# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208751Orig1s000

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

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| Application Type | NDA |
| Application Number(s) | 208751 |
| Priority or Standard | Standard |
| Submit Date(s) | March 29, 2017 |
| Received Date(s) | March 29, 2017 |
| PDUFA Goal Date | September 29, 2017 |
| Division / Office | Division of Metabolism and Endocrinology Products |
| Reviewer Name(s) | Hyon Kwon |
| Review Completion Date | September 18, 2017 |
| Established Name | Insulin aspart |
| (Proposed) Trade Name | FIASP |
| Therapeutic Class | Insulin |
| Applicant | Novo Nordisk |
| Formulation(s) | 100 units/mL in 10 mL vials and 3 mL FlexTouch |
| Dosing Regimen | Individualized |
| Indication(s) | To improve glycemic control in adults with diabetes mellitus |
| Intended Population(s) | Adults with diabetes mellitus |

# Table of Contents

# Table of Tables

## Table of Figures

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

I recommend Approval of FIASP, a new insulin aspart formulation, for the treatment of patients with diabetes mellitus both for basal-bolus therapy in combination with intermediate- or long-acting basal insulin. See section 1.2 for my rationale.

## 1.2 Risk Benefit Assessment

If FIASP is approved, it would offer another therapeutic option for patients with diabetes mellitus who would need prandial insulin therapy.

Please see the overall risk benefit assessment discussion in the Clinical Review dated October 7, 2016 for detailed discussion. The overall benefit-risk profile of FIASP as assessed during the original NDA review was not altered with additional safety data from this resubmission, which was mainly from the additional 26 weeks of treatment period with FIASP from study 3852 in type 1 diabetes.

In summary, mealtime FIASP was non-inferior (pre-specified margin of 0.4%) to mealtime NovoLog in terms of the change from baseline in HbA1c after 26 weeks of treatment in both type 1 diabetes (3852) and type 2 diabetes (3853) when used as a basal-bolus regimen. The postmeal administration of FIASP (administered 20 minutes after a meal) was only evaluated in study 3852 where it was also shown to be not inferior at the pre-specified margin of 0.4% compared to mealtime NovoLog.

Currently approved insulin aspart, NovoLog, is to be administered immediately before a meal. Approval of FIASP that can be administered either immediately before a meal or up to 20 minutes after a meal would theoretically offer added convenience for diabetic patients since they are better able to match their mealtime insulin dose to their meal content.

Overall, the efficacy and safety evaluation show that the benefit-risk profile remains favorable for FIASP as mealtime insulin, when used in combination with basal insulin in patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM).

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended.

### 1.4 Recommendations for Postmarket Requirements and Commitments

This application triggers the Pediatric Research Equity Act (PREA) because of the change in dosing regimen; therefore, pediatric studies under PREA are recommended.

The iPSP was agreed on August 28, 2015, subsequent to discussion and agreement with PeRC. A Phase 3 efficacy and safety study in children and adolescents with T1DM is recommended as a postmarketing requirement.

## 2 Introduction and Regulatory Background

Novo Nordisk developed a new formulation of insulin aspart, with additional excipients that differs from the currently available insulin aspart formulation, NovoLog (U.S. trade name; global trade name is NovoRapid).

Division of Medication Error Prevention and Analysis (DMEPA) reviewed and concluded that the Applicant's proposed trade name FIASP was conditionally acceptable on May 29, 2017. Therefore, in order to differentiate these two products with same active ingredient (i.e., insulin aspart), trade names will be used throughout this review to refer to the currently available formulation (NovoLog) and the new formulation of insulin aspart (FIASP) under review.

It should be noted that the clinical review during original submission used the trade name (b) (4) as this name was initially found to be acceptable on July 26, 2016. However, DMEPA subsequently amended the acceptability of (b) (4) because the name (b) (4) was determined to be vulnerable to name confusion with another proposed proprietary name that was under Agency review. As a result, the Applicant resubmitted the name FIASP for review on January 12, 2107 and DMEPA found the proposed proprietary name acceptable (see DMEPA review dated May 29, 2017).

### 2.1 Product Information

Compared to the currently approved insulin aspart (NovoLog), this new formulation of insulin aspart (i.e., FIASP) contains 2 addition excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride. Nicotinamide was added to increase the absorption of insulin aspart after administration, and L-arginine was added to stabilize the formulation.

Insulin aspart is an analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28, and is produced by recombinant DNA technology using *Saccharomyces cerevisiae* (baker's yeast).

The proposed indication for FIASP is to improve glycemic control in adults with diabetes mellitus (i.e., both T1DM and T2DM) and its intended use is for treatment of adult

patients with diabetes mellitus both for basal-bolus therapy in combination with basal insulin (with or without OADs [oral antidiabetic drugs]). FIASP can be injected at the start of a meal or postmeal (within 20 minutes after starting a meal). FIASP can also be given intravenously by a health care professional when needed.

(b) (4) will be provided in a prefilled PDS290 pen-injector (3 mL) and in vials (10 mL) all with 100 U/ml insulin aspart. The prefilled device will have a dosage range of 1-80 units in increments of 1 unit.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The currently approved treatment of T1DM and T2DM include:

- Insulin and insulin analogs
- Sulfonylureas (SU)
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)
- Alpha-glucosidase inhibitors
- Glucagon-like peptide 1 (GLP-1) agonists
- Synthetic analogues of human amylin
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Bile acid sequestrant
- Dopamine agonists
- SGLT-2 inhibitors

## 2.3 Availability of Proposed Active Ingredient in the United States

NovoLog and FIASP have the same active ingredient, insulin aspart. NovoLog was approved for treatment of adult patients with diabetes mellitus on June 7, 2000. NovoLog was approved for use in pediatric patients on September 13, 2005.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Two important safety issues arise with all insulin treatment: hypoglycemia and formation of insulin antibodies.

Hypoglycemia is the most common adverse event for insulin regimen. The severity of hypoglycemia can result in a range of impairment from temporary to permanent. The risk of hypoglycemia increases with increased intensive glycemic control. Refer to section 7.3.4 for discussion of hypoglycemia.

Exposure to insulin products may lead to formation of insulin antibodies. The formation of these antibodies may affect glycemic efficacy and require dose adjustment for

glycemic control, or may affect safety and lead to increased incidence of allergic reactions. See section 7.4.6 for discussion of immunogenicity.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

See Section 2.6 for discussion of regulatory activity since the Complete Response was issued for the original submission on October 7, 2016.

### 2.6 Other Relevant Background Information

The initial NDA was submitted on December 8, 2015. The application received a Complete Response Letter (CRL) on October 7, 2016 due to deficiencies related to Clinical Pharmacology and Immunogenicity. Please see the Clinical Pharmacology Review by Dr. Shalini Wickramaratne Senarath Yapa dated September 8, 2016 and Immunogenicity Review by Dr. Steven Bowen dated September 29, 2016 discussing the deficiencies that were identified in their respective disciplines. Of note, no clinical deficiencies precluding approval were identified from the original NDA.

An End-of-Review (EOR) meeting was held between FDA and Applicant on December 15, 2016. During the EOR meeting, the following agreements were made:

- Using the total insulin aspart ELISA assay to characterize the pharmacokinetics of faster aspart;
- (b) (4)
- (b) (4)

Applicant resubmitted a Complete Response addressing deficiencies described in the CRL. Further information to address our additional comments in the CRL about IV Route of Administration is also included in this resubmission.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The submission was well organized and information was not difficult to find. The overall quality of the submission was acceptable.

### 3.2 Compliance with Good Clinical Practices

All trials were conducted according to Good Clinical Practice.

### 3.3 Financial Disclosures

No new financial disclosures were included in this resubmission as results of a new Phase 3 studies were not submitted for this resubmission.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

All clinical studies were conducted with the final formulation of FIASP that is to be marketed. No new CMC information was submitted in this resubmission.

### 4.2 Clinical Microbiology

No new information submitted.

### 4.3 Preclinical Pharmacology/Toxicology

For a detailed review of the Preclinical Pharmacology/Toxicology, refer to Dr. Miyun Tsai-Turton's review dated August 28, 2016 and September 20, 2016. Dr. Arulasanam Thilagar also reviewed additional nonclinical information to support the safety of intravenous administration of FIASP since it contains 20. (b) (4) mg/mL nicotinamide as an absorption modifier. Please see Dr. Thilagar's review dated July 12, 2017.

The Pharmacology/Toxicology Reviewer recommends approval of FIASP, including its chronic use as intravenous administration.

### 4.4 Clinical Pharmacology

For a detailed review of clinical pharmacology, refer to Dr. Shalini Wickramaratne Senarath Yapa's review dated September 6, 2017. The Office of Clinical Pharmacology recommends an Approval and I defer to her evaluation of pharmacokinetic data using total insulin aspart concentrations. My Clinical Review dated October 7, 2016 already discussed the pharmacodynamics data, which was not affected by the issues related to the bioanalytical method used.

#### 4.4.1 Mechanism of Action

FIASP, like endogenous insulin and other insulin analogues, acts through binding to insulin receptor to regulate glucose metabolism. FIASP lowers blood glucose by

stimulating peripheral glucose uptake by skeletal muscle and fat, and inhibits hepatic glucose production.

### 4.4.2 Pharmacodynamics

Please see my Clinical Review dated October 7, 2016 for discussion of pharmacodynamics related to FIASP.

### 4.4.3 Pharmacokinetics

Please refer to Dr. Shalini Wickramaratne Senarath Yapa's review dated September 6, 2017 for discussion of pharmacokinetics data using total insulin aspart levels.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

The initial NDA submission included the following studies:

- Nine clinical pharmacology studies;
- Three confirmatory trials evaluating the efficacy and safety of FIASP in subjects with T1DM and T2DM (studies 3852, 3853, and 4049), and
- (b) (4)

Please see the Clinical Review dated October 7, 2016 for discussion of these studies.

As discussed previously, (b) (4) will not be relevant in this resubmission. As a result, clinical studies relevant for this resubmission are:

- Eight clinical pharmacology studies of faster aspart (3978, 38887, 3889, 3921, 3891, 3918, 3922, and 3949),
- Three confirmatory studies for efficacy (3852, 3852, and 4049), and
- Updated safety data with cut-off date of January 2, 2017 in the resubmission. For study 3852, the update includes additional 26 week extension period (for a total 52 weeks data) in two mealtime treatment groups, mealtime FIASP and NovoLog, which was ongoing at the time of original NDA submission (and was submitted in the 4 Month Safety Update for the original submission). The postmeal FIASP group did not continue additional 26 weeks of treatment.

The evaluation of clinical pharmacology is based on the results of 8 clinical pharmacology trials, and meal test and population pharmacokinetic analyses from study 3852.

The evaluation of efficacy is based on results from 3 confirmatory studies, 3852, 3853, and 4049. The results of these studies were submitted and reviewed during the initial submission, and there are no new efficacy results to be reviewed in this resubmission.

The evaluation of safety is primarily based on data from 2 confirmatory basal-bolus studies in subjects with T1DM (study 3852) and T2DM (study 3853) and a 'diabetes pool' consisting of studies 3852, 3853, 4049, and 3931. These were submitted in the original NDA (cut-off date of March 10, 2015), and results from the initial 26 weeks of study 3852 were completed and the additional 26 weeks of study were ongoing at that time. In the 120-Day Safety Update of the original NDA submitted on April 4, 2016 (cut-off date of October 1, 2015), the data from the entire 52 weeks of study 3852 (with the unblinded data from the additional 26 weeks) and updated safety data for the 'diabetes pool' with data from the additional 26 weeks of study 3852 were submitted.

The safety update submitted in this resubmission includes an updated evaluation of all available safety data from completed and ongoing trials using the cut-off date of January 2, 2017. Since the 120-Days Safety Update of the original NDA, only one clinical pharmacology study has been completed (study 3922). Therefore, the results in this resubmission safety update includes: the data submitted in the 120-Day Safety Update, results from study 3922, and blinded data from ongoing studies (4101, 4131, 3854, and 4265).

Therefore, the adverse events that will be mainly discussed in this safety update will include the full 52 weeks of treatment in two treatment groups, mealtime FIASP and mealtime NovoLog, the updated diabetes pool incorporating additional 26 weeks from study 3852, and data from clinical pharmacology study 3922.

**Reviewer's Comment: This safety update was agreed upon during the EOR meeting.**

Although FIASP was approved in the European Union and Canada in January 2017, it was not launched as of the cut-off date for this resubmission. Therefore, no post-marketing data with FIASP is submitted; instead, the Applicant submitted the recent Periodic Safety Update Report for NovoLog covering the period October 2015 to September 2016.

## 5.2 Review Strategy

I mainly reviewed the safety update to determine whether the additional available safety data with FIASP altered the overall safety profile since the original review. Although I looked through the blinded results on ongoing clinical studies (Studies 4101, 4131, 3854, and 4265), my main evaluation was related to completed clinical studies that showed unblinded data.

Since no new efficacy results are available in this resubmission, the majority of subsections in Section 6 are deleted from the template.

### 5.3 Discussion of Individual Studies/Clinical Trials

The only new study that was completed since the original NDA was the clinical pharmacology study 3922.

Study 3922 was a randomized, single-center, double-blind, single-dose, two-period, crossover study investigating the postprandial glucose metabolism after treatment with FIASP in subjects with type 1 diabetes. The primary objective of this study was to compare the postprandial glucose properties of FIASP and NovoLog when given immediately before a meal, and 42 subjects were randomized in this study. See Clinical Pharmacology Review dated September 6, 2017 for detailed discussion of this study design and clinical pharmacology results.

# 6 Review of Efficacy

***Efficacy Summary***

The efficacy is primarily evaluated based on results from studies 3852, 3853, and 4049. The efficacy results were already reviewed during the initial NDA review, and no further efficacy results are submitted in this resubmission. Please refer to Section 6 of the Clinical Review dated October 7, 2016 for detailed discussion of efficacy for FIASP.

### 6.1 Indication

Faster aspart is intended to be used for the treatment of patients with diabetes mellitus both for basal-bolus therapy in combination with intermediate- or long-acting basal insulin.

Faster aspart can be injected at the start of a meal or postmeal (up to 20 minutes after starting a meal).

Faster aspart can also be administered intravenously by health care professionals when needed.

# 7 Review of Safety

***Safety Summary***

The majority of safety data comes from two basal-bolus studies in subjects with T1DM (3852) and T2DM (3853). Safety data were assessed separately for each study since each trial was different in study design and were conducted in different diabetic patient population.

My review of updated safety data did not identify any new safety issues related to FIASP. The overall rates of hypoglycemia with FIASP in T1DM and T2DM were comparable to NovoLog, with a slight increased risk of severe or BG confirmed hypoglycemia with FIASP compared to NovoLog during 1 hour and within 2 hour after a meal. This shift in hypoglycemic episodes related to a meal is likely a reflection of pharmacokinetic and pharmacodynamic properties of FIASP compared to NovoLog, and do not present an unacceptable safety risk for a patient since insulin dose will be individually titrated and hypoglycemia events can be monitored.

## 7.1 Methods

Safety data were assessed separately for each trial since each trial was different in study design and were conducted in different diabetic patient population.

In this resubmission, I mainly reviewed the 'new' safety data since the original NDA submission.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

At the time of original NDA submission (cut-off date of March 10, 2015), 13 studies were completed and the initial 26 weeks of treatment for study 3852 were available while the additional 26 weeks were still ongoing. The 120-day safety update (submitted April 4, 2016) presented data up to the cut-off date of October 1, 2015 and included unblinded data from the full 52 weeks from study 3852.

In this resubmission safety update (cut-off date of January 2, 2017), one clinical pharmacology study has been completed (study 3922), and the Applicant also provided presentation of data that were submitted in the 120-Day Safety Update that included data for the entire 52 weeks of study 3852 along with updated safety data for the 'diabetes pool'.

### 7.1.2 Categorization of Adverse Events

Definitions related to AEs, SAEs, deaths, AEs leading to withdrawal and AEs that were to be adjudicated for the completed trials remain the same in this resubmission as the original NDA. AEs in study 3852 (52 weeks) were coded using the version 17.0 of the MedDRA, and the clinical pharmacology study 3922 used MedDRA version 19.0.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As discussed in the original NDA review, the safety of FIASP was also evaluated using a 'diabetes pool' that included studies 3852, 3853, 4049, and 3931 where all FIASP groups were combined and compared against comparator (NovoLog and basal insulin comparator). The majority of exposure (about 93%) in this overall safety pool came from study 3852 and 3853.

The proportion of subjects experiencing events and event rates in the diabetes pool are adjusted using the Cochran-Mantel-Haenszel method to account for study differences in exposure.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

After the first 26 weeks of treatment, subjects in the mealtime treatment groups FIASP and NovoLog continued for an additional blinded 26 weeks of treatment; 88.5% (337/386) subjects from the mealtime FIASP group and 88.9% (338/380) subjects from the mealtime NovoLog group completed the 52 weeks of treatment period. As noted before, subjects in the postmeal FIASP did not continue for additional 26 weeks.

The additional 26 week of study 3852 increased the exposure to mealtime FIASP and NovoLog by 171 and 173 person-year exposure (PYE), respectively. After 52 weeks of treatment period, the total exposure was 357.1 PYE for mealtime FIASP and 361.8 PYE for mealtime NovoLog.

In the updated diabetes pool including data from the additional 26 weeks of study 3852, the total exposure was 741.2 PYE for FIASP group compared to 566.3 PYE for the comparator treatment group.

In the clinical pharmacology study 3922, 41 additional subjects were exposed.

The size of the FIASP development program did not enable extensive exposure across racial and ethnic minority groups. However, given the extensive clinical experience and well-established safety profile in NovoLog, the current additional exposures are considered sufficient to provide information on the safety of FIASP within the groups of Black or African American, Asian or Hispanic origin.

### 7.2.2 Explorations for Dose Response

Not applicable.

### 7.2.3 Special Animal and/or In Vitro Testing

None.

### 7.2.4 Routine Clinical Testing

As discussed during the original NDA review, each clinical study had routine testing at specified intervals, and was appropriate for safety evaluation of FIASP.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

None.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 7.3.4 for discussion of hypoglycemia, which is a known adverse event for insulins.

## 7.3 Major Safety Results

### 7.3.1 Deaths

No new deaths since the original NDA submission were reported in the safety update of this resubmission.

One death that was blinded at the time of original NDA review (Subject (b) (6)) was unblinded and updated to be in the NovoLog group. This fatal event was classified as cardiovascular death and categorized as a MACE.

### 7.3.2 Nonfatal Serious Adverse Events

Study 3852 (52 Weeks):

Since the postmeal FIASP treatment arm in study 3852 did not continue for the additional 26 weeks of treatment period, the incidence rate of SAEs at 52 weeks were mainly assessed in the mealtime FIASP and mealtime NovoLog groups. With additional 26 weeks of treatment period, at the end of 52 weeks of treatment, a slightly higher rate of nonfatal SAEs were seen in the mealtime FIASP group compared to NovoLog, 14.0 and 10.8 events per 100 PYE, respectively.

During the additional 26 weeks of treatment period in mealtime FIASP and NovoLog, 33 subjects experienced 43 additional nonfatal SAEs, 23 subjects with mealtime FIASP and 9 subjects with NovoLog. One subject who received postmeal FIASP and experienced adenocarcinoma of colon about 3 months after starting postmeal FIASP reported peritoneal fibrosis during the follow-up. Table 1 lists all the non-fatal SAE reported during the additional 26 weeks of treatment period by treatment group.

In the overall 52 weeks data, no SAEs occurred in ≥5% of subjects, as summarized in Appendix 7.3.1, Table 10 of the Safety Update (not shown here). The only SAE that occurred ≥1% of subjects were *hypoglycemia* and *hypoglycemic unconsciousness.*

A slightly higher rate of SAE for *hypoglycemia* was seen in the mealtime FIASP group at 3% (4.5 per 100 PYE) compared to 2.6% (2.8 per 100 PYE) with mealtime NovoLog. SAE of *hypoglycemic unconsciousness* was 1.3% (2.2 per 100 PYE) with mealtime FIASP compared to 1.1% (1.4 per 100 PYE) with mealtime NovoLog.

Hypoglycemic episodes were reported on dedicated hypoglycemic episode forms and only reported on the AE forms if fulfilling the criteria for an SAE. Hypoglycemia is further discussed in Section 7.3.4.

**Table 1: Study 3852 – Nonfatal Serious Adverse Event During Additional 26-Week Period**

| Treatment Group | Subject ID | PT of nonfatal SAE |
|---|---|---|
| Mealtime FIASP | (b) (6) | Uterine polyp |
| | | Pyelonephritis |
| | | Thrombosis |
| | | Hypoglycemic unconsciousness |
| | | Hypoglycemic unconsciousness (2 events) |
| | | Hypoglycemia |
| | | Tendon rupture |
| | | Peritonsillar abscess |
| | | Immune thrombocytopenic purpura *(see the summary of event below)* |
| | | Lumbar vertebral fracture |
| | | Nasal septum deviation |
| | | Lung neoplasm malignant |
| | | Hypoglycemic unconsciousness |
| | | Peripheral arterial occlusive disease |
| | | Ankle fracture |
| | | Transient ischemic attack |
| | | Subarachnoid hemorrhage |
| | | Aneurysm, cardiac aneurysm repair, congestive cardiac failure, cardiac ventricular thrombosis |
| | | Appendicitis |
| | | Hypoglycemia |
| | | Hypoglycemia (3 events) |
| | | Fall, subdural hematoma |
| Postmeal FIASP | | Peritoneal fibrosis |
| Mealtime NovoLog | | Join stiffness |
| | | Hypoglycemia |
| | | Meniscal degeneration |
| | | Hypoglycemic unconsciousness |
| | | Hypoglycemia, mental status changes, diabetic ketoacidosis |
| | | Diabetic retinopathy, compartment syndrome |
| | | Hypoglycemia |
| | | Hypoglycemia |
| | | Premature baby |

*Subjects with CV event; #Subjects with severe hypoglycemia
Source: Modified from Safety Update, Appendix 7.6.1, Table 1-2

- **Immune Thrombocytopenic Purpura (b) (6)):** Subject (b) (6) was a 50 year old woman with past medical history including hypothyroidism, Hashimoto thyroiditis, nodular goiter, patellar arthrosis, lymphocyte meningitis. She completed one year of blinded treatment with FIASP with insulin detemir. About 3 weeks after study completion, she noticed several hematomas on her arms and back without trauma, and had epistaxis and aphthosus ulcer. She was admitted to the hospital and diagnosed with acute thrombocytopenia, considered to be idiopathic. Her platelet count was 1000 n/uL (reference range: 150,000-450,000). She received acyclovir and prednisolone. About 2 weeks later, her platelet count was 133,000 n/uL, she was discharged and started treatment with prednisolone. Ten days later, her platelet count was 170,000 n/uL, and she was diagnosed with idiopathic thrombocytopenic purpura (ITP). Her prednisolone was stopped few weeks later.

**Reviewer's comments: This ITP is unlikely to be related to FIASP treatment, as the event occurred several weeks after she completed a year of treatment with FIASP. Drop in platelet count due to drug-induced ITP usually occurs early after drug initiation.**

Study 3922: There were no SAEs in the clinical pharmacology study 3922.

