix 6.4 for studies 3852 and 3853.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	*			The sponsor included SAS code for confirmatory statistical analysis and sensitivity analysis for the primary endpoint.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?
Yes.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comments
Designs utilized are appropriate for the indications requested.	*			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	*			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			*	
Appropriate references for novel statistical methodology (if present) are included.			*	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	*			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	*			The sponsor performed several multiple imputation methods including copy-reference

				and jump to reference as well as tipping point analysis for studies 3852, 3853 and 4049. The latter two are post-hoc (summary of clinical efficacy)

Comments:

This submission contains 3 confirmatory efficacy and safety trials:

- Trial 3852 26+26 weeks basal bolus trial in subjects with T1DM
- Trial 3853 26-week basal bolus trial in subjects with T2DM
- Trial 4049 18-week basal-bolus versus basal trial in subjects with T2DM

And 2 continuous subcutaneous insulin infusion (CSII) trials:

- Trial 3931 6-week pump compatibility trial in subjects with T1DM
- (b) (4)

Comments for the 74-day letter:

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Alexander Cambon	1/27/2016
Reviewing Statistician	Date
Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEXANDER CAMBON
02/03/2016

MARK D ROTHMANN
02/03/2016
Concur