### 7.3.3 Dropouts and/or Discontinuations

Study 3852 (52 Weeks):

During the additional 26 weeks of treatment period, one subject in the mealtime FIASP and 2 subjects in the mealtime NovoLog discontinued due to AE.

One subject ((b) (6)) in the mealtime FIASP withdrew because they met the withdrawal criterion #4 (hypoglycemia posing a safety problem) after 33 weeks of treatment.

In the mealtime NovoLog, one subject ((b) (6)) also withdrew due to withdrawal criterion #4 related to hypoglycemia after about 30 weeks of treatment. Another subject ((b) (6)) experienced mental status changes about 42 weeks after treatment with mealtime NovoLog and withdrew; subject recovered from the event.

Study 3922: There were no withdrawals due to AEs in the clinical pharmacology study 3922.

**Reviewer's comment: No new notable safety findings were found based on review of dropouts due to AEs in this safety update.**

### 7.3.4 Significant Adverse Events - Hypoglycemia

The number of treatment emergent severer or BG confirmed hypoglycemic episodes from baseline until Week 52 was evaluated in study 3852.

**Study 3852 (52 Weeks):**

A summary of overall hypoglycemic episodes by classification in study 3852 with mealtime FIASP and NovoLog after 52 weeks of treatment is provided in Table 2.

**Table 2: Study 3852 (total of 52 Weeks) – Summary of Hypoglycemic Events by Classification**

| | Faster aspart (meal) | | | | NovoRapid (meal) | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 386 | | | | 380 | | | |
| Total exposure (yrs) | 357.09 | | | | 361.84 | | | |
| Total events | 377 | (97.7) | 41752 | 11692 | 378 | (99.5) | 41207 | 11388 |
| BG confirmed | 361 | (93.5) | 18962 | 5310 | 369 | (97.1) | 19165 | 5297 |
| Severe or BG confirmed symptomatic | 355 | (92.0) | 15498 | 4340 | 361 | (95.0) | 16302 | 4505 |
| Severe or BG confirmed | 362 | (93.8) | 19028 | 5329 | 370 | (97.4) | 19247 | 5319 |
| NN unclassifiable | 375 | (97.2) | 22724 | 6364 | 377 | (99.2) | 21960 | 6069 |
| ADA | | | | | | | | |
| Severe | 37 | ( 9.6) | 66 | 18 | 46 | (12.1) | 82 | 23 |
| Documented symptomatic | 366 | (94.8) | 29808 | 8347 | 366 | (96.3) | 30950 | 8554 |
| Asymptomatic | 336 | (87.0) | 11212 | 3140 | 343 | (90.3) | 9469 | 2617 |
| Probable symptomatic | 93 | (24.1) | 472 | 132 | 88 | (23.2) | 453 | 125 |
| Pseudo-hypoglycaemia | 44 | (11.4) | 168 | 47 | 52 | (13.7) | 243 | 67 |
| ADA unclassifiable | 15 | ( 3.9) | 26 | 7 | 9 | ( 2.4) | 10 | 3 |

N: Number of subjects, NN: Novo Nordisk; %: Percentage of subjects, E: Number of events R: Event rate per 100 exposure years, BG: Blood glucose, Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL).
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period. Rates are calculated based on the total PYE, irrespective of time interval. The category 'NN unclassifiable' includes episodes that were non-severe with blood glucose (BG) between 3.1 mmol/L (56 mg/dL) and 3.9 mmol/L (70 mg/dL), not BG confirmed, or that could not be classified due to missing data.

Source: Safety Update, Table 2-13

*Severe Hypoglycemia:*

Slightly lower proportion of subjects in the mealtime FIASP compared to NovoLog experienced at least one episode of severe hypoglycemia during 52 weeks of treatment, 9.6% (18 per 100 PYE) in the mealtime FIASP compared to 12.1% (23 per 100 PYE) in the NovoLog. This incidence is slightly higher compared to that seen after 26 weeks of treatment (6.7% and 8.4% in mealtime FIASP and NovoLog respectively at 26 weeks),

but slightly lower event rates compared to 26 weeks (25 and 27 per 100 PYE in mealtime FIASP and NovoLog respectively at 26 weeks).

The majority of subjects who had at least one episode of severe hypoglycemia had a single episode of severe hypoglycemia during the study, as shown in Table 3. One subject on NovoLog experienced 8 episodes of severe hypoglycemia.

**Table 3: Study 3852 (52 Weeks) – Frequency of Severe Hypoglycemic Events Per Subject who had at least one event**

| Number of episodes of severe hypoglycaemia experienced by subject | Number of subjects | | | |
|---|---|---|---|---|
| | After 26 weeks | | After 52 weeks | |
| | Mealtime faster aspart | NovoRapid®/ NovoLog® | Mealtime faster aspart | NovoRapid®/ NovoLog® |
| 1 | 14 | 21 | 22 | 31 |
| 2 | 8 | 5 | 8 | 6 |
| 3 | 0 | 4 | 2 | 3 |
| 4 | 4 | 2 | 3 | 4 |
| 5 | 0 | 0 | 2 | 0 |
| 6 | 0 | 0 | 0 | 1 |
| 7 | 0 | 0 | 0 | 0 |
| 8 | 0 | 0 | 0 | 1 |

Source: Safety Update, Table 2-14

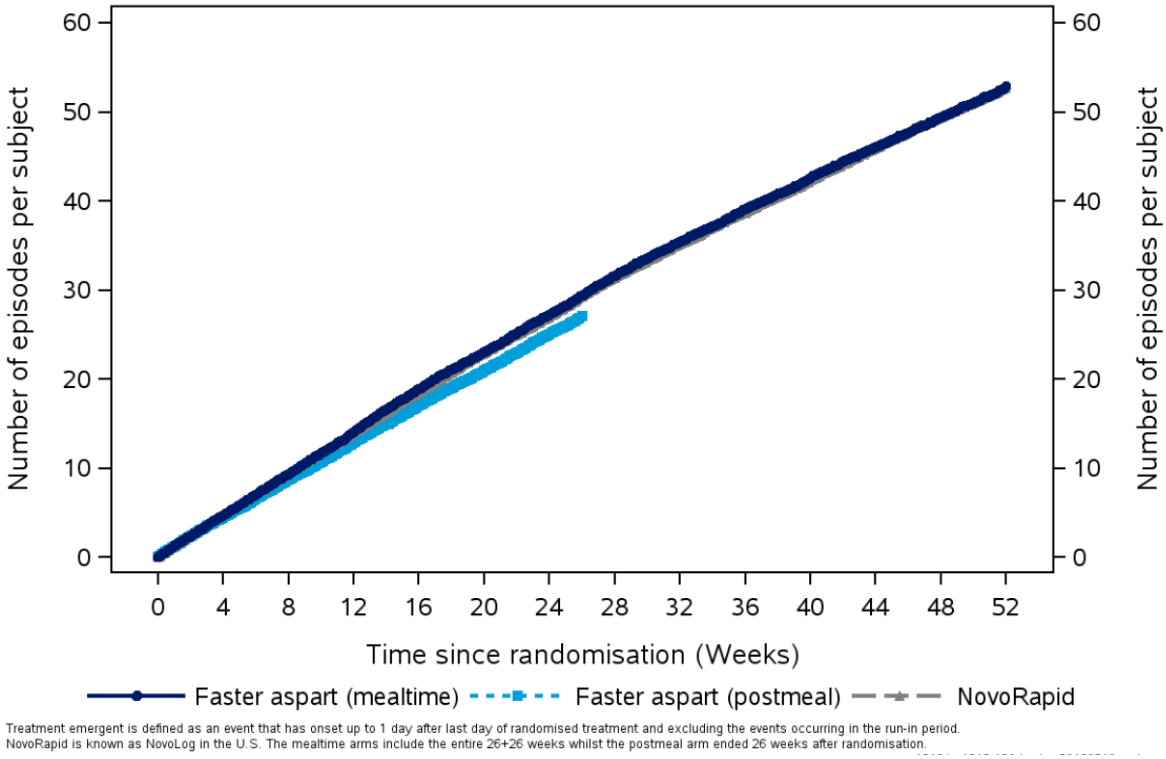
*Severe or BG Confirmed Hypoglycemia:*

After 52 weeks of treatment period, slightly lower proportion of subjects from the mealtime FIASP (93.8%) reported severe or BG confirmed compared to NovoLog (97.4%), which is similar to what was seen after 26 weeks.

The majority of severe or BG confirmed hypoglycemia occurred during daytime period. About 88% of hypoglycemic events in the mealtime FIASP group and 86% in the mealtime NovoLog group occurred during the daytime period. Similar to 26 weeks data, the highest frequency of severe or BG confirmed hypoglycemia events occurred around 12:00 pm (not shown here; see Safety Update, Appendix 7.4, Figure 22).

The overall rate of severe or BG confirmed hypoglycemic events remained relatively constant over 52 weeks of treatment period, as shown in Figure 1.

**Figure 1: Study 3852 (52 Weeks) – Severe or BG Confirmed Hypoglycemic Events – Mean Cumulative Function**




Source: Safety Update, Appendix 7.4, Figure 14

*Severe or BG Confirmed Hypoglycemia Related to A Meal:*

After 52 weeks of treatment, the rates for hypoglycemia related to a meal showed similar pattern as 26 weeks, where the rate for severe or BG confirmed hypoglycemia was statistically significantly higher with mealtime FIASP compared to NovoLog within the first hour after meal (estimated treatment ratio 1.37 [95% CI: 1.06, 1.76]). The rate for severe or BG confirmed hypoglycemia was also nominally higher with mealtime FIASP compared to NovoLog within 2 hours after a meal (estimated treatment ratio 1.17 [95% CI: 0.96, 1.42]). Refer to Table 4 and Figure 2 below.

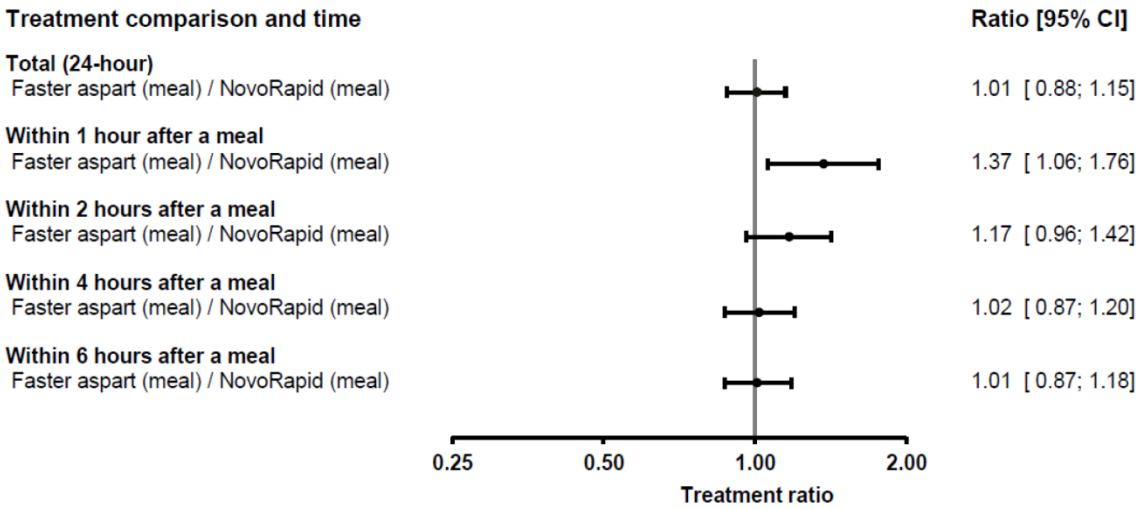
## Table 4: Study 3852 (52 Weeks) – Summary of Hypoglycemia Related to a Meal

| | Faster aspart (meal) | | | | NovoRapid (meal) | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 386 | | | | 380 | | | |
| **Severe or BG confirmed** | | | | | | | | |
| Within 1 h after a meal | 166 | (43.0) | 441 | 123.5 | 148 | (38.9) | 312 | 86.2 |
| Within 2 h after a meal | 279 | (72.3) | 2400 | 672.1 | 284 | (74.7) | 1971 | 544.7 |
| Within 4 h after a meal | 342 | (88.6) | 7989 | 2237.2 | 345 | (90.8) | 7752 | 2142.4 |
| Within 6 h after a meal | 350 | (90.7) | 12029 | 3368.6 | 353 | (92.9) | 11869 | 3280.2 |
| Total (24h) | 362 | (93.8) | 19028 | 5329 | 370 | (97.4) | 19247 | 5319 |
| **Severe or BG confirmed symptomatic** | | | | | | | | |
| Within 1 h after a meal | 152 | (39.4) | 383 | 107.3 | 141 | (37.1) | 278 | 76.8 |
| Within 2 h after a meal | 257 | (66.6) | 2156 | 603.8 | 270 | (71.1) | 1813 | 501.1 |
| Within 4 h after a meal | 330 | (85.5) | 6952 | 1946.8 | 338 | (88.9) | 7065 | 1952.5 |
| Within 6 h after a meal | 341 | (88.3) | 10259 | 2872.9 | 347 | (91.3) | 10578 | 2923.4 |
| Total (24h) | 355 | (92.0) | 15498 | 4340 | 361 | (95.0) | 16302 | 4505 |
| **ADA documented symptomatic** | | | | | | | | |
| Within 1 h after a meal | 193 | (50.0) | 667 | 186.8 | 190 | ( 50.0) | 503 | 139.0 |
| Within 2 h after a meal | 286 | (74.1) | 3694 | 1034.5 | 300 | ( 78.9) | 3024 | 835.7 |
| Within 4 h after a meal | 345 | (89.4) | 12822 | 3590.7 | 353 | ( 92.9) | 12811 | 3540.5 |
| Within 6 h after a meal | 356 | (92.2) | 19845 | 5557.4 | 357 | ( 93.9) | 20212 | 5585.9 |
| Total (24h) | 366 | (94.8) | 29808 | 8347 | 366 | (96.3) | 30950 | 8554 |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 exposure years, BG: Blood glucose
Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL).
'After a meal': after start of a main meal.
Episodes with missing time stamps or with missing main meal time are not included.
Treatment-emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

Source: Safety Update, Table 2-15

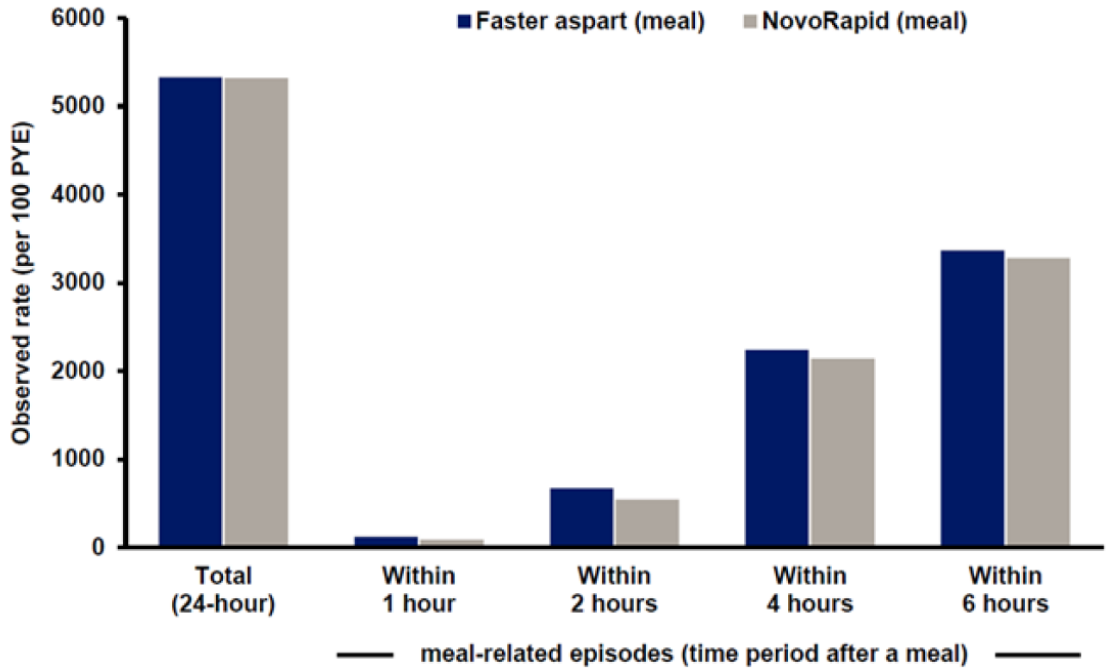
## Figure 2: Study 3852 (52 Weeks) – Estimated Treatment Rate Ratio for Severe or BG confirmed Hypoglycemic Events (Meal-Related and Total)




Source: Safety Update, Figure 2-7

However, the proportion of severe or BG confirmed hypoglycemic events that occur during the first hour was a small portion of total events: 2.3% (441/19028) in the mealtime FIASP and 1.6% (312/19247) in the NovoLog group (Table 4 and Figure 3).

**Figure 3: Study 3852 (52 Weeks) – Rate of Severe or BG Confirmed Hypoglycemia Related to a Meal and Total**




PYE: patient years of exposure. 'After a meal': after start of a main meal.
Source: Safety Update, Figure 2-8

**Study 3922:** No severe hypoglycemic events were reported.

### 7.3.5 Submission Specific Primary Safety Concerns

The method of collection for the following safety issues were same as discussed in the original NDA review.

**Medication Errors**

In study 3852, during 52 weeks of treatment period, the majority of medication errors (60 in 46 subjects) were reported as 'wrong drug administered', and the incidence was similar between mealtime FIASP and NovoLog. Thirty-seven events in 33 subjects were due to subjects taking bolus insulin instead of basal insulin, and 20 events in 15 subjects were due to subjects taking basal insulin instead of bolus insulin at mealtimes. Six medication errors in 6 subjects were reported as 'accidental overdose'.

Table 5 provides an overall summary of reported medication errors in each treatment groups by Preferred Terms during 52 weeks of treatment period in study 3852.

**Table 5: Study 3852 (52 Weeks) – Medication Errors by Preferred Term**

| | Faster aspart (meal) | | | | NovoRapid® (meal) | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 386 | | | | 380 | | | |
| Total events | 28 | (7.3) | 38 | 10.6 | 27 | (7.1) | 35 | 9.7 |
| Wrong drug administered | 23 | (6.0) | 32 | 9.0 | 23 | (6.1) | 28 | 7.7 |
| Accidental overdose | 4 | (1.0) | 4 | 1.1 | 2 | (0.5) | 2 | 0.6 |
| Incorrect dose administered | 0 | | | | 3 | (0.8) | 4 | 1.1 |
| Extra dose administered | 0 | | | | 0 | | | |
| Inappropriate schedule of drug administration | 0 | | | | 1 | (0.3) | 1 | 0.3 |
| Device failure | 1 | (0.3) | 1 | 0.3 | 0 | | | |

Medication errors based on a Novo Nordisk MedDRA query (NNMQ) search.
Source: Safety Update, Table 2-10

There was one serious and severe medication error of 'wrong drug administered' in the mealtime FIASP group ( (b) (6) ) reported during 52 weeks of treatment.

One medication error of 'incorrect dose administered' was reported in the clinical pharmacology study 3922.

**Reviewer's comment: Overall, the incidence of medication errors appears comparable between treatment groups during 52 weeks of treatment period, with no notable increased risk with FIASP. DMEPA will review human factor study to determine if packaging may lead to increased risk of medication errors due to mix-ups with other insulin products.**

**Cardiovascular Events**

During the additional 26 weeks of study 3852, additional 2 events were positively adjudicated as cardiovascular (CV) events. One was determined to be heart failure (non-MACE) in the mealtime FIASP and another was a fatal myocardial infarction in the

NovoLog group that was classified as cardiovascular death (MACE). The diabetes pool was updated with these 2 events. The updated estimated MACE risk difference for FIASP vevrsus NovoLog was -0.39 (95% CI: -1.25, 0.47).

**Reviewer's comment: The number of MACE events continues to be very low in the FIASP clinical development and do not indicate that FIASP may increase the CV risk compared to NovoLog. Insulin is exempted from FDA premarketing guidance to demonstrate CV safety with an acceptable hazard ratio.**

**Injection Site Reactions and Lipodystrophy**

The overall incidence of injection site reactions after 52 weeks of treatment in study 3852 was slightly imbalanced not favoring mealtime FIASP: 2.1% (3.9 per 100 PYE) and 1.3% (1.4 per 100 PYE) in the mealtime FIASP and NovoLog groups, respectively. At 26 weeks, the incidence of injection site reactions was 2.1% (4.9 per 100 PYE) in the postmeal FIASP treatment group.

During the additional 26 weeks of treatment period in Study 3852, 3 subjects (one subject reported 4 events) in the mealtime FIASP and 3 subjects in the mealtime NovoLog reported injection site reactions. All of these events were non-serious, and none led to study discontinuation or dose reductions.

One infusion site pain (reported as "pain at IV line insertion site") occurred in study 3922.

Overall, in the updated diabetes pool (3852 with 52 weeks of data, 3853, and 4049), the rates of injection site reactions was slightly imbalanced not favoring FIASP versus comparator (3.8 [1.6%] and 2.0 [1.0%] events per 100 PYE respectively).

**Reviewer's comments: The overall injection site reactions appear to show imbalance not favoring FIASP compared to NovoLog in both completed study 3852 and in the updated diabetes pool. However the overall incidence and imbalance is small and it is unclear if this represents true treatment difference in injection site reactions.**

In Study 3852, at the end of 52 weeks of treatment with either mealtime FIASP or NovoLog, 6 events of lipodystrophy were reported in 6 subjects (3 events in 3 subjects in each treatment group). No lipodystrophy events were serious or severe, and none led to study discontinuations or dose reductions.

**Reviewer's comment: Events of lipodystrophy were only reported in study 3852.**

**Allergic Reactions**

During the additional 26 weeks of study 3852, two additional allergic reactions (allergic reaction and urticaria) were reported, both in the mealtime FIASP treatment group.

One subject ([redacted]) reported allergic reaction on Day 289 of study, where he had a moderate skin rash and developed hives after consuming a meal that may have contained sesame (the narrative was unclear whether he was allergic to sesame). He went to emergency room, received epinephrine and intravenous prednisolone, and went home. Allergic reaction lasted about 8 hours and no action was taken to the study drug. Another subject ([redacted]) experienced urticaria on Day 229, 8 hours after detemir injection, which resolved on its own after 7 days. Study drug was continued and the subject completed the study.

**Reviewer's comment: These allergic reactions do not appear to be related to the study drug. Both reported resolution of events, continued the study drug, and completed the study without any further incident.**

No allergic reactions were reported in study 3922.

## 7.4 Supportive Safety Results

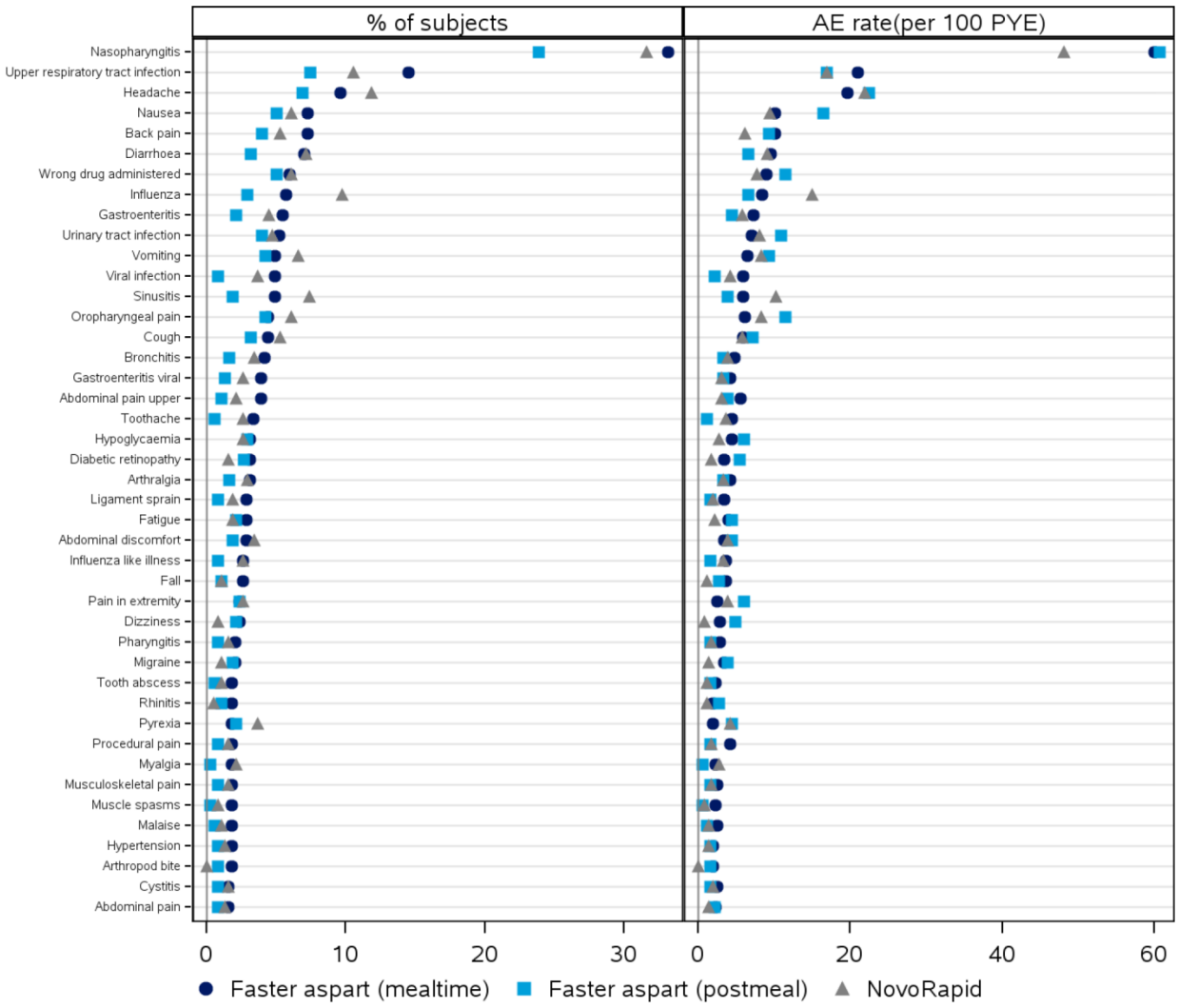
### 7.4.1 Common Adverse Events

Study 3852 (52 weeks):

The overall AE rate was 83.9% (445.8 PYE) in the mealtime FIASP and 84.2% (411 PYE) in the mealtime NovoLog after 52 weeks of treatment.

Figure 4 shows the treatment emergent AEs in ≥1% of subjects in any treatment arm after 52 weeks of treatment period.

**Figure 4: Treatment Emergent Adverse Events in ≥1% of Subjects in Any Treatment Arm – Study 3852 (52 Weeks) SAS**

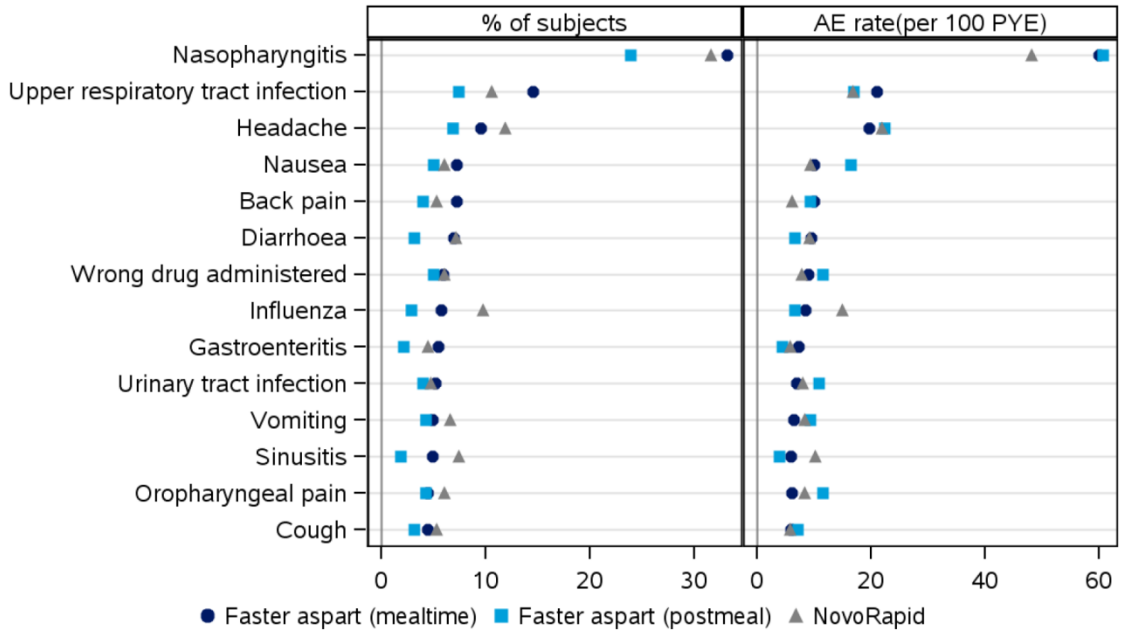



%: Percentage of subjects experiencing at least one event, PYE: Patient years of exposure
The mealtime arms include the entire 26+26 weeks whilst the postmeal arm ended 26 weeks after randomisation.
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.

Source: Safety Update, Appendix 7.3.1, Figure 4

Figure 5 shows the treatment emergent AEs in ≥5% of subjects in any treatment arm after 52 weeks of treatment period.

**Figure 5: Treatment Emergent Adverse Events in ≥5% of Subjects in Any Treatment Arm – Study 3852 (52 Weeks) SAS**




%: Percentage of subjects experiencing at least one event, PYE: Patient years of exposure
The mealtime arms include the entire 26+26 weeks whilst the postmeal arm ended 26 weeks after randomisation.
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.

Source: Safety Update, Appendix 7.3.1, Figure 6

The most frequently reported AEs with incidence of ≥5% and where the AE incidence was higher with FIASP were *nasopharyngitis* (33.2% mealtime FIASP compared to 31.6% mealtime NovoLog), *upper respiratory tract infection* (14.5% mealtime FIASP versus 10.5% mealtime NovoLog), *nausea* (7.3% mealtime FIASP versus 6.1% mealtime NovoLog), *back pain* (7.3% mealtime FIASP versus 5.3% mealtime NovoLog), *gastroenteritis* (5.4% mealtime FIASP versus 4.5% mealtime NovoLog), and *urinary tract infection* (5.2% mealtime FIASP versus 4.7% mealtime NovoLog).

Other notable differences in reported AEs with incidence of ≥2% with higher incidence seen with FIASP include *viral infection* (4.9% mealtime FIASP versus 3.7% mealtime NovoLog), *viral gastroenteritis* (3.9% mealtime FIASP versus 2.6% mealtime NovoLog), *diabetic retinopathy* (3.1% mealtime FIASP versus 1.6% mealtime NovoLog), *hypoglycemia* (3.1% mealtime FIASP versus 2.6% mealtime NovoLog), *fatigue* (2.8% mealtime FIASP versus 1.8% mealtime NovoLog), fall (2.6% mealtime FIASP versus 1.1% mealtime NovoLog), *ligament sprain* (2.8% mealtime FIASP versus 1.8% mealtime NovoLog), *dizziness* (2.3% mealtime FIASP versus 0.8% mealtime NovoLog), *migraine* (2.1% mealtime FIASP versus 1.1% mealtime NovoLog),

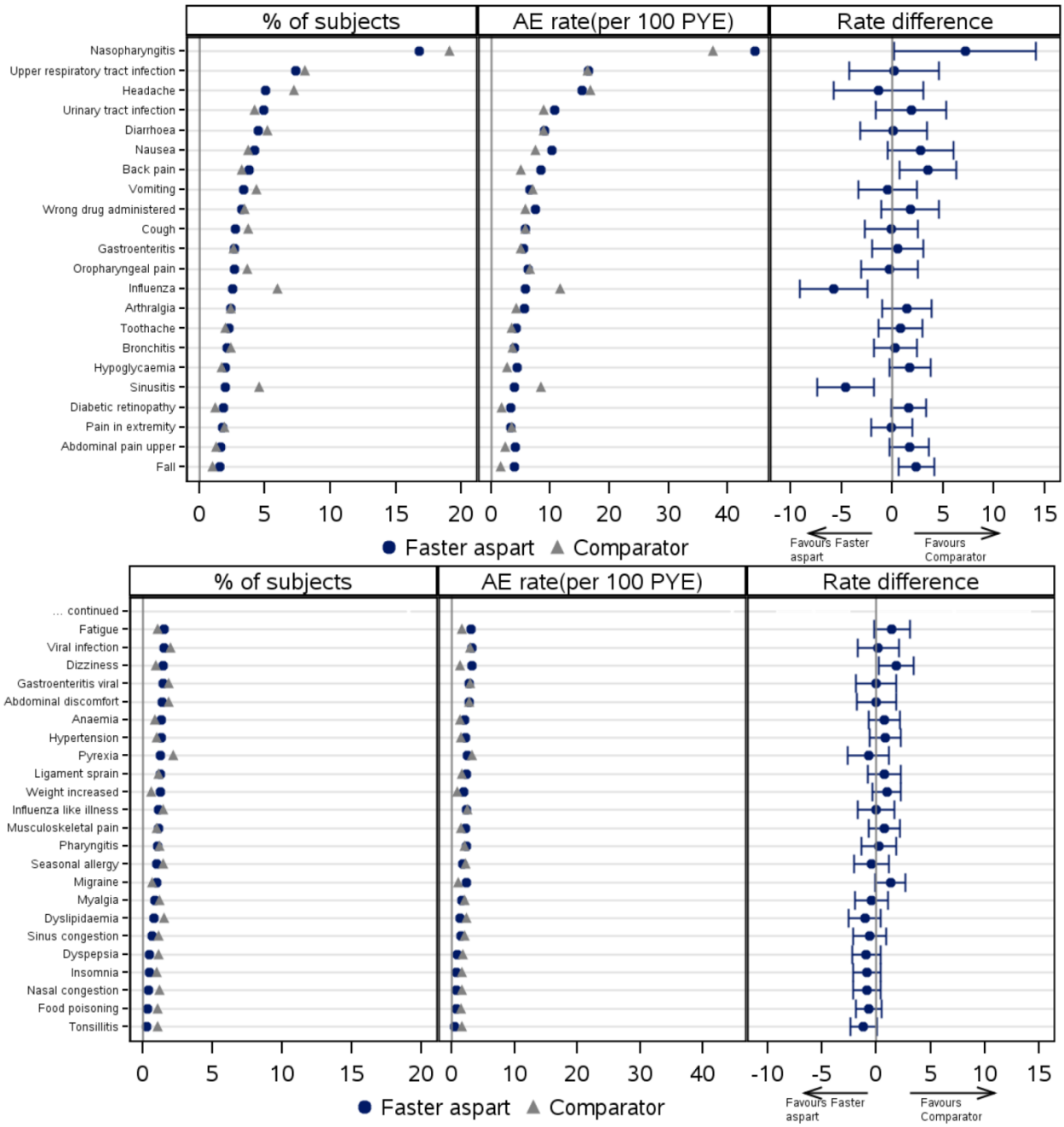
**Reviewer's comment: There were no clinically notable differences in the common adverse event reported in study 3852 with additional 26 weeks of exposure**

**between mealtime FIASP and mealtime NovoLog. It is unclear whether the observed small imbalance between treatment groups is by chance or represents a true risk.**

Diabetes Pool:

The AEs in the diabetes pool was updated with the full 52 weeks of exposure to mealtime FIASP and NovoLog in study 3852. Figure 6 shows the AEs that occurred in ≥1% of subjects in any treatment group by Preferred Terms, with rate difference calculated using adjusted Cochran-Mantel-Haenszel method.

**Figure 6: Adverse Events ≥1% of Subjects in Any Treatment Group by Preferred Term in the Updated Diabetes Pool (Sorted by the Frequency in FIASP Group) – Cochran-Mantel-Haenszel Adjusted**




%: Percentage of subjects experiencing at least one event, PYE: Patient years of exposure
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0. The 'Diabetes pool' consists of trials 3852(52w), 3853, 4049 and 3931.
'Comparator' consists of NovoRapid plus basal insulin. NovoRapid is known as NovoLog in the U.S.
Proportions, event rates and rate differences with associated 95% confidence intervals were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trials. If no events are experienced for the subjects in a trial, the subjects contribute with exposure.

Source: Safety Update, Figure 2-1

**Reviewer's comment: The updated diabetes pool also did not show any notable new safety issue with FIASP against the comparator group.**

Study 3922: Four subjects reported 5 events after a single dose of FIASP and one subject reported 1 event after a single dose of NovoLog. Five reported AEs with FIASP include a headache, abdominal pain, infusion site pain, incorrect dose administered, and oropharyngeal pain. One event of headache was reported with NovoLog. All subjects recovered/resolved from these events.

### 7.4.2 Laboratory Findings

In study 3852, laboratory assessments were continued during the additional 26 weeks to identify any possible cases of drug-induced liver injury. No subjects meeting the Hy's law criteria were identified during 52 weeks of treatment period.

### 7.4.3 Vital Signs

No new information is included in this safety update.

### 7.4.4 Electrocardiograms (ECGs)

No new information is included in this safety update.

### 7.4.5 Special Safety Studies/Clinical Trials

None.

### 7.4.6 Immunogenicity

For a detailed review and assessment related to immunogenicity and its assay, please refer to Dr. Bruce Huang's review dated September 6, 2017. I will provide an overview of results related to efficacy and safety of FIASP.

In study 3852, samples for antibody were collected at baseline, Week 12, Week 26, Week 40, and Week 52. The presence of antibodies (insulin aspart specific antibodies and antibodies cross-reacting with human insulin) is presented as the percent of bound radioactivity (B) out of total amount of radioactivity (T) (% B/T).

Anti-drug antibodies (ADA), antibodies against insulin aspart, and anti-insulin antibodies (AIA), antibodies cross-reacting with human insulin, are discussed here.

To determine the number of anti-insulin aspart positive subjects at each visit, the 99% percentile (the upper limit of the normal range) from 50 healthy individuals analyzed 6 times were used as cut-points for determining positivity for antibody. The 99%

percentile for each antibody population was determined as: >1.9% B/T for anti-insulin aspart specific antibodies, and >0.7% B/T for antibodies cross-reacting between insulin aspart and human insulin. The %B/T value above normal range values were considered as positive.

The majority of subjects in the study 3852 had antibodies at baseline, and antibody development was similar across treatment groups during the 52 weeks of treatment period (data not shown here; see Figure 3-1 and 3-2 in the Safety Update for plots of antibody titers).

The proportion of subjects testing positive for specific antibodies and cross-reacting antibodies were similar between mealtime FIASP and NovoLog (Table 6).

**Table 6: Study 3852 (52 Weeks) – Subjects Positive for Anti-Insulin Aspart Antibodies (Specific or Cross-Reacting) At 26 and 52 Weeks**

| | 26 week data cut (trial 3852) | | 52 week data cut (trial 3852) | |
|---|---|---|---|---|
| | Faster aspart[d] | NovoLog | Faster aspart (mealtime) | NovoLog |
| | Safety set: 763 | Safety set: 380 | Safety set: 386 | Safety set: 380 |
| | number of subjects (percent) | number of subjects (percent) | number of subjects (percent) | number of subjects (percent) |
| Subjects positive for insulin aspart specific[a] antibodies at baseline | 132 (17.3) | 70 (18.4) | 67 (17.4) | 70 (18.4) |
| Subjects positive for insulin aspart specific[a] antibodies at any time during the trial period | 189 (24.8) | 91 (23.9) | 103 (26.7) | 104 (27.4) |
| Subjects with a sustained[b] response of insulin aspart specific[a] antibodies | 171 (22.4) | 83 (21.8) | 91 (23.6) | 91 (23.9) |
| Subjects positive for cross-reacting[c] antibodies at baseline | 689 (90.3) | 353 (92.9) | 348 (90.2) | 353 (92.9) |
| Subjects positive for cross-reacting[c] antibodies at any time during the trial period | 742 (97.2) | 374 (98.4) | 382 (99.0) | 377 (99.2) |
| Subjects with a sustained[b] response of cross-reacting[c]antibodies | 740 (97.0) | 373 (98.2) | 380 (98.4) | 376 (98.9) |

[a] Corresponding to anti-drug antibodies, which represent antibodies specific against insulin aspart
[b] Two or more positive samples during the trial, including baseline, or positive at last observation
[c] Corresponding to anti-insulin antibodies, which represent anti-insulin aspart antibodies cross-reacting with human insulin
[d] Pooled mealtime and postmeal groups

Source: Safety Update, Table 3-1

*Treatment induced* was defined as subjects that were antibody negative at baseline and became antibody positive after baseline. The incidence of subjects with treatment induced cross-reacting antibodies were slightly higher in subjects treated with FIASP (97%) compared to NovoLog at 52 weeks (71%), and treatment induced anti-insulin

antibodies were not notably different between subjects treated with FIASP (7.6%) and NovoLog (7.3%) at 52 weeks.

*Treatment boosted* were defined as subjects with baseline value above cut-point and below 18%B/T and either 1) an absolute increase from baseline to a post baseline visit of 3%B/T or more; or 2) an absolute increase from baseline to a post baseline visit of 9%B/T or more. There was no notable treatment difference in treatment boosted cross-reacting antibodies between FIASP and NovoLog after 52 weeks of treatment, and treatment induced anti-insulin antibodies were slightly lower in subjects treated with FIASP (5.2%) compared to NovoLog (12.7%).

Antibodies and Glycemic Efficacy: The spearman rank correlation for antibody levels and their HbA1c levels, change in HbA1c, and total daily insulin dose after 26 and 52 weeks did not show any correlation (data not shown, see Tables 3-9 and 3-10 in the Safety Update).

Antibodies and Allergic Reactions: Of 52 subjects with 61 allergic reactions after 52 weeks of treatment in study 3852, 14 subjects were positive for at least one sample of anti-insulin aspart specific antibodies and 51 subjects were positive for at least one sample of cross-reacting antibodies. The rates of allergic reactions were similar between FIASP and NovoLog in subjects with positive antibody levels and subjects that were not positive for antibody levels (data not shown here; see Tables 3-5 and 3-6 in the Safety Update). The scatter plots showing titers of antibodies and subjects with or without allergic reactions also did not show any apparent association.

Antibodies and Injection Site Reactions: Of 22 subjects with injection site reactions after 52 weeks of treatment in study 3852, 4 subjects were positive for at least one sample of specific antibodies. Rates of injection site reaction events for subjects positive and not positive for specific antibodies were comparable between treatment groups (data not shown here; see Tables 3-7 and 3-8 in the Safety Update). All 22 subjects were positive for at least one sample of cross-reacting antibodies. However, about 99% of all subjects were positive for cross-reacting antibodies at least once during the 52 weeks of treatment period. Thus no apparent association between antibody development and injection site reaction AEs were seen.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Dose-dependency for hypoglycemia was discussed in section 7.3.4.

### 7.5.2 Time Dependency for Adverse Events

Time dependency for hypoglycemia was discussed in section 7.3.4.

### 7.5.3 Drug-Demographic Interactions

No new analysis done.

### 7.5.4 Drug-Disease Interactions

No new analysis done.

### 7.5.5 Drug-Drug Interactions

No new analysis done.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

The number and types of cancers reported from the updated data were reviewed; the reported events were small and no apparent trend/grouping in the types of cancer was seen. Thus there was no suggestion of any safety signal related to cancer with FIASP with additional 26 weeks of exposure (up to 52 weeks). However, the duration of studies in the clinical development program of FIASP would be too short to fully evaluate the carcinogenic potential for a product.

### 7.6.2 Human Reproduction and Pregnancy Data

FIASP has not been studied during pregnancy and lactation in clinical studies.

Since the original submission, one pregnancy ( (b) (6) ) was reported during the additional 26 weeks of treatment period of study 3852. She reportedly delivered without complications.

Two additional pregnancies are reported in the ongoing trials, without any adverse consequence yet since delivery is expected in the future. The treatment group also remains blinded in these two subjects.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant is currently conducting a Phase 3 study in children and adolescents with type 1 diabetes (study 4101).

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information is available.

### 7.7 Additional Submissions / Safety Issues

None.

## 8 Postmarket Experience

FIASP received marketing authorization in European Union, Canada, Norway and Island during 2017, but post-marketing data are not yet available as launch in each country likely occurred during the year subsequent to approval.

The Applicant submitted a Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report (PSUR/PBRER) for NovoLog covering October 1, 2015- September 30, 2016 in this resubmission. This latest PSUR did not impact the overall benefit risk profile of insulin aspart.

# 9 Appendices

## 9.1 Literature Review/References

## 9.2 Labeling Recommendations

Labeling recommendations are contained within this review as appropriate. Labeling is not finalized at the time of this review.

## 9.3 Advisory Committee Meeting

No advisory committee meeting was convened for this application.

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/s/

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HYON J KWON
09/22/2017

LISA B YANOFF
09/22/2017

# Division Director Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Jean-Marc Guettier, MDCM |
| **Subject** | Division Director Summary Review |
| **NDA/BLA # Supplement #** | 208751 |
| **Applicant** | Novo Nordisk |
| **Date of Submission** | December 8th, 2015 |
| **PDUFA Goal Date** | October 8th, 2016 |
| **Proprietary Name / Non-Proprietary Name** | (b) (4) insulin aspart injection |
| **Dosage Form(s) / Strength(s)** | Solution for subcutaneous injection/100 units per mL |
| **Applicant Proposed Indication(s)/Population(s)** | To improve glycemic control in adults with diabetes mellitus |
| **Action/Recommended Action for NME:** | Complete Response |
| **Approved/Recommended Indication/Population(s)** (if applicable) | *Not applicable* |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | **Hyon Kwon, PharmD** |
| Statistical Review | **Alexander Cambon PhD; Mark Rothman, PhD** |
| Pharmacology Toxicology Review | **Miyun Tsai-Turton, PhD** |
| OPQ Review | **Muthukumar, Ramaswamy, PhD** |
| OBP | **Steven Bowen, PhD; Susan Kirshner, PhD** |
| Clinical Pharmacology Review | **Shalini Wickramaratne Senarath Yapa, PhD** |
| OSI | **Cynthia Kleppinger, MD** |
| CDTL Review | **Lisa Yanoff, MD** |

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

**Benefit-Risk Summary and Assessment**

*NN1218, (b) (4) from hereon in, is a new formulation containing insulin aspart that is purported to be more rapidly absorbed from the subcutaneous tissue than Novolog, a currently approved and marketed insulin aspart containing drug product. The difference in rate of absorption between the two formulations is measured in terms of minutes (<10 minutes per the applicant's data). I use the word "purported" intentionally because the clinical pharmacology data on which this claim is based was deemed to be unreliable by the Office of Clinical Pharmacology due to issues with the bioanalytical assay method that was used for the quantitative measurement of aspart from human serum. Absent a valid bioanalytical assay, it is not possible to conclude with certainty that pharmacokinetic differences between (b) (4) and Novolog exist and that differences between these products were reliably and accurately estimated. Reliable pharmacokinetics data related to (b) (4) per se, is required to inform the sections of the drug label that rely on this information before this product can be approved. I recommend a Complete Response for this deficiency.*

*In the clinical program, the applicant demonstrated that (b) (4) administered by subcutaneous injection immediately before meals improves glycemic control in patients with type 1 and 2 diabetes mellitus who were not optimally controlled at trial enrollment. Effectiveness was established by comparing the glucose lowering effect of (b) (4) to Novolog in two pivotal trials where doses of each insulin were adjusted and individualized to achieve a pre-prandial glucose within a specific target range. Non-inferiority comparisons, as well as responder analyses, showed that (b) (4) provided approximately the same level of glucose control compared to Novolog in type 1 and type 2 diabetes mellitus. Improvement in glucose control with insulin was established to delay the onset and progression of complications (injury to the retina, injury to the kidneys and injury to nerves) caused by chronic glucose elevation in type 1 and 2 diabetes and is used as a surrogate to establish the benefits of insulin products. In the type 1 DM trial, (b) (4) appeared to offer numerically better glycemic control than Novolog. The difference was small and of unknown clinical significance. Interpretation of the effect was further limited due to issues related to an imbalance in baseline demographic variables (baseline age, sex, and HbA1c), differential missing data between arms, and differential increase in daily mealtime insulin dose between arms. The findings from the type 2 DM trial did not provide support to the finding of improved efficacy observed in the type 1 DM trial as no difference in efficacy was noted between (b) (4) and Novolog in this trial.*

*In the clinical program, the applicant adequately characterized most of the risks of the new aspart formulation for subcutaneous injection except for risks associated with immunogenicity. Product related risks identified were hypoglycemia, weight gain, and injection site reactions. Risks of weight gain and hypoglycemia were similar between the two formulations and risks of injection site reactions slightly higher with (b) (4) Immunogenicity was not adequately characterized because of deficiencies in the validation of the anti-drug antibody assays. (b) (4)*

*The new aspart formulation was not observed to offer a clear and persuasive advantage over Novolog in terms of improvements in efficacy or safety for the treatment of patients with type 1 or 2 diabetes mellitus.*

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Patients with type 1 diabetes are dependent on insulin for survival.<br>• Patients with type 2 diabetes whose disease cannot be controlled with oral antidiabetic agents may require insulin. | • In type 1 diabetes, insulin prevents acute metabolic complications caused by absolute insulin deficiency (e.g., severe hyperglycemia and DKA) and delays the onset and the progression of complications caused by chronic elevation in glucose.<br>• In type 2 diabetes, insulin reverses acute metabolic complications related to severe hyperglycemia (Hyperosmolar Hyperglycemia Syndrome) and reduces complications caused by chronic elevation in blood glucose. |
| **Current Treatment Options** | • There are multiple basal, mealtime, and mixed insulin products that are approved and used to manage hyperglycemia in patients with type 1 and type 2 diabetes mellitus.<br>• Marketed insulins that can be used to control glucose rises associated with meals are: Apidra, Humalog, Humalog 50/50, Humalog 75/25, Novolog, Novolog 50/50, Novolog 70/30, Ryzodeg 70/30, Humulin R, Humulin 70/30, Novolin R, Novolin 70/30 and Afrezza | • (b) (4) is purported to be absorbed faster than Novolog (this is to be confirmed with a reliable and reproducible bioanalytical assay).<br>• Increased rate and extent of absorption of insulin before a meal could in theory more closely match mealtime glucose rises associated with absorption of macronutrients with resultant improvement in glycemic control and reduction in the risk of hypoglycemia. |
| **Benefit** | • (b) (4) was demonstrated to provide a level of glucose control that was clinically similar to Novolog.<br>• In one trial (b) (4) offered numerically larger HbA1c reduction compared to Novolog although the difference was small and of unknown clinical significance. A second trial did not confirm that (b) (4) offered superior HbA1c than Novolog. | • (b) (4) was demonstrated to improve glucose control through comparison to a known effective drug. Improvement in glucose over years reduces the risks of short and longterm complications caused by chronic elevation in glucose levels in type 1 and 2 diabetes.<br>• The data in the application do not persuasively establish that (b) (4) will have superior efficacy compared to Novolog in the treatment of diabetes. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Risk** | • Hypoglycemia, sometimes severe, weight gain, injection site reactions and hypersensitivity reactions are the main risks associated with (b) (4) | • The risk of hypoglycemia, weight gain and hypersensitivity were found to be similar between Novolog and (b) (4) when administered before or 20 minutes into the meals.<br>• Injections site reactions occurred slightly more frequently with (b) (4) compared to Novolog.<br>• The data in the application do not persuasively establish that (b) (4) will have less risks compared to Novolog in the treatment of diabetes. |
| **Risk Management** | • Not applicable at this time, application will receive a Complete Response due to Clinical Pharmacology Deficiencies. | • Not applicable at this time, application will receive a Complete Response due to Clinical Pharmacology Deficiencies. |

## 1. Background

On December 8, 2015 Novo Nordisk submitted a New Drug Application (NDA) for (b) (4) under section 505(b)(1) of the Federal Food Drug and Cosmetic Act. The applicant is seeking to indicate (b) (4) to improve glycemic control in adults with diabetes mellitus. (b) (4) is a solution for injection containing 100 units per mL of insulin aspart [i.e., an insulin analog]. (b) (4) is to be administered by subcutaneous injection before each daily meal to control glucose rise that accompany ingestion and absorption of macronutrients in a meal.

There are a number of marketed insulins that can be used to control glucose excursion associated with meals including; Apidra, Humalog, Humalog 50/50, Humalog 75/25, Novolog, Novolog 50/50, Novolog 70/30, Ryzodeg 70/30, Humulin R, Humulin 70/30, Novolin R, Novolin 70/30 and Afrezza.

(b) (4) is a reformulation of Novolog and differs from this product by two excipients. The excipient nicotinamide [vitamin B3 (niacinamide)] is added to enhance absorption and L-arginine hydrochloride (an amino acid) is added as a stabilizing agent. The change in formulation is purported to enhance the rate and extent of absorption of insulin aspart from the subcutaneous depot.

It is theorized that an insulin that is more rapidly absorbed could offer the following clinical benefit;

- Improvement in glycemic control: More rapid and extensive absorption may lead to better glucose control in the early part of the meal which in turn may reduce post-meal hyperglycemia and lead to an improvement overall glycemic control (i.e., HbA1c)
- Less hypoglycemia: More rapid and complete absorption of insulin may limit insulin action to the post-prandial time period (0-4 hours after a meal) when it is most needed and reduce risk of late hypoglycemia (> 4 hours after a meal) that occurs when insulin is still active but is no longer needed.
- Less weight gain: Better glycemic control and fewer hypoglycemic events could result in less weight gain (i.e., less doses of insulin to correct for post-meal hyperglycemia and less snacking to compensate for hypoglycemia related to insulin overdosing).

This document serves as the division director's memorandum for the application.

## 2. Product Quality

I concur that there are no outstanding product quality issues that preclude approval. For details refer to the executive summary prepared by Dr. Ramaswamy.

The applicant references NDA 20989 (Novolog) for CMC information related to the drug substance, insulin aspart, in this NDA. This is acceptable.

The (b) (4) drug product contains 100 units of insulin aspart and the following amount of compendial grade excipients per mL of solution; 3.3 mg of glycerol, 1.50 mg of phenol, 1.72 mg of metacresol; 19.6 mcg of zinc (as zinc acetate); 0.53 mg of disodium phosphate dehydrate; 3.48 mg of arginine (as L-arginine hydrochloride); 20.8 mg of niacinamide and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH to 7.1.

The composition of (b) (4) and Novolog are identical with respect to amount of insulin aspart (100U/mL), (b) (4) 1.50 mg/mL of phenol and 1.72 mg/mL of metacresol), and zinc concentration (19.6 µg/mL). (b) (4) differs from Novolog with respect to pH (7.1 versus 7.4), glycerol (3.3 mg/mL vs. 16 mg/mL), phosphate (0.53 mg/mL vs (b) (4) mg/mL), nicotinamide ((b) (4) mM vs. none), and arginine concentration (L-arginine HCl, 20mM vs. none).

The drug product is filled in USP (b) (4) glass cartridge (3-mL) vials sealed with a (b) (4) rubber disc on one end and a (b) (4) rubber plunger on the other end. The drug product is also available in 10 mL vial sealed with a (b) (4) rubber (b) (4) The container closure system components proposed for use are the same as those of the approved Novolog and are acceptable.

The (b) (4) pen-injector (PDS-290 platform) is a manual, pressure operated, injector device designed to deliver variable volumetric doses of (b) (4) (10-800 microliter equivalent to 1-80 units of insulin aspart). Each pen injector can dispense up to 80 units. A new needle is attached prior to each dose and a priming step is required. The review of the auto-injector was completed by Dr. Cochenour. Biocompatability of the device was completed by Dr. Mollo. Neither reviewers identified an issue with the auto-injector.

(b) (4) These will be communicated in the complete response letter.

An expiration date of 30 months is granted for the finished product when stored between 2 and 8 °C in vials and in the prefilled pen. An in-use period of up to 28 days is granted when the finished product is stored at room temperature [below 86° F (30 °C)]. Shelf life determination was based on real-time stability data for the primary using the commercial formulation.

## 3. Nonclinical Pharmacology Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval. A full nonclinical

program was previously conducted for Novolog and is referenced for (b) (4) approval. The applicant conducted several nonclinical pharmacokinetic and local tolerance toxicity studies with (b) (4) to qualify the new excipients. No significant toxicity, impurity, degradant, leachable or extractable issues were identified in the review. Refer to Dr. Tsai-Turton's memorandum for details.

## 4. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there is a major outstanding clinical pharmacology issue that precludes approval of this product.

The applicant purports that the clinical pharmacology data in the application establish that aspart is absorbed at a faster rate from the (b) (4) product than from the Novolog product. Dr. Kwon reviews the summary of the applicant's pharmacodynamics and pharmacokinetic data in 4.4.2 and 4.4.3 of her review. Insulin aspart is detected in circulation ~ 5 minutes sooner when administered as (b) (4) compared to when it is administered as Novolog at an equivalent dose (refer to Figure 10 in Dr. Kwon's review). Insulin aspart concentration peaks 7 minutes sooner when (b) (4) is injected compared to when the equivalent dose of Novolog is injected (refer to Figure 10 in Dr. Kwon's review). The largest difference in aspart exposure between the two products, based on area under the curve determination, is observed in the first 15 minutes after injection (i.e., a low insulin concentration) and diminishes considerably thereafter (refer to figure 11 in Dr. Kwon's review). Relative to Novolog, aspart concentration is 4-fold, 1.32-fold and 1.10 fold higher in the first 15 minutes, hour, and two hours, respectively, following injection of (b) (4) Total exposure and terminal half-life were similar between the two aspart insulin products.

The applicant evaluated the impact of PK differences on pharmacodynamic changes using the glucose clamp and the standardized meal tolerance test techniques. In clamp experiments relatively more glucose was infused in the first hour (~20% more) when aspart was injected as (b) (4) (refer to Figure 3 in Dr. Kwon's review). Differences in glucose infusion rates between the two aspart products decreased when glucose infusion over 2 hours were considered (~13% more). Standardized meal tolerance testing (refer to Figure 4 in Dr. Kwon's review) showed that subjects treated with (b) (4) or Novolog had similar glucose values 2 hours after a standardized meal.

According to the applicant's data there appears to be a small difference in PK and PD between (b) (4) and Novolog. The clinical significance of small early changes on the overall management of glycemic control in patients with diabetes is unclear from these data and will be reviewed in Section 6.

Dr. Wickramaratne Senarath Yapa found the clinical pharmacology data submitted in the NDA to be unreliable because of major flaws in the bioanalytical method that was used to measure and quantify insulin aspart in pharmacokinetic studies. The specific bioanalytical deficiencies identified are reviewed in her memorandum and included; (b) (4)

(b) (4)

The applicant characterized the bioavailability and the pharmacokinetics (PK) of (b) (4) and the PK differences between (b) (4) and Novolog using an unreliable bioanalytical assay. The results of the pharmacokinetic studies cannot be used as they may be inaccurate and may not be reproducible. The novelty of (b) (4) lies in its purported novel pharmacokinetics. Absent assurance that the bioanalytical method used to characterize the pharmacokinetics of (b) (4) reliably and reproducibly captures insulin aspart concentration, it is not possible to conclude with certainty that pharmacokinetic differences between (b) (4) and Novolog exist. If differences in the rate and extent of aspart absorption do indeed exist, it is uncertain that the estimates of the differences reported are accurate. The pharmacokinetics of insulin products are used to inform dosage and administration of insulin products (i.e., timing of administration in relation to meals, (b) (4) etc.) and the time concentration profile is described in the full prescribing information. Accurate and reliable pharmacokinetic information is required for safe use of this product and the application cannot be approved without it.

## 5. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

## 6. Clinical/Statistical-Efficacy

This section provides a brief overview of the key efficacy findings in the application. Detailed reviews are provided in Drs. Kwon, Cambon and Yanoff's respective reviews. No major efficacy issues were identified in the application. (b) (4) is a new formulation of an existing, approved and marketed, mealtime insulin (insulin aspart). The applicant demonstrated that changes to the formulation did not have an important impact on the already established efficacy of insulin aspart. (b) (4) improved glycemic control in two adequate and well-controlled trials involving patients with type 1 diabetes and type 2 diabetes to an extent similar to the active comparator Novolog (i.e., the currently marketed formulation of insulin aspart).

The applicant did not provide persuasive data to suggest that the novel formulation offers a clinically meaningful advantage over Novolog in terms of efficacy. Differences in efficacy noted in one study between the two formulations were small, confounded by differential dosing and were not replicated in a second study.

Two other studies were submitted in the application. In trial 4049, the applicant compared the effect of adding (b) (4) versus continuing "failed" pre-trial therapies (i.e., basal insulin and oral anti-diabetic drugs) on the change from baseline in HbA1c to 18-weeks in patients with type 2 diabetes inadequately controlled at baseline. (b) (4)

(b) (4) These two studies were reviewed by Drs. Kwon and Yanoff and will not be discussed in this memorandum.

***Type 1 Diabetes Trial versus Novolog (Multiple Daily Subcutaneous Injections)***

Trial 3852 was a 26-week randomized, multicenter, multinational, double blind, active-controlled, parallel group trial comparing the efficacy and safety of mealtime (b) (4) (N=381) to mealtime Novolog (N=380) in adults with type 1 diabetes mellitus who were also receiving insulin detemir to cover basal insulin requirements. (b) (4) and Novolog were administered 0 to 2 minutes before each daily meal. The trial also included a third, open-label, (b) (4) arm (N=382) where (b) (4) was administered 20 minutes after the start of the meal[1].

The primary objective of the trial was to demonstrate that, after 26-weeks, using (b) (4) before meals did not result in unacceptably worse glucose control than using Novolog before meals (i.e., non-inferiority objective).

Eligible participant were adults diagnosed type 1 diabetes for at least one year, who had inadequate glycemic control at baseline (HbA1c between 7 and 9.5%), were not severely obese (BMI less than or equal to 35 kg/m$^2$), had been receiving basal-bolus insulin therapy for at least 12 months and were on a basal insulin analogue (either insulin detemir or insulin glargine) for at least 4 months.

Patients were ineligible if they used an anti-diabetic drug other than insulin in the past 3 months; if changes to concomitant drugs known to interfere significantly with glucose metabolism (corticosteroids, beta blockers, monoamine oxidase inhibitors or anti-obesity drugs) were anticipated or if they had had a major adverse cardiovascular event in the 6 months preceding the trial. They were also ineligible if they had uncontrolled hypertension, impaired liver or renal function (serum creatinine ≥2 mg/dL), recurrent severe hypoglycemia (more than one episode in the past 12 months), hypoglycemic unawareness, hospitalization for diabetic ketoacidosis in the past 6 months, or proliferative retinopathy or maculopathy requiring treatment.

The trial was divided into a screening visit, an 8-week run-in phase, a randomization visit, a 26-week intervention phase and a 26-week safety extension phase.

The mean age of the study population was 45 years, and the mean duration of type 1 diabetes mellitus was 21 years. 59% were male. 93% were White, 2% were Black or African American. 7% were Hispanic. The mean BMI was 27 kg/m$^2$. Some differences were noted in baseline characteristics between groups. The group randomized to pre-meal (b) (4) was slightly older, randomized more females, and had slightly worse baseline glycemic control (based on HbA1c and FPG) than the group randomized to pre-meal Novolog.

[1] One potential advantage is that estimating meal nutrient content (carbohydrate counts) for the purposed of determining mealtime insulin dose can be more accurate. One potential disadvantage is that absorption of nutrients and duration of insulin action can be potentially mismatched.

At the beginning of the run-in phase, patients who had been treated with a pre-trial basal insulin other than detemir were placed on insulin detemir with no change in dose or administration schedule (i.e., once daily or twice daily). Detemir dose was adjusted weekly during the run-in based on pre-breakfast or, if applicable[2], based on both pre-breakfast and pre-dinner levels[3]. During the intervention phase basal insulin dose was to be changed only for safety reasons.

At randomization, mealtime insulin dose used in the run-in was converted to an equivalent dose of (b) (4) or Novolog. During the intervention phase, the dose of (b) (4) or Novolog was adjusted either continuously based on carbohydrate counting or twice weekly based on a standard algorithm targeting a pre-meal glucose between 71 to 108 mg/dL.

The primary outcome measured was the difference between randomized groups in the mean change from baseline in HbA1c at 26 weeks (i.e., the delta delta). The objective of the trial was to demonstrate that (b) (4) was not unacceptably worse than Novolog by a non-inferiority margin of greater than 0.4%. There was not pre-specified plan to test for superiority.

Secondary objectives were to demonstrate superiority (i.e., lower) of (b) (4) to Novolog on a 2-hour post prandial glucose following ingestion of a standard liquid meal, to demonstrate non-inferiority of post-meal (b) (4) to mealtime Novolog, and to demonstrate body weight differences between (b) (4) and Novolog (i.e., less weight gain on (b) (4) A sequential hierarchical testing strategy was used to control for type-1 error across multiple tests.

The treatment policies in the protocol compare an accepted "gold standard" treatment regimen containing Novolog to a new treatment regimen containing (b) (4) The trial addresses the following clinical question; how does the new regimen compare to the "gold-standard" regimen in terms of efficacy in patients with type 1 diabetes? The population of interest was the intent to treat population. The estimand of most interest was the effect in all participants in whom the treatment regimen was initiated (i.e., the de facto estimand).

The primary outcome measure was considered missing if no HbA1c measurement was available for the week 26 visit. The sponsor's primary analysis was based on a Mixed Effects Repeated Measures (MMRM) model[4]. This model assumes that data missing for the endpoint visit are missing at random (i.e., that dropping out was unrelated to the intervention). This is almost never a valid assumption as at least some of the missing data are related to the intervention itself (i.e., lack of efficacy/tolerability/safety issue). Dr. Kwon

[2] For those injecting twice daily.
[3] The dose of detemir was to be adjusted until pre-breakfast self-monitoring glucose levels reached a target glucose of 71 to 90 mg/dL and, in those injecting twice daily, pre-dinner glucose levels reached a target of 71 to 108 mg/dL.
[4] 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]).

reviews disposition categories in Table 14 of her review. She notes, for example, that in both arms some subjects were withdrawn because of hypoglycemia (a safety issue associated with insulin).

Overall, less missing data was observed in the Novolog arm than in the two (b) (4) arms (5% for Novolog, compared to 8% for each of the (b) (4) arms). Fewer subjects in the Novolog arm discontinued treatment before 25 weeks (5% for Novolog group, compared to 7% for mealtime (b) (4) arm and 8% for postmeal (b) (4)

During the intervention phase, subjects randomized to mealtime (b) (4) had a larger increase (i.e., 50% larger relative increase) from baseline in average mealtime insulin doses (0.09 units per kg for mealtime (b) (4) versus 0.06 units per kg for mealtime Novolog). Insulin detemir dose was unchanged in both arms. These data are shown in Table 22 of Dr. Kwon's review.

The results based on the sponsor's primary analysis are shown in the table below.

**Table 1: Primary Analysis Results Type 1 DM trial 3582 (Adapted from Table 2 in Dr. Kwon's Review)**

| Treatment Group | N | Baseline Mean | End of Trial Mean | LS Mean Change from Baseline | Treatment Difference (95% CI) |
|---|---|---|---|---|---|
| **Type 1 Diabetes Mellitus** | | | | | |
| ***Trial 3852:*** *26-week basal-bolus in combination with insulin detemir* | | | | | |
| Mealtime (b) (4) | 381 | 7.62 | 7.31 | -0.32 | -0.15 (-0.23, -0.07) |
| Postmeal (b) (4) | 382 | 7.63 | 7.51 | -0.13 | 0.04 (-0.04, 0.12) |
| Mealtime Novolog | 380 | 7.58 | 7.42 | -0.17 | |

N=Number of Randomized Individuals.

Subjects randomized to (b) (4) had clinically similar, small, HbA1c reduction from baseline compared to subjects randomized to Novolog. It is unclear whether the observed numerical difference between arms is clinically meaningful (recall that a difference of 0.4% was not considered unacceptably worse for the purpose of setting the non-inferiority margin). It is also unclear whether the observed difference is attributable to; (b) (4) potentially new pharmacokinetic properties (see clinical pharmacology section above for major reliability issues related to PK characterization), to differences in baseline characteristics between (b) (4) and Novolog, to differential dose increases between (b) (4) and Novolog, to the impact of early and differential discontinuation between arms or to one or more of these factors.

Dr. Cambon begins to explore the impact of missing data on the estimate of efficacy in his review. For this application, methods that can be applied to evaluate the impact of missing data on efficacy are limited because virtually no data were obtained post-discontinuation in any of the participants (refer to Tables 7 of his review). The applicant's results based on the primary analysis method are not optimal because certain assumptions that underlie the method may not be valid (e.g., the assumption that data are missing at random). The sponsor carried out some sensitivity analyses. In one (a pattern mixture ANCOVA model), it

was assumed that subjects randomized to [redacted] and missing endpoint data were switched to Novolog (refer to Table 3 in Dr. Cambon's review). Other methods are also referred to in the statistical review but Dr. Cambon does not comment on which method of missing data handling provides the most valid estimate of efficacy (and why) for the purpose of labeling. This will have to be revisited at the time of re-submission.

With regard to secondary endpoints, HbA1c responder analyses were qualitatively consistent with analyses based on mean change in HbA1c. Small numerical differences in glucose rise one and two hour after a standardized meal were noted between [redacted] and Novolog in subjects who were not missing at week 26 and underwent a standardized meal challenge in the applicant's analyses.

No difference in weight was noted between groups as shown below.

**Table 2: Trial 3852 Mean (SD) Change in Body Weight (kg) After 26 Weeks (FAS)[Refer to Table 28 in Dr. Kwon's review]**

| | Meal [redacted] (N=381) | Postmeal [redacted] (N=382) | Meal NovoLog (N=380) |
|---|---|---|---|
| Baseline | 78.56 (14.89) | 80.49 (15.93) | 80.21 (15.21) |
| Week 26 | 79.47 (15.34) | 81.28 (16.59) | 80.83 (15.40) |
| Adjusted change from baseline* | 0.67 | 0.70 | 0.55 |
| Treatment difference versus NovoLog (95% CI)* | 0.12 (-0.30; 0.55) | 0.16 (-0.27; 0.58) | |

*Change from baseline in body weight is analyzed using MMRM including Week 12 and Week 26 visits; model includes treatment, region, strata as fixed effects, subject as random effect, baseline body weight as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 3852, Table 14.2.104 and 14.2.105

Secondary endpoints were not reviewed in the statistical review and the impact of missing data on these endpoints was not considered. For the purpose of labeling these will have to be reviewed and analyzed using appropriate methods to handle missing data.

***Type 2 Diabetes Trial versus Novolog (Multiple Daily Subcutaneous Injections)***

Trial 3853 was a 26-week randomized, multicenter, multinational, double blind, active-controlled, parallel group trial comparing the efficacy and safety of mealtime [redacted] to mealtime Novolog in adults with type 2 diabetes mellitus receiving metformin and insulin glargine to cover basal insulin requirements. [redacted] and Novolog were administered 0 to 2 minutes before the meal. The primary objective of the trial was to demonstrate that, after 26-weeks, using [redacted] before meals did not result in unacceptably worse glucose control than using Novolog before meals (a non-inferiority objective).

Eligible participant were adults diagnosed type 2 diabetes for at least six months, who had inadequate glycemic control at baseline (HbA1c between 7 and 9.5%), were not morbidly obese (BMI less than or equal to 40 kg/m2), had been receiving basal insulin therapy (NPH,

determir, glargine) for at least 3 months and were on more than 1000 mg of metformin either alone or in combination with an eligible oral anti-diabetic drug for at least 3 months.

Patients were ineligible if they used a mealtime insulin, a GLP-1 receptor agonist or a thiazolidinedione in the past 3 months; if changes to concomitant drugs known to interfere significantly with glucose metabolism were anticipated or if they had had a major adverse cardiovascular event in the 6 month time period preceding the trial. They were also ineligible if they had uncontrolled hypertension, impaired liver or renal function (serum creatinine ≥2 mg/dL), recurrent severe hypoglycemia (more than one episode in the past 12 months), hypoglycemic unawareness, hospitalization for diabetic ketoacidosis in the past 6 months, or proliferative retinopathy or maculopathy requiring treatment.

The trial was comprised of a screening visit, an 8-week run-in phase, a randomization visit, a 26-week intervention phase and follow-up visit which occurred four weeks after discontinuing interventions.

The mean age of the study population was 60 years, and the mean duration of type 2 diabetes mellitus was 13 years. 49% were male. 81% were White, 6% were Black or African American and 6% were Hispanic. The mean BMI was 31 kg/$m^2$.

The outcome of interest was the difference between randomized groups in the mean change from baseline in HbA1c at 26 weeks (i.e., the delta delta). The objective of the trial was to demonstrate that (b) (4) was not unacceptably worse than Novolog by a margin of greater than 0.4%.

Secondary objectives were to; demonstrate superiority of (b) (4) to Novolog on 2-hour post prandial glucose following a standard liquid meal at week 26, demonstrate the superiority of (b) (4) to mealtime Novolog for severe or "Novo Nordisk confirmed hypoglycemia", demonstrate body weight differences between (b) (4) and Novolog (i.e., less weight gain on (b) (4) A sequential hierarchical testing strategy was used to control for type-1 error.

The treatment policies in the protocol reasonably reflect the clinical care setting and the intervention compared the glucose lowering effect that results from adding a standard of care drug (i.e., Novolog) or a new drug ( (b) (4) to a pre-existing anti-diabetic regimen that is inadequate and includes both oral antidiabetic drugs and a basal insulin. The population of interest was the intent to treat population. The estimand of most interest was the effect in all participants in whom the treatment was initiated regardless of what occurred after randomization (i.e., the de facto estimand).

The primary outcome measure was regarded as missing for a subject if there was no HbA1c measurement during the week 26 visit. The sponsor's primary analysis was based on a Mixed Effects Repeated Measures (MMRM) model[5]. This model assumes that data missing for the

[5] 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.

endpoint visit are missing at random (i.e., that all early dropouts were not related to the intervention). This may not be valid if the reason some data are missing is related to the intervention (i.e., lack of efficacy/tolerability/safety issue).

Dr. Kwon reviews disposition in Table 16 of her review. For Study 3853, the proportion of subjects with missing data was 11% (12% on the (b) (4) and 10% on the Novolog arm). Dr. Cambon evaluated the impact of missingness on overall study conclusions using alternative analyses methods. These are described in his review.

During the intervention phase, subjects randomized to mealtime (b) (4) had a slightly smaller mean increase from baseline in mealtime insulin doses (0.46 units per kg for mealtime (b) (4) versus 0.43 units/ kg for mealtime Novolog). Insulin glargine dose was virtually unchanged [i.e., reduced by 0.04 units/kg in both arms (refer to Table 35 in Dr. Kwon's review)].

**Table 1: Primary Efficacy Analysis Type 2 DM trial 3583 (Adapted from Table 2 in Dr. Kwon's Review).**

| Treatment Group | N | Baseline Mean | End of Trial Mean | LS Mean Change from Baseline | Treatment Difference (95% CI) |
|---|---|---|---|---|---|
| **Type 2 Diabetes Mellitus** | | | | | |
| ***Trial 3853:*** *26-week basal-bolus in combination with insulin glargine and metformin* | | | | | |
| Mealtime (b) (4) | 345 | 7.96 | 6.63 | -1.38 | -0.02 (-0.15, 0.10) |
| Mealtime Novolog | 344 | 7.89 | 6.59 | -1.36 | |

N=Number of Randomized Individuals.

With regard to secondary endpoints, HbA1c responder analyses were qualitatively consistent with analyses based on mean change in HbA1c. No numerical differences between groups were observed. There were also no numerical differences in glucose rise two hour after a standardized meal between (b) (4) and Novolog in subjects who underwent the standardized meal challenge test at week 26 (refer to Table 32 and figure 38 in Dr. Kwon's review). Finally, no differences in body weight were noted between Novolog and (b) (4) both groups gained about 2.7 kg (refer to Table 34 in Dr. Kwon's review).

# 7. Safety

Insulin aspart is not a new molecular entity and the safety of this insulin analog, per se, has been established previously (refer to NDA 020986). The main objective of the clinical safety assessment in the (b) (4) application was to characterize the risks (particularly the hypoglycemia, local tolerability and immunogenicity risks) associated with the formulation change. The size and scope of safety database provided is adequate for this objective.

As Dr. Kwon points out, there is no rationale to justify pooling the few disparate trials in this development program for the purpose of safety analyses because of important differences

between individual trials and studies. Indeed, disease states (type 1 versus type 2 diabetes mellitus) differed, (b) (4) dosing differed (pre and post-meal), trial design differed, number of subjects exposed differed and duration of exposure differed. Dr. Kwon has analyzed the safety information in individual trials and I agree with this approach.

Most of the data to inform safety for the type 1 diabetes population comes from trial 3852. In this trial; 386, 377 and 380 patients were exposed to (b) (4) pre-meal, (b) (4) post-meal and Novolog pre-meal for a total duration of 186, 183 and 189 patient years of exposure respectively.

Most of the data to inform safety for the type 2 diabetes population comes from trial 3853. In this trial, 341 and 342 were exposed to (b) (4) pre-meal and Novolog pre-meal for a total duration of 160 and 162 patient years of exposure respectively.

There was a single death in the type 1 trial (in the post-meal (b) (4) arm) and three deaths in the type 2 trials (two in (b) (4) and one in Novolog arms). Adjudicated causes of death were events prevalent in the population under study (ASCVD events and pulmonary embolus) and were confounded by the presence of baseline co-morbid conditions which could have contributed to these events. Information in narratives did not suggest an obvious causal relationship between test agent and fatal events. Review of serious adverse events, adverse events leading to discontinuations and adverse events leading to dose reduction identified hypoglycemia, injection site reactions, and severe allergic reactions as drug related reactions.

*Hypoglycemia*

*Type 1 DM*

The most commonly reported non-fatal serious[6] adverse events in patients with type 1 DM were related to hypoglycemia. These events were split across several system organ classes (e.g., Metabolism and Nutrition Disorders, Nervous System Disorders) and were coded to the terms "hypoglycemia" (2.1%, 2.9% versus 1.3% for (b) (4) pre-meal, (b) (4) post-meal versus Novolog pre-meal respectively) and "hypoglycemic unconsciousness" (1.0%, 0.8% versus 0.5% for (b) (4) pre-meal, (b) (4) post-meal versus Novolog pre-meal respectively). Hypoglycemia was also a common reason for trial discontinuation (refer to Table 55 in Dr. Kwon's review) and for dose reduction (particularly in the (b) (4) arm; refer to Table 71 in Dr. Kwon's review).

The applicant also performed analyses of hypoglycemia using several other definitions of hypoglycemia. In trial 3852; 6.7%, 8.0%, and 8.4% of study participants in the (b) (4) pre-meal, (b) (4) post-meal and Novolog pre-meal arms, respectively, had at least one event that fulfilled the definition for a "severe" event (i.e., an episode where a third party administered rescue treatment). 46, 47 and 51 total "severe" hypoglycemic events occurred

[6] Reaction that is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity

in each of these three respective arms in the trial. In addition, 93%, 95% and 97% had at least one event that fulfilled the definition for a Novo Nordisk "confirmed" hypoglycemic event (i.e., a self-reported glucose value of less than 56 mg/dL regardless of symptoms). Finally, a total of 10947, 9914, and 11027 "confirmed" events were captured in the (b) (4) pre-meal, (b) (4) post-meal and Novolog pre-meal arms, respectively, in the trial. These descriptive analyses are imbalanced in favor of (b) (4)

There is some inconsistency in the direction of change between analyses based on serious and severe events but overall no large increase (or decrease) in the risk of hypoglycemia between (b) (4) and Novolog was observed. Dr. Kwon examined hypoglycemia rate for the combination of severe and confirmed events per hour increment over 24 hours (Figure 37) and for up to 6 hours following the ingestion of a meal (Table 58). The latter analyses provide some support to the PK/PD findings which suggests that aspart is more rapidly absorbed as (b) (4) than as Novolog as there was a greater risk of hypoglycemia with (b) (4) in the first hour following meal ingestion. No difference in post-prandial hypoglycemia risk was noted when the entire 6-hour time-period following the meal was considered.

*Type 2 DM*

The most commonly reported non-fatal serious[7] adverse events in patients with type 2 DM were also related to hypoglycemia. These events were more rare than in type 1 DM and were all coded to the term "hypoglycemia" (0.6% versus 0.9% for (b) (4) pre-meal versus Novolog pre-meal respectively). Hypoglycemia was also a reason cited for trial discontinuation (refer to Table 56 in Dr. Kwon's review) and for dose reduction (particularly in the (b) (4) arm; refer to Table 81 in Dr. Kwon's review) in both arms.

The applicant performed analyses of hypoglycemia using several other definitions. In trial 3853; 3.2% versus 3.8% of study participants in the (b) (4) pre-meal versus Novolog pre-meal arms, respectively, had at least one event that fulfilled the definition for a "severe" event (i.e., an episode where a third party administered rescue treatment [refer to Table 61 in Dr. Kwon's review)]. 27 and 17 total "severe" hypoglycemic events occurred in the (b) (4) and Novolog arm respectively. In addition, 77% and 73% had at least one event that fulfilled the criterion for the definition of a Novo Nordisk "confirmed" hypoglycemic event (i.e., a self-reported glucose value of less than 56 mg/dL regardless of symptoms). A total of 2830 and 2675 "confirmed" hypoglycemic events were captured in the (b) (4) pre-meal, and Novolog pre-meal arms, respectively, in the trial.

Time to first event (severe and confirmed hypoglycemia) analyses shown in figures 42 and 43 of Dr. Kwon's review were consistent with overall rates shown above and appear to trend toward slight harm rather than benefit (particularly at night). In patients with type 2 DM, no large increase (or decrease) in the risk of hypoglycemia between (b) (4) and Novolog was observed.

[7] Reaction that is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity

*Injection Site Reactions*

Dr. Kwon reviews data on injection site reactions in Section 7.3.5.3 of her review. Injection site reactions were more frequently reported on (b) (4) Injection site reactions were reported in 1.8%, 2.4% and 0.8% of type 1 DM patients randomized to (b) (4) pre-meal, (b) (4) post-meal and Novolog, respectively. Injection site reactions were reported in 0.9% and 0.6% of patients with type 2 DM randomized to (b) (4) pre-meal and Novolog pre-meal, respectively.

*Severe Allergic Reactions*

Dr. Kwon notes that treatment emergent adverse event terms that are included in standardized MedDRA queries for allergic reactions were balanced between groups. No serious allergic reaction was noted in the program.

*Immunogenicity*

Dr. Kwon summarized the applicant's immunogenicity data in Section 7.4.6 of her review. The applicant measured anti-human insulin antibody, anti-insulin aspart antibody. The applicant performed several analyses to explore the potential relationship between presence of these antibodies and changes to efficacy and pharmacokinetic in Trial 3852. The applicant concludes from these data that no efficacy or safety issues related to immunogenicity were identified. The Office of Biotechnology Product reviewed the immunogenicity assessment and does not agree with the applicant's assessment. Drs. Bowen and Kirshner identified major deficiencies in the validation of the anti-drug antibody assays used in this application and recommend a complete response due to these deficiencies.

*Cardiovascular Risk*

Insulin products are not subject to the strict requirements of the 2008 CV-risk guidance for antidiabetic drugs to treat adults with type 2 diabetes mellitus. The applicant did prospectively define, capture and adjudicate major adverse cardiovascular (non-fatal MI, non-fatal stroke and cardiovascular death) in trials 3852, 3853, 4049 and 3931. Nine events were adjudicated as MACE and all events were derived from trial 3852 and 3853. Four events occurred on (b) (4) and 5 on all comparators. There are little cardiovascular outcomes information on which to base a CV-risk analyses in this program. This is illustrated by the wide confidence intervals in the estimates of CV-risk in trials 3852 and 3853 respectively [Hazard Ratio and 95% CI; 1.02 (0.09; 11.20) for 3852 and 0.51 (0.09, 2.76)]

# 8. Advisory Committee Meeting

(b) (4) is not a new molecular entity and no issues rising to the level of requiring an Advisory Committee meeting was identified in the application.

## 9. Pediatrics

Relevant issues have been summarized by in Dr. Yanoff's CDTL memorandum.

## 10. Other Relevant Regulatory Issues

Relevant issues have been summarized by in Dr. Yanoff's CDTL memorandum.

## 11. Labeling

*Prescribing Information*
*Provide a high-level summary of the labeling recommendations and rationale for critical changes to the applicant's proposed prescribing information. In particular, consider:*

- *INDICATIONS AND USAGE section:*
  - *Should the indication(s) be limited to certain subpopulations [e.g., are the applicant's proposed indicated population(s) inappropriately broader than the studied populations]?*
  - *Should a Limitation of Use be included because of reasonable concerns about the benefit-risk profile of the product for certain uses?*
- *DOSAGE AND ADMINISTRATION section:*
  - *Do you agree with the proposed recommended dosage regimen(s)?*
- *Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:*
  - *Do you want to add, modify, or delete important information in these sections?*

*Other Labeling*
*Provide a high-level summary of the recommendations and rationale for critical changes to other labeling proposed by the applicant (if applicable):*

- *Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use)*
- *Carton and container labeling*

## 12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

*Includes restricted distribution, components of REMS*

- Other Postmarketing Requirements and Commitments

*Provide rationale whether required under FDAAA or voluntary, post vs. preapproval, significant negotiations or discussions, and questions to be addressed*

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

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/s/

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JEAN-MARC P GUETTIER
10/07/2016

# Cross-Discipline Team Leader Review

| | |
|---|---|
| **Date** | 7 Oct 2016 |
| **From** | Lisa Yanoff, M.D. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA #** | 208751 |
| **Applicant** | Novo Nordisk |
| **Date of Submission** | 8 Dec 2015 |
| **PDUFA Goal Date** | 8 Oct 2016 |
| **Proprietary Name / Established (USAN) names** | (b) (4) insulin aspart |
| **Dosage forms / Strength** | 100 units/mL in 10 mL vials and 3 mL FlexTouch device |
| **Proposed Indication(s)** | to improve glycemic control in adults with diabetes mellitus |
| **Recommended:** | Complete Response |

## Cross Discipline Team Leader Review

# 1. Introduction

This document contains the summary review for New Drug Application 208751, submitted under the 505(b)(1) regulatory pathway for marketing approval of [redacted] (b) (4) (insulin aspart) to improve glycemic control in adults with diabetes mellitus. The reader is referred to the multiple discipline reviews for a more detailed discussion of the issues.

This memo relies upon or references the following documents:

| Subject | Author | Date |
|---|---|---|
| **Clinical Efficacy and Safety review** | Dr. Hyon Kwon | 7 Oct 2016 |
| **Nonclinical review** | Dr. Miyun Tsai-Turton | 28 Aug 2016<br>20 Sep 2016 |
| **Office of Clinical Pharmacology (OCP) review** | Dr. Shalini Wickramaratne Senarath Yapa | 8 Sep 2016 |
| **Office of Pharmaceutical Quality (OPQ) review** | Multiple reviewers | 9 Sep 2016 |
| **Office of Biotechnology Products (OBP) review** | Dr. Steven Bowen | 29 Sep 2016 |
| **Statistical review (OB/DBII)** | Dr. Alex Cambon | 2 Sep 2016 |
| **Division of Pediatric and Maternal Health review (DPMH)** | Dr. Jane Liedtka | 6 May 2016 |
| **Division of Medication Error Prevention and Analysis (DMEPA) labeling review** | Dr. Sarah Vee | 19 Jul 2016 |
| **Proprietary Name review** | Dr. Todd Bridges | 28 Jul 2016 |
| **Office of Prescription Drug Promotion (OPDP) labeling review** | Dr. Ankur Kalola | 9 Sep 2016 |
| **OPDP and Division of Medical Policy Programs (DMPP) Patient Labeling review** | Amanpreet Sarai | 8 Sep 2016 |
| **Clinical Inspection Summary** | Dr. Cynthia Kleppinger | 15 Aug 2016 |
| **CDRH Compliance review** | Crystal Lewis | 27 Apr 2016 |
| **CDRH consult review** | Lead reviewer Carolyn Cochenour | 21 Sep 2016 |

## 2. Background

Insulin aspart is an insulin analog indicated to improve glycemic control in patients with diabetes mellitus. A rapid-acting insulin, it is used to reduce postprandial hyperglycemia, i.e. increase in blood glucose related to meals. It is typically administered in conjunction with a basal insulin product, although in patients with type 2 diabetes it can be used without basal insulin. Rapid-acting insulin analogs are also used in continuous subcutaneous insulin infusion therapy (i.e. insulin pumps) for both basal and bolus coverage in type 1 diabetes patients. The currently marketed insulin aspart product is approved in the U.S. under the tradename NovoLog, and is one of three rapid-acting insulin analogs currently marketed in the U.S. NovoLog was approved for treatment of adult patients with diabetes mellitus on June 7, 2000.

The product under review in this NDA (proposed tradename (b) (4) is a new formulation of insulin aspart that contains 2 additional excipients intended to change the pharmacokinetic/pharmacodynamic (PD/PD) profile of the drug to make the onset of action faster than NovoLog. NovoLog and (b) (4) have the same active ingredient. In (b) (4) nicotinamide (also known as niacinamide or vitamin B3) was added to increase the absorption of insulin aspart after administration, and L-arginine was added to stabilize the formulation. Insulin products with a faster onset of action than those currently available are considered desirable because the earlier onset of action would allow for dosing closer to mealtime or even after the meal with resultant better matching to carbohydrate intake. This altered PK profile was the rationale for development of this product.

The Agency engaged in discussion with the Applicant during the development program during milestone meetings and multiple Type C advice meetings. A summary of presubmission regulatory activity is provided in Dr. Kwon's Clinical review in section 2.5.

## 3. CMC / Device

The recommendation from the Office of Pharmaceutical Quality (OPQ) (including the manufacturing inspection recommendation) is approval. However, the recommendation from the Office of Biotechnology Products (OBP) is a Complete Response due to deficiencies identified in the validation of the antidrug antibody (ADA) assays and the clinical immunogenicity data.

This section provides a summary of the OPQ/CMC review which is followed by a summary of the OBP review.

**Drug Substance/Drug Product:** Insulin aspart is an analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28, and is produced by recombinant DNA technology using *Saccharomyces cerevisiae* (baker's yeast). The drug substance is the same as that of NovoLog (insulin aspart). Insulin aspart was approved under NDA 20986. This NDA relies on available CMC information for drug substance insulin aspart provided under NDA 20986, which is acceptable.

Drug product: The proposed multi-dose product is a clear, colorless solution filled in 10mL vial or in 3mL cartridge preassembled in a pen injector for subcutaneous injection (b) (4) . Drug product contains 100 units of insulin aspart, glycerol USP (3.3 mg), phenol USP (1.50 mg), metacresol USP (1.72 mg); zinc (as zinc acetate) USP (19.6 mcg); disodium phosphate dehydrate USP (0.53 mg); arginine (as L-arginine hydrochloride) USP (3.48 mg); niacinamide USP (20.8 mg) and water for injection USP. Hydrochloric acid or sodium hydroxide may be added to adjust pH (to 7.1).The prefilled pen-injector has a range of 1 to 80 units adjustable in increments of 1 unit. Excipients proposed for use are of compendial grade excipients.

**Container Closure**: Two different container closure systems (3ml cartridge and 10ml vial) are used for filling of the drug product. The CMC reviewer stated that the applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility and that it is acceptable. The container closure system components proposed for use are the same as in approved insulin aspart injection.

**Microbiology/Sterility:** A microbiology review recommended approval of this NDA. Microbiology was reviewed 04/13/2016 by Dr. Koushik Paul including container-closure integrity testing of the 10 mL vials, overall manufacturing operations, environmental monitoring, sterilization (b) (4) of the container, closure, equipment and components and media fill. Please see the OPQ review. The container closure integrity test (CCIT) for 3mL cartridges were reviewed and approved by V. Pawar dated 05/29/2012.

**Stability:** The stability data provided in the application supported the compatibility of active ingredient with excipients and container closure components. Extractable and leachable data are reported in the NDA with supporting safety information. The DMEP Pharm Tox reviewer concluded that the safety information for excipient related impurities and leachables for container closure system showed no safety risk to humans per ICH M7, ICH Q3B and ICH Q3C guidelines.

**Manufacturing Process:** The proposed control strategy is adequate to assure the quality of the product. See also microbiology above.

**Expiration Date & Storage Conditions:** Stability information available for the proposed product in vials and cartridges was reviewed by drug product reviewer. An expiration period of 30 months is granted when stored at 2-8 °C for the finished product in vials and in prefilled pen with an in-use period of up to 28 days at room temperature (below 86° F (30 °C) after first use. Shelf life is based on real-time stability data for the primary batches with the commercial formulation.

(b) (4)

**Stability during IV Infusion:** In support of intravenous administration, the Applicant submitted stability data of (b) (4) when diluted in two types of intravenous infusion fluids (0.9% NaCl and 5% glucose) at concentrations of 0.5 U/mL and 1.0 U/mL. The applicant also evaluated the compatibility of faster-acting insulin aspart injection in intravenous (IV) infusion bags. Microbiology and chemistry review concluded that the product is stable for 24 hours at room temperature post dilution.

**Manufacturing inspection:** Facility compliance information for drug product and drug substance facilities was reviewed by Dr. Juandria Williams. Her review concluded that there are no outstanding manufacturing or facility risks that prevent approval of this application.

CDRH Office of Compliance was consulted to evaluate the applicant's compliance with applicable Quality System Requirements. An inspection is not required because a recent inspection of the firm was acceptable. An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted on 3/31/2016 to 4/8/2016. The inspection covered drugs and was classified NAI. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies.

The following section provides an overview of the OBP review.

Serum samples were analyzed for anti-drug antibodies (ADA) and ADA that cross-react with human insulin using a radioimmunoprecipitation (RIP) assay. The radioimmunoprecipitation (RIP) assay involves the overnight incubation of patient serum samples with a radiolabeled insulin aspart tracer. The level of radioactivity of the precipitated sample is proportional to the level of ADA bound to the radiolabeled tracer. Values for each sample are expressed as %B/T (the percentage of bound tracer after precipitation to total tracer). Dr. Bowen notes that *the Sponsor does not use a tiered approach for ADA assessment as recommended by FDA guidance. The immunogenicity assessment is based on a single assay where the "background" is determined by competition with cold drug. Although this is not the recommended practice for immunogenicity assessment it is acceptable provided the assay is specific and sensitive.*

Initial assay validation was performed in 1997 and is included in Validation Study Report 960358: *Validation of RIA used for the determination of Insulin, X14 and NN304 antibodies*. Insulin aspart is referred to as X14 in many of the validation exercises. Additional validation was performed in 2015 and the data are included in Validation Study Report 215373: *Validation to document assay sensitivity and normal ranges in an anti-insulin aspart antibody RIA method.*

A six item information request for more information about the development, validation, and routine performance of the assays was sent to the Sponsor on August 1st 2016. The response was received on August 25th, 2016 and will be reviewed in the next review cycle.

At this time the following deficiencies are noted by Dr. Bowen's review. The majority are related to the assay validation.

Regarding the validation of the radioimmunoprecipitation assay (RIA) for the detection of insulin aspart-specific and cross-reactive anti-human insulin anti-drug antibodies refer to the comments below.

1. Validation Report 215373 describes the QC3 suitability control as a guinea pig polyclonal anti-human insulin (GPα Insulin). Table 1-6 of Section 2.7.1 of the application (Summary of biopharmaceutic studies and associated analytical methods) describes QC3 as a polyclonal anti-insulin aspart antibody. Explain the discrepancy between the two descriptions of QC3 and indicate what immunogen was used to raise the QC3 antibodies used during the testing of clinical samples.

2. It is not clear whether the patient samples were diluted prior to testing. If patient samples are diluted prior to testing, provide data demonstrating the suitability of the minimum required dilution.

3. Serum samples were tested in three parallel conditions: D, E, and F. Conditions E and F involved competition with unlabeled insulin aspart and human insulin respectively. However, the concentrations of unlabeled insulin aspart and human insulin used in the assay are not provided. Indicate the concentrations of unlabeled insulin aspart and human insulin used in the assay as well as the rationale for the selected concentrations.

4. The Sponsor did not provide data demonstrating the tolerance of the assay to onboard insulin aspart. The tolerance of the assay to human insulin was determined during assay development but supporting data was not provided. Provide data demonstrating the assay tolerance of insulin aspart and human insulin to ensure that on-board levels of these proteins will not interfere with assay performance.

5. The levels of total anti-drug antibodies (ADA), insulin aspart-specific antibodies, and antibodies cross-reactive with human insulin are quantitated using the percentage of total radiolabeled tracer (insulin aspart) that is co-precipitated with Ig (%B/T). However, there is insufficient data in the Validation Reports to demonstrate that the assay is quantitative. One approach to address this deficiency and support the use of the %B/T value as a quantitative measure of antibodies in patient samples would be to demonstrate that there is a linear relationship between the positive control antibody concentration and the %B/T signal. Include a graphical and tabular analysis for each series (D, E, F) and the subtracted (D-E, D-F, F-E) values.

6. Section 2.7.1 Table 1-6 indicates that the two positive suitability controls used for analysis of clinical samples were QC2, monoclonal anti-insulin aspart, 560 ng/ml, and QC3, guinea pig polyclonal anti-human insulin antibody, 23-230 ng/ml. The sensitivity analysis described in Validation Report 215373 indicates that the amounts of both QC2 and QC3 used are close to the upper limit of quantitation of the assay. This raises concerns that your suitability controls are inadequate to ensure the detection of low levels of ADA and suitable assay performance. Low positive controls should be set to have a 1% failure rate based on the assay cutpoint. Indicate how the detection of low levels of ADA was demonstrated during clinical testing. For guidance refer to FDA Draft Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016).

7. Some of the assay parameters, such as intra-assay precision, inter-assay precision, and robustness were validated by analyzing only the D-E series. However, the clinical samples were evaluated using the D-F and F-E series. Therefore, assay parameters validated using only the D-E conditions need to be validated using the D-F and F-E series using appropriate suitability controls to demonstrate that the assay performs appropriately for the detection of insulin aspart specific (D-F) and cross-reactive (F-E) antibodies.

8. The Sponsor did not provide data demonstrating the stability of the positive control antibodies used during the testing of clinical samples. In order to demonstrate that the X14-6F34 and GPa Insulin antibodies remain stable under normal testing conditions assess the performance of the antibodies under long-term storage, freeze-thaw, and benchtop conditions.

9. The acceptance criteria used for the QC2 and QC3 suitability controls were calculated from a nominal value for each control +/- 20%. It is unclear how the nominal values for QC2 and QC3 indicated in Table 1-6 of Section 2.7.3 were calculated or what the upper and lower acceptance limits were for each series. Provide a description of how the calculations were done to establish the acceptance criteria for the suitability controls (including the QCneg) used during testing of clinical samples.

10. Validation data for the labeling efficiency, batch-to-batch consistency, and stability of the radiolabeled insulin aspart tracer were not provided. Provide data validating these attributes of the radiolabeled insulin aspart tracer used in the RIA.

Regarding the analysis of clinical data from Study NN1218-3852 refer to the following comment:

1. Section 2.7.1 of your application notes that most patients were positive for ADA at baseline and that no cut-points were established to evaluate treatment-boosted ADA responses. In order to compare the immunogenicity of "faster aspart" and NovoRapid® the frequency of patients with treatment-emergent and treatment-boosted ADA should be determined. Indicate how treatment-emergent and treatment-boosted patients were mathematically defined in your analysis as well as the frequency of patients in each treatment group with treatment-induced or treatment-boosted ADA.

[redacted] (b) (4)

# 4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology reviewer, Dr. Tsai-Turton recommends approval of this NDA. See her review dated August 28, 2016.

**Drug substance insulin aspart**: The nonclinical development of insulin aspart injection relies upon the nonclinical program conducted to support NDA 020986 (NovoLog). Since a full nonclinical program was previously conducted for NovoLog, no additional toxicity studies (aside from those pharmacokinetic and local toxicology studies discussed here) were conducted for insulin aspart injection. See product labeling for Novolog for a brief description of reproduction, genetic toxicity and carcinogenicity studies conducted for Novolog.

**Impurities:** The drug substance-related impurity profiles were determined to be comparable between [redacted] (b) (4) and NovoLog. One excipient-related impurity ([redacted] (b) (4)) and two leachables of [redacted] (b) (4) were determined not to pose a safety risk to humans per ICH guidances.

**Excipients:** At the End-of-Phase 2 presubmission meeting the Agency agreed that safety of the excipients (L-arginine hydrochloride, nicotinamide and [redacted] (b) (4)) for chronic subcutaneous injection could be based on a combination of literature review, their use in currently marketed products, and local tolerance studies of previous formulation, i.e. without additional nonclinical investigations.

Local tolerance studies for insulin aspart injection were performed in the rat, rabbit, and minipigs models. The tissue reactions observed in local tolerance studies with minipigs and rats were similar when comparing four formulations of [redacted] (b) (4) and NovoLog. The rabbit studies were intended to assess for inadvertent dosing in the muscle or blood vessel. Local tissues reactions observed for all three routes of administration (intravenous, intramuscular, and intra-arterial) of insulin aspart injection were comparable to controls (0.9% sodium chloride for injection).

Excipients proposed for use in the drug product are known for use in pharmaceutical products. The Applicant provided safety literature data to support the levels of nicotinamide and L-arginine used in the insulin aspart injection. Dr. Tsai-Turton has reviewed this information and concluded that there are no significant safety concerns.

*Nicotinamide* is part of the vitamin B3 complex. Dr. Tsai-Turton states that in a highly insulin-resistant patient receiving 200 U/day, the highest dose of nicotinamide to be administered with insulin aspart injection is approximately 42 mg/person/day (comparable to dietary intake; the mean and maximum daily intake of nicotinamide in food = 34-57 mg/person/day). Nonclinical literature suggests that nicotinamide does not cause general toxicities and is not teratogenic, genotoxic or carcinogenic.

*L-arginine* is a naturally occurring amino acid and the precursor of nitric acid through conversion by endothelial nitric oxide synthase and has a number of effects on the cardiovascular system (e.g., blood vessel dilation in rats and rabbits). In addition, L-arginine has other activities on blood clotting (inhibition of platelet aggregation in rats/rabbits), endocrine function (stimulation of insulin secretion), and weight loss (reduction of adipose tissue and serum glucose concentrations). All of the effects of L-arginine described above are not expected at the levels proposed for use in insulin aspart injection formulations. In a highly insulin-resistant patient receiving 200 U/day, the highest dose of L-arginine to be administered with insulin aspart injection is considerably lower (~ 7 mg/person/day; ~ 1 mg/kg/day) than an Observed Safe Level of arginine of 20,000 mg/day for oral administration in normal healthy adults. Based on available nonclinical literature, L-arginine is not expected to induce adverse effects in toxicity studies and has no adverse effect on animal reproduction. L-arginine is not genotoxic, and is not considered to possess carcinogenic potential as it is a naturally occurring amino acid.

(b) (4)

**Labeling**: In addition to recommendations for labeling Section 13 of the PI (Nonclinical toxicology), Dr. Tsai-Turton's review also contains recommendations for labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR). However, labeling discussions are deferred at this time.

## 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer Dr. Shalini Wickramaratne Senarath Yapa (from the Office of Clinical Pharmacology [OCP]) recommends a Complete Response. The OCP review states that the bioanalytical method used for (b) (4) (primary pharmacokinetic analysis) is deemed unreliable due a number of issues which affect the reliability of the pharmacokinetic data for all clinical pharmacology studies generated using the bioanalytical methodology for the application. The following, taken verbatim from the OCP review, outlines the deficiencies:

(b) (4)


I agree with the recommendation of the OCP review because as she notes, the time-action profile of the product (time to onset, peak action, and duration of action) is fundamental in guiding the safe and effective clinical use of this insulin product. While clinical safety and efficacy studies were conducted, accurate and reliable Clinical Pharmacology data are crucial for labeling for the safe and effective use of the product.

During the review cycle for this NDA, the Agency issued information requests to the Applicant to help elucidate the rationale for the approach to the bioanalytical methodology. Responses to these information requests provided some insight but did not resolve the concerns of the OCP review team. In an effort to enhance transparency between the Agency and Applicant, comments 1-5 above were conveyed to the Sponsor late in the review cycle. A Complete Response is recommended because there were no additional data available that would have been sufficient to resolve the deficiencies and allow approval during this review cycle. It is recommended that the following comments also be conveyed to the Applicant:

Clinical pharmacology recommendations to address the deficiency are as follows –

- Develop and validate a new analytical method where (b) (4) The sponsor is strongly recommended to use the validation acceptance criteria that are outlined in the Agency's Guidance Document on Bioanalytical Method Validation. If the analytical method meets the validation acceptance criteria, we recommend that (b) (4) reported in this NDA submission, we recommend that sponsor communicate this to the Agency for further discussion.
- (b) (4)
- (b) (4)

Dr. Wickramaratne Senarath Yapa states that because of the identified deficiencies in the bioanalytical method used to generate the clinical pharmacology data for this NDA, the clinical pharmacology memo focuses on the deficiencies identified during review of the submission and captures the clinical pharmacology recommendations to resolve the deficiencies. Dr. Kwon's review contains a summary of the clinical pharmacology studies as reported by the Applicant. While the *absolute* accuracy of the PK data is unclear, there is still some value in the comparison of (b) (4) to NovoLog, i.e. the *relative* differences would not be expected to be affected by the bioanalytical method problems. Further, the PD data have been determined to be reliable. The results of these studies help in understanding the rationale for development of this product and, in part, for interpreting the Phase 3 program.

The clinical pharmacology development program consisted of 10 trials, all in patients with T1DM, except in 1 trial which enrolled healthy subjects. Please see Dr. Kwow's review for a detailed discussion of the Applicant's clin pharm study findings.

| Clinical Pharmacology Studies | |
|---|---|
| 3887 | Euglycemic clamp –T1DM |
| [redacted] (b) (4) | |
| 3889 | Standardized meal test – T1DM |
| [redacted] (b) (4) | |
| 3891 | Euglycemic clamp –T1DM |
| 3918 | PK/PD in Japanese subjects – T1DM |
| 3921 | PK/PD of postmeal [redacted] (b) (4) vs. premeal Novolog – T1DM |
| 3978 | Euglycemic clamp –T1DM |
| 3949 | PK in healthy volunteers |

*PK*

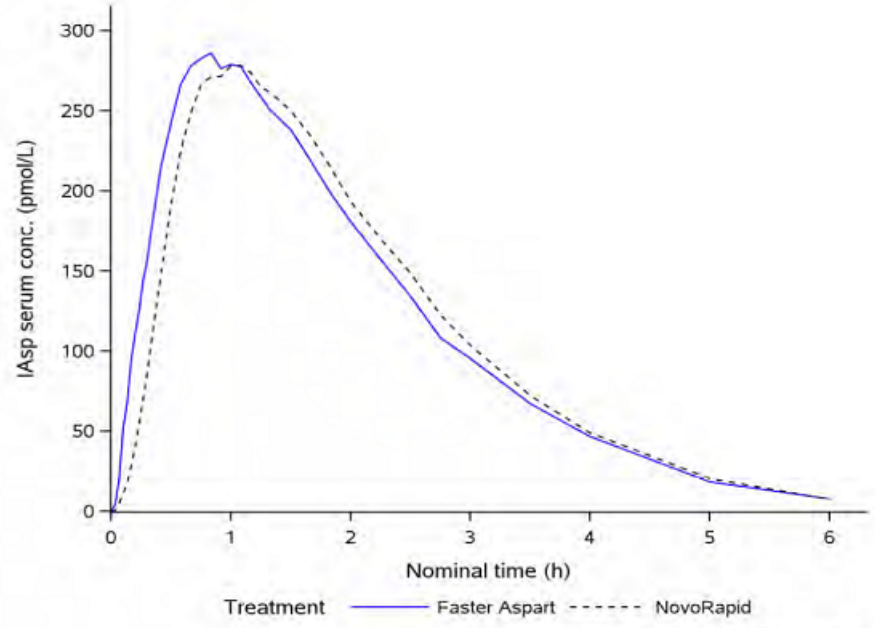
Bioavailability

Trial 3949 showed that the absolute bioavailability of insulin aspart after subcutaneous administration of [redacted] (b) (4) in the abdomen, deltoid, and thigh was about 80% and the overall results support dosing instructions of administration in the abdomen, deltoid, or thigh.

Single dose PK

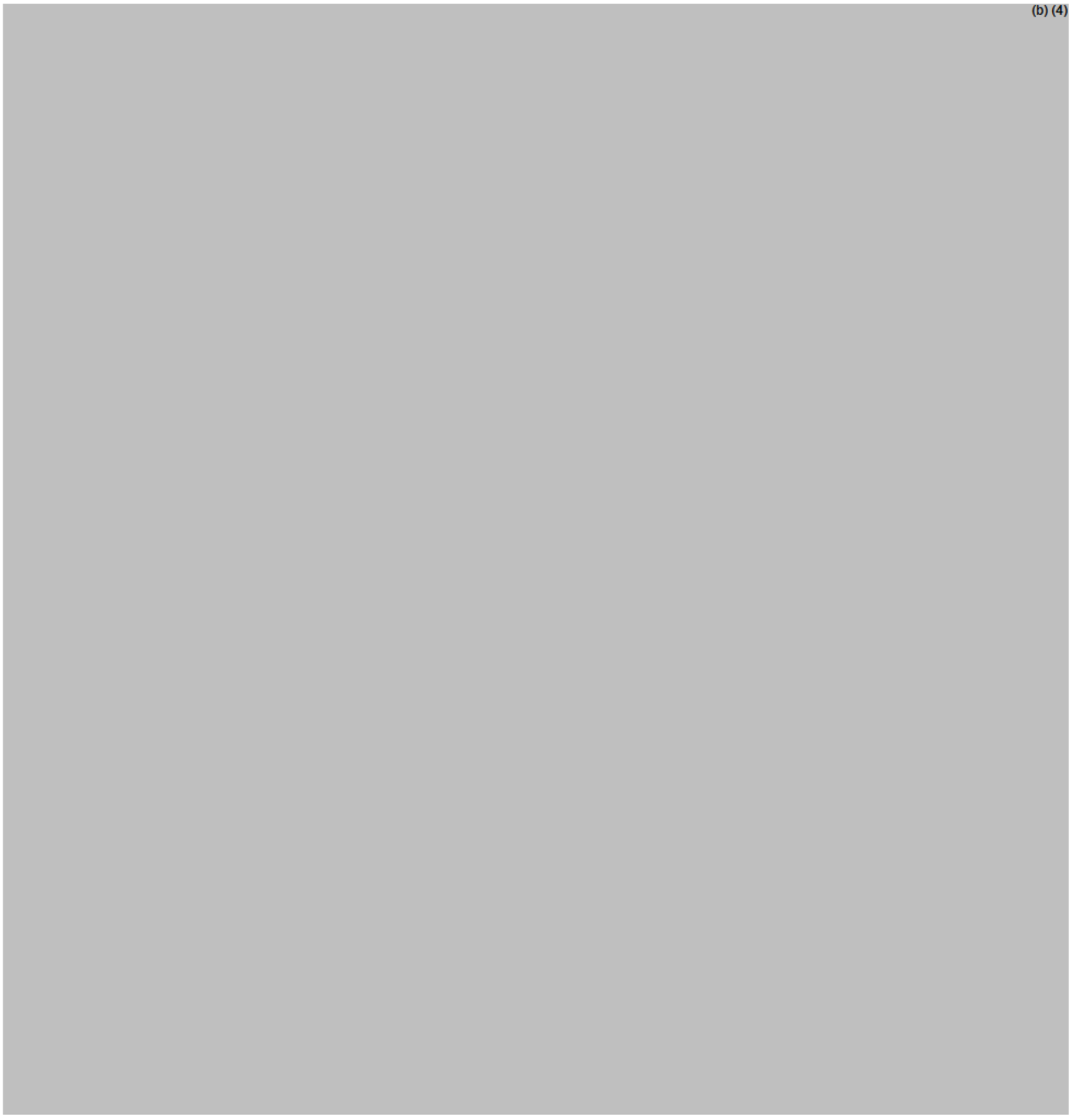
The pooled PK analysis included clinical pharmacology trials 3887, [redacted] (b) (4) 3889, 3891, 3921, and 3978. The pooled PK profile showed a left shift of [redacted] (b) (4) compared to NovoLog. Dosing was by single subcutaneous injection.

**Mean Insulin Aspart Profiles (0-6 hours) for Adults with T1DM in the Pooled Analysis (0.2 U/kg)**




The mean onset of insulin aspart ranged between 3.1 and 5.5 minutes with [redacted] (b) (4) and between 5.9 and 12.3 minutes with NovoLog in individual trials. In the PK pooled analysis, insulin aspart

appeared in the circulation about 4 minutes after administration of (b) (4) compared to about 9 minutes with NovoLog. The estimated time to reach 50% of the maximum serum insulin aspart concentration (time to 50% $C_{max}$) ranged between 18.9 and 26.3 minutes with (b) (4) and 26.6 and 37.0 minutes with NovoLog in individual trials. In the PK pool, time to 50% $C_{max}$ was about 9.5 minutes earlier with (b) (4) (22.6 minutes versus 32.1 minutes). The time to reach the maximum serum insulin aspart concentration ($t_{max}$) was 7.3 minutes earlier with (b) (4) (62.4 minutes) compared to NovoLog (69.8 minutes).



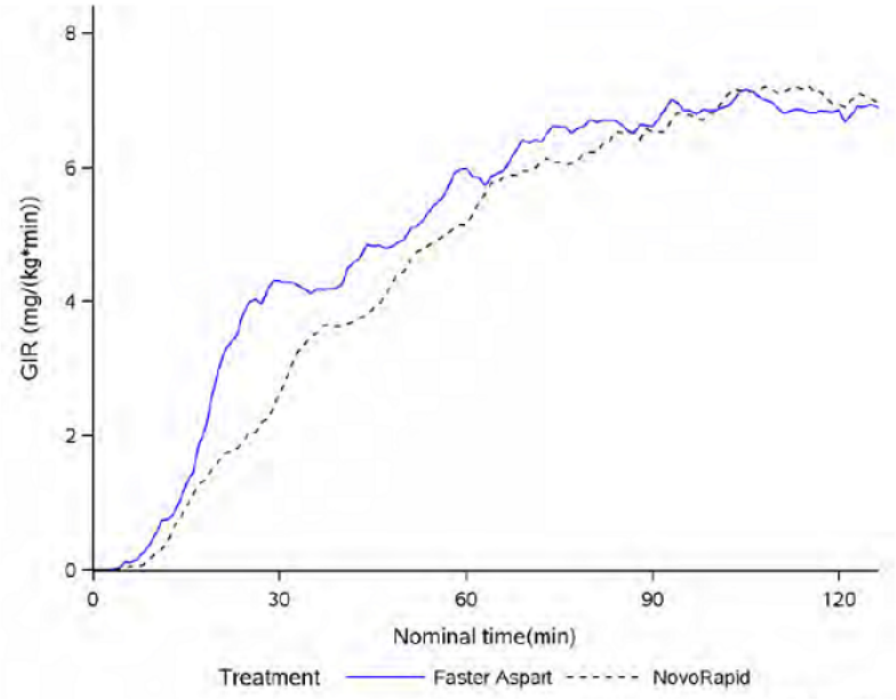

*PD*

Euglycemic clamp

In brief, in a pool of 3 euglycemic clamp studies in T1DM (Trials 3887, 3891, and 3978) the estimated onset of action was about 5 minutes earlier and time to 50% $C_{max}$ was about 9.5 minutes earlier with (b) (4) compared to NovoLog. The apparent difference in glucose-lowering effect with (b) (4) compared to NovoLog was most pronounced during the first 30 minutes. See figure below.

However, the total ($AUC_{GIR\ 0\text{-}12h}$) and maximum glucose-lowering effect ($GIR_{max}$) were comparable between (b) (4) and NovoLog both in individual trials and in the pooled analysis.

**Mean GIR Profiles (0-2 hours) in Adults with T1DM in the Pooled Analysis (0.2 U/kg, Trials 3887, 3891, and 3978)**




Source: Summary 2.7.2, Figure 3-12

Meal Test Studies

Trials 3889 (b) (4) evaluated the PD properties of (b) (4) and NovoLog after single subcutaneous injection (0.2 U/kg) immediately before a standardized meal in adults with T1DM. In trial 3889, the plasma glucose parameters over 2 hours were not statistically different between (b) (4) and NovoLog. (b) (4) The treatment difference between (b) (4) and NovoLog in mean PPG increment over 1 hour was smaller than at 2 hours (-5.6 mg/dL [95% CI: -26.71;15.52]).

The meal test findings are not consistent with the euglycemic clamp studies in that the change in time action profile (greater early exposure and faster onset of action with (b) (4) meaningful clinical differences in glucose effect with (b) (4) compared to NovoLog are not apparent (when both are given at mealtime).

Trial 3921 compared the PK and PD properties of [redacted] when given postmeal (i.e., 20 minutes after start of a standardized meal), compared to NovoLog when given premeal (i.e., immediately before a standardized meal) in adults with T1DM. The insulin dose was 0.2 U/kg. The mean plasma glucose concentration from 0-6 hours after standardized meal was 13% higher with postmeal [redacted] compared to premeal NovoLog (treatment ratio 1.13 [95% CI: 1.06; 1.21]). Further 1 hour and 2 hour glucose concentrations were higher with postmeal [redacted] compared to premeal NovoLog.

[redacted]

Overall, the Applicant's PK data suggest an earlier absorption but overall similar exposure for [redacted] compared to NovoLog. The difference in absorption is small…on the order of 5 to 10 minutes. How this translates into glucose lowering is not entirely clear as the meal test Clin Pharm studies did not clearly show a difference in glucose lowering between [redacted] and NovoLog.

# 6. Clinical Microbiology

See Section 3: CMC

# 7. Clinical/Statistical- Efficacy

The Sponsor has submitted three 'adequate and well controlled trials' (confirmatory safety and efficacy studies) to support efficacy of [redacted] one trial in T1DM and two trials in T2DM. Dr. Kwon reviewed these studies in detail; please see her review for additional information. Dr. Alex Cambon, in addition, provided a statistical review of the three studies; he confirmed the primary efficacy analyses for all three studies and provided some discussion of issues related to missing data.

The table below shows the 3 pivotal phase 3 studies submitted in the application.

| **Phase 3 Efficacy and Safety Studies** | |
|---|---|
| 3852 – T1DM<br>26 weeks + 26 week extension | [redacted] premeal vs. NovoLog premeal, both on basal insulin (blinded)<br>[redacted] postmeal vs. NovoLog premeal, both on basal insulin Levemir (open-label) |
| 3853 – T2DM<br>26 weeks | [redacted] premeal vs. NovoLog premeal, both on basal insulin glargine and metformin (blinded) |
| 4049 – T2DM<br>18 weeks | [redacted] premeal + basal insulin + metformin vs. basal insulin + metformin (open-label) |

All clinical trials in the development program (including the pivotal phase 3 studies) used the final to-be-marketed formulation of [redacted] 100 U/mL solutions of [redacted] and NovoLog were provided in identical disposable 3 mL PDS290 pen-injector devices so that blinding could occur for the premeal study arms in Trial 3852 (the postmeal arm was open-label because the dosing instructions were different) and in Trial 3853 which had only two arms. All three trials had an 8-week run-in period for titration of basal insulins.

Subjects who withdrew or dropped out underwent a complete follow-up visit but were not necessarily followed any further, i.e. few retrieved dropout data for the 26-week HbA1c measurement; this has implications for issues regarding missing data discussed below.

*Endpoints:*

For both Trial 3852 and 3853 the primary endpoint was the change in HbA1c at 26 weeks between the premeal [redacted] (b) (4) arm and the premeal NovoLog arm. A hierarchical testing procedure was used to control for type 1 error for secondary endpoints (e.g. body weight, post-prandial glucose (PPG)). A standardized meal test was performed at baseline and Week 26 for PPG measurement over 1, 2, 3, and 4 hours after the meal ingestion. The 1, 2, 3 and 4-hour PPG increments were derived separately by subtracting each PPG measurement from the plasma glucose measured before the meal test (-2 minutes). Glucose values used in PPG analyses were centrally measured laboratory values. The Applicant pre-specified the 2-hour value as a key secondary endpoint. The Applicant also included a hypoglycemia endpoint in the testing hierarchy; however, this should be considered a safety endpoint as the trial was not designed for a hypoglycemia benefit claim.

The primary endpoint for Trial 4049 was change in HbA1c from baseline to the end of treatment period (0 to 18 weeks), and there were no secondary endpoints.

The evaluation of efficacy was based all randomized subjects as randomized. The primary hypothesis test was non-inferiority of [redacted] (b) (4) mealtime vs. NovoLog mealtime for trials 3852 and 3853 and superiority in trial 4049. The primary endpoint was analyzed using MMRM. Continuous endpoints which were measured at visits between baseline and end of treatment were analyzed using MMRM model, which included treatment, region, and strata as fixed effects, subjects as a random effect, baseline measure as a covariate and interactions between all fixed effects and visit and between 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]).

Continuous endpoints that only measured at baseline and end of treatment only such as change in 1-4h Post-prandial glucose (PPG) increment were analyzed using an ANCOVA model including treatment, region and strata as factors and with endpoint at baseline as a covariate. Dichotomous endpoints were analyzed using logistic regression model using treatment, region and strata as factors, and endpoint at baseline as a covariate.

The Applicant 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. Dr. Cambon's review describes the 'Switch-to-NovoLog' methodology in detail and the rationale. He notes that this method is not ideal, e.g. 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. Further, he notes that whether or not there is rescue therapy included in a trial an affect the choice of methodologies for handling missing data, e.g. a Return-to-Baseline approach may not be reasonable in situations where rescue medication is used. For Trial 3853 Dr. Cambon also performed a Return-to- Baseline (or "wash-out") analysis. The noninferiority method used a 0.4% penalty equal to the non-inferiority margin specified by the sponsor.

**Trial 3852 - T1DM**

*Design*: Trial 3852 was a 26-week, randomized, active-controlled, trial with three parallel arms: a premeal (b) (4) arm, a postmeal (b) (4) arm, and a premeal NovoLog arm. The trial included a 26-week extension of open-label postmeal (b) (4) The trial was multi-national with 163 sites in 9 countries randomizing subjects. Randomization was 1:1:1.

*Objective*: The primary objective was to establish the non-inferiority of mealtime (b) (4) compared to mealtime NovoLog, both in combination with basal insulin, by assessing the change from baseline to Week 26 in HbA1c with a margin of 0.4%. This pre-specified margin was agreed upon at a pre-submission meeting.

*Subjects*: Eligible subjects were adults with T1DM for at least 12 months using a basal-bolus regimen. Therefore, the design was essentially a 'switch' study, except that subjects had to have HbA1c 7.0%-9.5%, i.e. 'uncontrolled'. This enrollment criterion allows for lowering of HbA1c during the trial so that the assay validity of the primary efficacy endpoint (change in HbA1c at 26 weeks) is acceptable.

An 8-week run in period was included during which subjects switched their basal insulin to insulin detemir and their bolus insulin to NovoLog, both on a unit-to-unit basis.

*Basal insulin dosing*: Dosing of Levemir during the run-in period was based on a 'treat-to-target' approach on a weekly basis to a fasting glycemic target of 71-90 mg/dL (and pre-dinner target of 71-108 mg/dL if on a twice daily regimen).

*Bolus insulin dosing*: At randomization, subjects were switched on a unit-to-unit basis from NovoLog to the blinded bolus insulin treatment ((b) (4) or NovoLog) to be administered either mealtime (0-2 minutes before each main meal) or postmeal (20 minutes after start of the meal; (b) (4) only in the open-label arm). Additional bolus doses were allowed if necessary. Subjects who were considered adequately trained during the run-in period to do flexible bolus adjustments based on the carbohydrate content of their meals were able to continue to do so after randomization. The subjects who were not proficient with carbohydrate counting used predefined bolus dosing algorithms to adjust their bolus doses twice a week during the treatment period. The bolus insulin was titrated to preprandial or bedtime SMPG target of 71-108 mg/dL at the subsequent meal or bedtime (for dinner dose) in a treat-to-target approach. Please see Dr. Kwon's review for the details of the titration algorithm. Note that in general, insulin products are individually titrated and do not have a clinically maximal dose.

*Results:* 1143 subjects were randomized. The distribution of baseline demographic characteristics for study 3852 according to Dr. Cambon's review is shown below. There are no notable imbalances across treatment groups. Overall, the mean age of subjects was 44 years (range 18 to 83 years), and the majority of subjects (93%) were 18 to 64 years of age with the remaining (7.5%) 65 years of age or older. 59% of subjects were male. About half of subjects (53%) were from the United States, majority of subjects (93%) were White, and very small proportion of subjects were African-American (2.3%) or Asian (1.2%). The mean BMI at baseline was 26.7 $kg/m^2$ with a range of 17 to 37.9 $kg/m^2$. The mean duration of diabetes in this patient population was about 20 years (range 1.2 to 65.4 years) with mean HbA1c at baseline of

7.6% (range 5.6 to 9.8%). About 42.5% of randomized subjects reported one or more diabetes complications with diabetic retinopathy (28.4%) and diabetic neuropathy (20.1%) most frequent.

| Treatment Group | (b) (4) Meal | (b) (4) Post Meal | NovoLog |
|---|---|---|---|
| **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

The table below is taken from Dr. Cambon's review and shows the results of the FDA analyses of the primary and sensitivity analyses for trial 3852.

**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

Dr. Cambon concluded that the FIAsp Mealtime group was statistically non-inferior to the NovoLog Mealtime group. While he notes that the 0.4% margin was not properly justified in the submission (it is based on historical precedent) the upper treatment bounds are negative. Further, the margin was agreed upon at the End-of-Phase 2 meeting. In addition, since the upper treatment bounds are negative superiority of mealtime (b) (4) vs. mealtime NovoLog can be concluded for this trial. A finding of superiority was not found in the T2DM trial.

The table below shows the results of trial 3852 as reported by the Applicant using the MMRM model as discussed previously. Postmeal (b) (4) was non-inferior to mealtime NovoLog although the absolute treatment difference favored NovoLog (estimated treatment difference 0.04%, 95% CI (-0.04, 0.12)). Therefore, the primary outcomes of the trial were met.

| Treatment Group | N | Baseline Mean | End of Trial Mean | LS Mean Change from Baseline | Treatment Diff versus NovoLog (95% CI) |
|---|---|---|---|---|---|
| Mealtime (b) (4) | 381 | 7.62 | 7.31 | -0.32 | -0.15 (-0.23, -0.07) |
| Postmeal (b) (4) | 382 | 7.63 | 7.51 | -0.13 | 0.04 (-0.04, 0.12) |
| Mealtime NovoLog | 380 | 7.58 | 7.42 | -0.17 | |

*Issues Regarding Missing Data:* Dr. Kwon's review discusses subject disposition in detail and reasons for withdrawal. Per Dr. Cambon's review with regard to a 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.

Dr. Cambon notes that the impact of the shortcoming described above of the 'Switch-to-NovoLog' approach to handling missing data is somewhat lessened by the fact that the missing rate on the NovoLog Meal arm is only 5%. The Applicant'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. The Statistical review did not conduct an additional 'return-to-baseline' analysis for this trial (see Trial 3853 discussion). Dr. Cambon also noted that it does not appear that treatment discontinuation is associated with baseline HbA1c values.

In the Applicant's sensitivity analysis, the 'Switch-to-NovoLog' results were similar to the primary results (shown in Dr.Cambon's table). The 'Switch-to-Inferior Treatment' method used a 0.4% penalty equal to the non-inferiority margin specified by the sponsor. 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). Using either sensitivity analysis approach, the treatment difference is somewhat diminished, but conclusions remain the same.

*Responder analyses:* conducted by the Applicant showed that a higher percentage of subjects in the mealtime [(b) (4)] achieved HbA1c target of <7% (15.7%) compared to NovoLog (10.3%), and a lower percentage of subjects in the postmeal [(b) (4)] achieved HbA1c target of <7% (6%) compared to NovoLog. None of these treatment differences reached statistical significance. The responder analyses are consistent with the primary HbA1c change from baseline analyses.

The Applicant conducted exploratory analyses of composite endpoints combining glycemic control and hypoglycemia risk. These are shown in Table 21 in Dr. Kwon's review. Overall, it appears that mealtime [(b) (4)] has a better profile with regard to these types of composite outcomes than does postmeal [(b) (4)] For example, the estimated odds of achieving HbA1c<7% without severe hypoglycemia with [(b) (4)] at mealtime was 1.36 (0.95, 1.96) compared to NovoLog, but postmeal [(b) (4)] had an odds of this same outcome of 0.66 (0.44, 0.96).

*Insulin Doses Achieved*: Basal insulin dose did not change appreciably from baseline to end of study. The study was designed to enroll 'uncontrolled' T1DM subjects to allow for adequate titration of study bolus insulin after randomization. Thus, the mean daily bolus insulin dose increased during 26 weeks of treatment period in all three treatment groups. The mean change in bolus insulin dose from baseline to end of treatment was slightly larger in the mealtime [(b) (4)] treatment arm (7.3 U or 0.09 U/kg dose) compared to mealtime NovoLog (5.5 U or 0.06 U/kg dose); mealtime [(b) (4)] group received about 0.03 U/kg additional dose compared to NovoLog treatment group. The mean change in bolus insulin dose from baseline to end of treatment was similar between postmeal [(b) (4)] (6.0 U or 0.07 U/kg) and mealtime NovoLog (5.2 U or 0.06 U/kg). The small differences in insulin dose may be responsible for the better HbA1c reduction observed in the mealtime [(b) (4)] arm since the molar potency of [(b) (4)] and NovoLog is the same. Given that in the mealtime [(b) (4)] arm hypoglycemia rate was similar than that of NovoLog in the trial (hypoglycemia is discussed in Section 7 of this review), it remains possible that the better HbA1c reduction was achieved because the dose could be pushed higher without excess overall hypoglycemia. Superiority of [(b) (4)] vs. NovoLog when both are given at the same time in relation to meals should be confirmed in a separate trial.

*Fasting plasma glucose:* values did not change significantly from baseline to end of study (refer to table below). The basal insulin was to be kept consistent during the trial so this finding is not surprising.

| | (b) (4) | P l (b) (4) | Meal NovoLog |
|---|---|---|---|
| Baseline | 151.41 | 145.63 | 141.76 |
| Week 26 | 145.02 | 143.56 | 146.64 |
| Adjusted change from baseline* | -3.08 | -2.69 | 1.43 |
| Treatment difference versus NovoLog (95% CI)* | -4.51 (-12.28; 3.26) | -4.12 (-11.83; 3.59) | |

*Secondary Endpoints*: Treatment with mealtime (b) (4) led to statistically larger decrease in 2-hour PPG increment (key secondary endpoint) compared to NovoLog (treatment difference of -12.01 mg/dL [95% CI: -23.33, -0.70]), but sensitivity analyses to address the impact of missing data did not confirm this statistical significance. The 2-hour PPG increment was numerically increased with postmeal (b) (4) compared to NovoLog with treatment difference of 5.32 mg/dL (95% CI: -6.05, 16.68). The larger decrease in 2-hr PPG increment for (b) (4) compared to NovoLog may be driving the better HbA1c reduction, although this cannot be known for certain. It is also notable that there was less of a reduction in PPG with postmeal (b) (4) than with mealtime NovoLog. The clinical significance of this finding independently is unclear and is not likely to be appropriate for labeling, but it is reassuring that the PPG data are consistent with the HbA1c data. While not a prespecified comparison it is evident from the data that mealtime (b) (4) results in more PPG reduction than is afforded by postmeal (b) (4) at 1 and 2 hrs. At 3 hours the difference is small.

Please see Dr. Kwon's review for a discussion of body weight change which was unremarkable.

**Trial 3853 – T2DM**

*Design:* Trial 3853 was a 26-week, randomized, active-controlled, trial with two parallel arms: a premeal (b) (4) arm, and a premeal NovoLog arm. The trial was multi-national (total of 135 sites screened subjects and 123 sites randomized subjects in 9 countries across North America, Europe, and Asia (India)), and randomization was 1:1.

*Objective*: The primary objective was to establish the non-inferiority of mealtime (b) (4) compared to mealtime NovoLog, both in combination with one daily insulin glargine and metformin in a basal-bolus regimen, by assessing the change from baseline to Week 26 in HbA1c with a margin of 0.4%. This pre-specified margin was agreed upon at a pre-submission meeting.

*Subjects*: Eligible subjects were adults with T2DM using a basal insulin regimen for at least 6 months. HbA1c entry criteria were 7.0%-9.5%, i.e. 'uncontrolled'.

An 8-week run in period was included during which all OADs other than metformin were discontinued and basal insulin treatment was optimized. All subjects continued their pre-trial metformin treatment without changing the frequency or dose during the trial duration.

*Basal insulin dosing*: Dosing of glargine during the run-in period was based on a 'treat-to-target' approach on a weekly basis to a fasting glycemic target of 71-90 mg/dL.

*Bolus insulin dosing*: At randomization, subjects were started on 4 units of the blinded bolus insulin treatment ([redacted] or NovoLog) to be administered at mealtime (0-2 minutes before each main meal). Additional bolus doses were allowed if necessary. The bolus insulin was titrated to preprandial or bedtime SMPG target of 71-108 mg/dL at the subsequent meal or bedtime (for dinner dose) in a treat-to-target approach. Please see Dr. Kwon's review for the details of the titration algorithm.

*Results:* 689 subjects were randomized. The distribution of baseline demographic characteristics for study 3853 according to Dr. Cambon's review is shown below. There are no notable imbalances across treatment groups. The mean age was 59.5 years (range 21 to 83 years) with the majority of subjects (71%) being 18-64 years of age. About 51% of subjects enrolled were women, and the majority of subjects were White (81%) and not Hispanic or Latino (93.6%). The mean HbA1c was 7.9% (range 5.3-10%) and the mean FPG was 122.2 mg/dL (range 45.1 to 293.7 mg/dL) at baseline. The mean duration of diabetes was 12.7 years (range 1-9 years). In addition to basal insulin, about 53.8% of subjects were also treated with metformin, and 43.7% of subjects were treated with metformin and another OAD.

| **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) |

The table below is taken from Dr. Cambon's review and shows the results of the FDA analyses of the primary and the 'Switch-to-NovoLog' sensitivity analyses for trial 3853. Mealtime (b) (4) is non-inferior to mealtime NovoLog. The estimated treatment difference in the primary analysis is -0.02%.

**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

The table below shows the results of trial 3853 as reported by the Applicant. The results are essentially the same as those derived from Dr. Cambon's analysis.

| Treatment Group | N | Baseline Mean | End of Trial Mean | LS Mean Change from Baseline | Treatment Diff versus NovoLog (95% CI) |
|---|---|---|---|---|---|
| Mealtime (b) (4) | 345 | 7.96 | 6.63 | -1.38 | -0.02 (-0.15, 0.10) |
| Mealtime NovoLog | 344 | 7.89 | 6.59 | -1.36 | |

*Issues Regarding Missing Data:* Dr. Kwon's review discusses subject disposition in detail and reasons for withdrawal. With regard to a 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.

Dr. Cambon notes that the impact of the shortcoming of the 'Switch-to-NovoLog' approach to handling missing data is somewhat lessened by the fact that the missing rate on the NovoLog arm is only 10%. The findings are consistent with those in the primary analysis. Using the 'Switch-to-Inferior Treatment' approach, the estimated difference in 26-Week reduction in HbA1c is 0.03 (95% CI: -0.10, 0.15), but conclusions remain the same.

Dr. Cambon 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. Conclusions remain the same, however. Similar to Trial 3852, Dr. Cambon noted that it does not appear that treatment discontinuation is associated with baseline HbA1c values.

*Responder analyses:* showed that after 26 weeks of treatment, 74.8% and 75.9% of subjects achieved HbA1c of <7%, and 54.5% and 56.4% of subjects achieved HbA1c of <6.5% in the (b) (4) and NovoLog group respectively. No statistically significant treatment difference was observed in the proportion of subjects achieving HbA1c <7% and ≤6.5% after 26 weeks of treatment.

*Insulin doses achieved:* After 26 weeks of treatment period, the mean daily basal insulin dose was 0.55 U/kg (0.04 U/kg decrease since baseline) in the (b) (4) group and 0.54 U/kg (0.03 U/kg decrease since baseline) in the NovoLog group. All subjects received a mean of 0.22 U/kg of daily bolus insulin dose by Week 1, which increased to a mean daily bolus dose of 0.68 U/kg in subjects receiving (b) (4) and 0.65 U/kg in subjects receiving NovoLog; however the median daily bolus dose was similar between (b) (4) group (0.49 U/kg; 0.08 to 4.90) compared to NovoLog group (0.51 U/kg; range 0.08 to 4.75 U/kg). After 26 weeks of treatment, the mean total insulin dose increased to 1.24 U/kg (0.43 U/kg increase since baseline) in subjects receiving (b) (4) and 1.18 U/kg (0.38 U/kg increase since baseline) in subjects receiving NovoLog. The median total insulin dose was similar in both treatment groups at the end of study period (1.02 U/kg). It does not appear that there is a clinically significant different in insulin doses achieved that would be expected to impact the fairness of the primary efficacy comparison.

*Fasting plasma glucose:* After 26 weeks of treatment, the estimated change from baseline in FPG was 0.36 mg/dL and -4.31 mg/dL in the (b) (4) and NovoLog treatment groups, respectively, and there was no statistically significant treatment difference between treatment groups.

*Secondary Endpoints:* Numerically there was a larger decrease in the 2-hour PPG increment in the (b) (4) group compared to NovoLog group in patients with T2DM (trial 3853), but this decrease was not statistically significant (treatment difference of -6.57 mg/dL [95% CI: -14.54, 1.41]). The estimated treatment difference in change from baseline in 1-hour PPG increment after 26 weeks reached statistical significance favoring (b) (4) group, with treatment difference between (b) (4) versus NovoLog of -10.63 mg/dL (95% CI: -19.56, -1.69). There were no statistically significant differences between treatment for change from baseline in 3 hour and 4 hour PPG increments.

*Body weight change*: both treatment groups had similar weight gain of about 2.7 kg over 26 weeks of treatment without any treatment difference.

**Subgroup analyses/special populations for Trials 3852 and 3853**

Dr. Cambon's review provides analyses for trials 3852 and 3853 based on gender, race, age, and geographic region. He did not find any clinically relevant treatment differences for these subgroup analyses. Please see his review for details.

Per Dr. Kwon's review the Applicant also did not find any clinically relevant treatment differences based on baseline demographic variables.

**Trial 4049 – T2DM**

*Design:* This was an 18 week, randomized, open-label, parallel group trial. It was multinational (total of 51 sites screened subjects and 45 sites randomized subjects in 6 countries across North and South America, Europe, and India), and randomization was 1:1. Randomization was stratified by type of once daily basal insulin (insulin detemir, insulin glargine, or NPH insulin).

*Objectives:* to test for superiority of (b) (4) plus basal insulin vs. basal insulin alone, both in combination with metformin in subjects with T2DM.

*Subjects:* T2DM ≥6 months before screening; treatment with once daily insulin detemir, insulin glargine or NPH for at least 3 months, HbA1c 7.5-9.5%

An 8-week run in period was included during which all OADs other than metformin were discontinued and basal insulin treatment was optimized using a treat-to-target approach (pre-breakfast SMPG glycemic target of 71-108 mg/dL). All subjects were to continue their pre-trial metformin treatment without changing the frequency or dose during the trial duration except in the case of safety concerns.

*Basal insulin*: In both treatment arms, the basal insulin was the subject's pretrial basal insulin (once daily insulin detemir, insulin glargine or human NPH insulin).

*Bolus insulin*: At randomization, subjects in the basal-bolus insulin treatment arm initiated 4 Units of (b) (4) 0-2 minutes before each main meal in addition to their basal insulin and metformin treatment, and subjects in the basal insulin treatment arm continued on the basal insulin and metformin treatment. During the 18 week treatment period, the dose of (b) (4) in the basal-bolus treatment arm was adjusted daily based on premeal and bedtime SMPGs according to titration guideline.

*Results*:

236 subjects were randomized. The mean age was 57.4 years (range 27 to 77 years), where 75% of subjects were 18- 64 years of age and 25% were ≥65 years of age. Slightly more than half of subjects were female (51.7%). The majority of subjects were White (69.9%) and not Hispanic or Latino (62.7%), and about 26% were Asian. The mean duration of diabetes was 11.3 years (range 1 to 33 years) with mean baseline HbA1c of 7.9% (range 6.4 to 11.4%). At screening, about 65% of subjects were on being treated with insulin glargine, 21% with NPH insulin and 14% with insulin detemir. At screening, the majority of randomized subjects (59.3%) were receiving basal insulin plus one OAD (i.e., metformin), and over one-third (38.6%) were receiving basal insulin plus 2 OADs (mostly metformin+SU). Only a small proportion of enrolled subjects were receiving basal insulin plus more than 2 OADs (2.1%). There was no notable difference in

previous anti-diabetic treatment across treatment groups at screening. Overall, there were no notable differences in the baseline characteristics or demographics between treatment groups.

The primary efficacy endpoint was the change from baseline in HbA1c after 18 weeks of treatment. After 18 weeks of treatment, the estimated change from baseline in HbA1c was -1.16% in the basal-bolus group and -0.22% in the basal only group, with treatment difference of 0.94% statistically significant (95% CI: -0.17, -0.72).

The table below is taken from Dr. Cambon's review and shows the results of the FDA analyses of the primary and sensitivity analyses for trial 4049.

**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); NovoM.-NovoLog

Dr. Cambon did not further discuss missing data issues for this trial because it was considered a supportive trial. However, the completion rate was relatively high: 107 subjects (92%) in the basal-bolus insulin arm and 115 subjects (96%) in the basal insulin arm, and it is unlikely lack of study completion notably affected study results.

Please see Dr. Kwon's review for a discussion of supportive endpoint of HbA1c responder rate; this was consistent with the superiority finding for (b) (4) Fasting plasma glucose did not appreciably change in either group which is consistent with the study design of adding a prandial insulin therapy and keeping basal insulin the same. The mean daily basal insulin dose at baseline/randomization (Week 0) was 0.6 U/kg in both treatment groups, and was 0.5 U/kg and 0.6 U/kg after 26 weeks of treatment period in (b) (4) plus basal group and basal group respectively. The mean daily bolus dose increased to 55.6 U (0.66 U/kg) after 18 weeks of treatment period.

*Body weight:* The estimated mean body weight increased 1.83 kg in the basal-bolus treatment group compared to 0.17 kg in the basal group, and this treatment difference was statistically significant (1.66 [95% CI: 0.89, 2.43]).

*Labeling Discussion*:
Dr. Cambon states that (b) (4) . I agree with his assessment. However, labeling discussions will not occur during this review cycle, and this is not an approvability issue. Further, with regard to labeling, Dr. Cambon notes that the MMRM primary analysis does not adequately address missing data and should not be the analysis used

for labeling purposes, and that the sensitivity analysis which most closely addresses missing data should be the one put in the label; however he did not specifically state which analysis should be used. Descriptive statistics for missing data by arm should be included in the label. Again, these issues will be deferred until the appropriate time.

## 8. Safety

Dr. Kwon's Clinical review contains a comprehensive review of safety for this NDA. As noted above, the safety profile of (b) (4) was expected to be similar to that of NovoLog. The primary safety concerns with NovoLog (and with insulin products in general) are hypoglycemia and immunogenicity/hypersensitivity reactions. The (b) (4) Phase 3 program was sufficient to assess these concerns, and no new or worsening safety concerns were identified by Dr. Kwon. However, the reviewer from Office of Biotechnology Products noted that the assay validation has several deficiencies as noted above that will require additional review of antibody data in a future resubmission.

*Evaluation of safety - methods:*
The extent of data to inform safety and safety pools for review were agreed upon at presubmission meetings between the Applicant and the Agency. Because the safety profile of active ingredient insulin aspart has been well characterized the goal of the safety program was to evaluate for any additional safety concerns stemming from the new formulation. T1DM and T2DM are different diseases with different safety concerns, and safety is evaluated separately for the two trials. However, a pooled dataset for review (the pool of the two pivotal Phase 3 trials of basal-bolus insulin regimen in T1DM (trial 3852) and T2DM (trial 3853) was examined to look for rarer adverse events that may not be apparent without a larger database. The safety data from the remaining three trials (4049, 3931, (b) (4)) provide supportive safety information. Trials (b) (4) 3931 evaluated the use of (b) (4) in CSII with external pumps. (b) (4)

*Overall Exposure:*
In five clinical trials (3852, 3853, 4049, 3931, (b) (4)), a total of 1287 subjects were exposed to (b) (4) for a total of 572.2 patient year of exposure (PYE). The majority of subjects exposed to (b) (4) were exposed to for at least 6 months (78% [967/1244]).

Major Safety Results:
*Deaths*
No imbalance in the incidence of deaths was observed between (b) (4) and NovoLog, and none of the deaths were likely to have been caused by the study drug.

*Serious Adverse Events*
*Trial 3852 – T1DM*
Overall, more SAEs were reported in postmeal (b) (4) group (7.4% [28 subjects] or 19.7 per 100 PYE) compared to mealtime (b) (4) (4.9% [19 subjects] or 13.4 per 100 PYE) or NovoLog groups (5.8% [22 subjects] or 12.7 per 100 PYE). Based on frequency of occurrence,

hypoglycemia was the only notable SAE. Aside from hypoglycemia, there were no SAE that occurred at ≥1% and occurred more frequently in the mealtime (b) (4) compared or postmeal (b) (4) compared to NovoLog as most other events occurred in one subject.

Diabetic ketoacidosis – there was one SAE of DKA with mealtime (b) (4) versus 2 SAE of DKA with NovoLog, a slight imbalance not favoring NovoLog (Note 'all' DKA AEs (not SAEs only) were similar between mealtime arms: 2 with mealtime (b) (4) 2 with mealtime NovoLog, and none with postmeal (b) (4) Given that DKA is a potentially life threatening event all DKA should be considered serious.

*Trial 3853 – T2DM*

There were 20 SAEs in 15 subjects (4.4%; 12.5 events per 100 exposure years) in the (b) (4) group and 31 in 24 subjects (7.0%; 19.1 events per 100 exposure years) the NovoLog group. Again, the most frequently reported PT in both groups was hypoglycemia.

Dr. Kwon's review discusses SAEs for the additional trials; no notable findings were identified. Please see her review for details.

I agree with Dr. Kwon's conclusion that overall there is no safety concern with regard to (b) (4) as compared to NovoLog apparent in the review of SAE data. Numerical imbalances are expected based on the trial size; the numerical imbalances favored (b) (4) in the T2DM trial and favored comparator in the T1DM trial. In addition, aside from hypoglycemia events there is no apparent pattern of SAE differences between treatment groups. Hypoglycemia is a safety concern with all insulin products.

*Adverse Events Leading to Dropout*

*Trial 3852 – T1DM*

Eleven subjects withdrew from the trial due to AEs, 5 subjects (1.3%) in the mealtime (b) (4) group, 4 subjects (1.1%) in the postmeal (b) (4) group, and 2 subjects (0.5%) in the NovoLog group. While there is a small numerical imbalance in these events, the reasons for dropout do not suggest a new safety concern. Dr. Kwon notes that the most common AE leading to dropouts was related hypoglycemia, most frequently in the postmeal (b) (4) group (4 subjects with either hypoglycemia or hypoglycemic unconsciousness) compared to NovoLog group (3 subjects with hypoglycemia or hypoglycemia unconsciousness) and least frequently in the mealtime (b) (4) group (one subject with hypoglycemia and another subject with neuroglycopenia [this subject had 6 episodes of hypoglycemia before neuroglycopenia]). However, based on the overall review of hypoglycemia it appears that the mealtime (b) (4) group has the highest relative risk of hypoglycemia compared to both mealtime NovoLog and postmeal (b) (4) These findings are consistent with the efficacy results, i.e. pattern of glycemic improvement mirrors hypoglycemia risk, which is not unexpected.

*Trial 3853 – T2DM*

Five subjects withdrew from the trial due to adverse events, 2 in subjects receiving (b) (4) and 3 in subjects receiving NovoLog. Four events were fatal SAEs and one was non-serious AE of 'post infarction angina.' Dr. Kwon also noted that four subjects in the 'withdrawal by subject' category had notes in CRF indicating withdrawal due to other safety-related reasons: 1 in the

(b) (4) group reported "withdrawal due to frequent hypoglycemia" and 3 subjects in the NovoLog group reported "mainly hypoglycemic episodes", "subject believes dizziness and vomiting are due to trial product", or "frequent hypoglycemia". Also, one subject in the (b) (4) group who withdrew due to 'other' reason discontinued the study due to weight gain and an increasing number of hypoglycemic events after 10 weeks of treatment. Even when taking these additional events into consideration no unexpected safety concern is noted from these data. Again, hypoglycemia is an expected AE for an insulin product.

Dr. Kwon's review discusses AEs leading to dropout for the additional trials; no notable findings were identified. Please see her review for details.

*Hypoglycemia*
As noted above, hypoglycemia is the major known safety issues with insulin and is expected to occur with (b) (4) Hypoglycemia findings must be interpreted in light of the relative glycemic control observed in the study because hypoglycemia is more likely to occur with 'tighter' (more intensive) glycemic control.

In diabetes trials, hypoglycemia is typically assessed using the American Diabetes Association criteria (rather than criteria that distinguish serious from nonserious adverse events). It is common for hypoglycemic episodes to be recorded on a specific hypoglycemia episode form and generally not reported as AEs as occurred in the (b) (4) trials. If a hypoglycemic episode met the SAE criteria, then AE and SAE forms were also filled out; however, the review of hypoglycemia generally looks at 'severe' episodes rather than by SAE criteria.

The applicant's definition of '**severe hypoglycemia**' was same as ADA definition (i.e., an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions). In addition to ADA classification of hypoglycemia, the applicant also used the following additional categories using the plasma glucose cut-off level of 56 mg/dL rather than ADA criteria of 70 mg/dL:

- **Severe or BG confirmed symptomatic hypoglycemia**: An episode severe according to ADA classification or BG confirmed by a plasma glucose value <56 mg/dL <u>with</u> symptoms consistent with hypoglycemia;
- **BG confirmed hypoglycemia:** An episode that is BG confirmed by plasma glucose value <56 mg/dL <u>with</u> or <u>without</u> symptoms consistent with hypoglycemia;
- **Severe or BG confirmed hypoglycemia:** An episode severe according to ADA classification or BG confirmed by a plasma glucose value <56 mg/dL <u>with</u> or <u>without</u> symptoms consistent with hypoglycemia;

Hypoglycemia events were also classified as to whether they were:

- nocturnal (00:01-05:59 inclusive) or daytime;
- related to or unrelated to meals (relation to time since start of meal as occurring during first 1, 2, 4 and 6 hours after a meal).

Capture of hypoglycemia events: plasma glucose was to be measured and recorded when hypoglycemia was suspected. Plasma glucose was also measured for 7-point and 4-point SMPG profiles during trials.

Dr. Kwon points out that because these trials excluded patients who had recurrent severe hypoglycemia or hypoglycemic unawareness these trials excluded patients with known predisposition to hypoglycemia. Therefore, the observed rates may be lower than those that would be expected in clinical practice.

Dr. Kwon's review discusses all of the definitions of hypoglycemia reported by the Applicant. Severe and BG confirmed hypoglycemia was a key secondary endpoint in the trials. This summary review also highlights BG confirmed symptomatic hypoglycemia which is a more specific definition than the one that doesn't require symptoms (and also more specific than the 'ADA documented symptomatic' definition because the plasma glucose cutoff is lower).

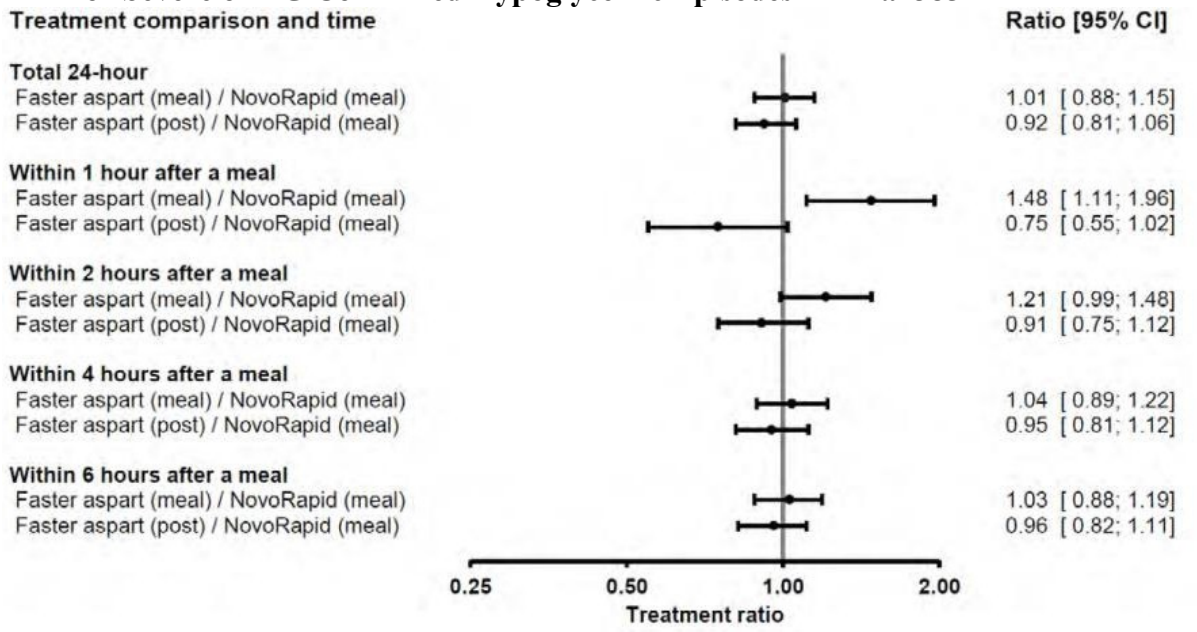
*Trial 3852 – T1DM*

A slightly higher proportion of subjects reported severe hypoglycemia in the NovoLog group (8.4%) compared to mealtime (b) (4) (6.7%) or postmeal (b) (4) (8.0%) groups, but the event rate was more similar across the treatment groups although numerically not favoring NovoLog. For severe or BG confirmed symptomatic 90.4% of subjects reported events in the mealtime (b) (4) group, 92.0% in the (b) (4) postmeal group, and 93.9% in the NovoLog group. Event rates had a slightly different pattern with the lowest rate observed in the (b) (4) postmeal group. Overall, however, the proportion of subjects and event rates were similar enough that it is difficult to draw any conclusions about meaningful differences between groups. Further given slightly different HbA1c reduction among groups, comparisons are more challenging. Also, severe and BG confirmed symptomatic would be expected to be consistent with each other; the finding that the different definitions favored different study arms is evidence that the findings are due to chance rather than any real difference between groups.

Although exploratory, the observation that severe or BG confirmed hypoglycemia rates within 1 to 2 hrs after a meal tended to be higher for the (b) (4) premeal group compared to NovoLog is of note. In the Applicant's analysis this difference was statistically significant (estimated rate ratio 1.48 [95% CI: 1.11, 1.96]). Also observed was a lower hypoglycemia rate within 1 and 2 hours after a meal in the postmeal (b) (4) group compared to NovoLog, although not statistically significant. The data for severe or BG confirmed *symptomatic* hypoglycemia were similar. Thus, it appears that while the overall 24 hr risk of hypoglycemia is likely similar among groups, hypoglycemia risk is higher earlier in relation to meals when given at mealtime because of the earlier onset of action. It is well understood that hypoglycemia risk is dependent on the timing of administration and the PK profile of the insulin administered. Most insulin labels currently contain the Warning and Precaution that *The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal.*

A useful figure (created by the Applicant) to understand the hypoglycemia risk with (b) (4) vs. NovoLog is shown below. While this forest plot includes non-symptomatic events, the pattern of the hypoglycemic events is the factor of interest. Overall 24-hour hypoglycemia is similar among groups. The greatest relative difference occurs at 1 hr after the meal when the glucose lowering effect among the three arms is most distinguishable, the difference among arms declines over time. By 6 hours after the meal the risk appears similar to the overall 24 hr risk.

**Meal-Related and Total Estimated Treatment Ratios Based on Estimated Rates per 100 PYE for Severe or BG Confirmed Hypoglycemic Episodes in Trial 3852**




*Trial 3853 – T2DM*

During the treatment period, severe hypoglycemia was reported in 11 subjects (3.2%) and 13 subjects (3.8%) in the (b) (4) and NovoLog treatment groups respectively. Event rate analysis favored the NovoLog group [27 events (16.9 events per 100 PYE) were reported in the (b) (4) group and 17 events (10.9 events per 100 PYE)] were reported in the NovoLog group, but overall it appears the risk of severe hypoglycemia is not appreciably different between groups. For severe or BG confirmed symptomatic 71.8% of subjects reported events in the mealtime (b) (4) group and 65.4% in the mealtime NovoLog group (1412 events per 100 PYE vs 1318 events per 100 PYE, respectively). For the Applicant's analysis of severe or BG confirmed hypoglycemia, i.e. with our without symptoms, the estimated rate ratio was 1.09 ( (b) (4) versus NovoLog) and was not statistically significant (95% CI: 0.88; 1.36). A slightly larger proportion of subjects reported severe or BG confirmed hypoglycemic episodes in the (b) (4) group (76.8%) compared to the NovoLog group (73.3%).

Analysis of the timing of hypoglycemia events in relation to meals is similar to Trial 3852, showing that the highest risk of hypoglycemia occurs when glucose lowering is highest (earlier for (b) (4)

Hypoglycemia for the remainder of the trials is discussed in Dr. Kwon's review. Because insulin dose was much higher in the treatment arm in Trial 4049 than in the control arm, hypoglycemia events are expected to occur more frequently (which was observed). A comparison between groups within the trial is not necessarily meaningful. The overall event rate in the (b) (4) arm in trial 4049 appeared similar to the T2DM trial 3835.

*Major Cardiovascular Adverse Events (MACE)*

The results from a pre-specified meta-analysis of major adverse cardiovascular events (MACEs) using pooled data showed no safety signal. An external independent Endpoint Adjudication Committee (EAC) was established to adjudicate cardiovascular events after randomization in a blinded and independent manner. Major adverse cardiovascular events (MACE) were defined as a composite endpoint consisting of positively adjudicated non-fatal myocardial infarction (ST segment elevation myocardial infarction [STEMI] or non-STEMI), non-fatal stroke and CV death. There were few events and no safety signal was identified. Note that the analysis conducted by the Applicant would not be sufficient to satisfy the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. However, insulin products are not necessarily expected to follow the Guidance recommendations.

*Common Adverse Events*

*Trial 3852 – T1DM*

Exposure for subjects with T1DM in pivotal phase 3 studies of 6 months duration for the purposes of comparing common adverse events across treatment arms is derived only from trial 3852: 386 subjects exposed to (b) (4) mealtime, 377 (b) (4) postmeal (763 total (b) (4) Adverse events (MedDRA preferred terms) occurring with 5% frequency or greater in one of the (b) (4) treatment groups (other than hypoglycemia) are shown in the table below. The proportion of subjects with AEs was adjusted using the Cochran-Mantel-Haenszel (CMH) method to take study differences in exposure into account. It is unlikely that any of these AEs are drug related and hence adverse reactions from (b) (4) However, Division practice is to label AEs occurring above a certain cutoff (typically 5% for insulin products). However, it may be appropriate to pool the (b) (4) arms because showing the data separately is not likely to be useful for prescribers. Note: it would not be appropriate to label 'wrong drug administered'.

**Adverse Events Occurring in 26-Week T1DM Trial with Frequency 5% or Greater and Higher with (b) (4)**

| | premeal | (b) (4) postmeal | NovoLog premeal |
|---|---|---|---|
| | N=386 | N=377 | N=380 |
| Nasopharyngitis | 20.2% | 23.9% | 19.5% |
| Upper respiratory tract infection | 9.1% | 7.4% | 7.6% |
| Nausea | 4.9% | 5.0% | 4.2% |
| Diarrhea | 5.4% | 3.2% | 4.7% |
| Wrong drug administered | 4.4% | 5.0% | 5.0% |
| Back pain | 5.2% | 4.0% | 3.4% |

*Trial 3853 – T2DM*

Exposure for subjects with T2DM in pivotal phase 3 studies of 6 months duration for the purposes of comparing common adverse events across treatment arms is derived only from trial 3853: 341 subjects exposed to (b) (4) at mealtime.

Adverse events (MedDRA preferred terms) occurring with 5% frequency or greater in the (b) (4) treatment group (other than hypoglycemia) is shown in the table below. The proportion

of subjects with AEs was adjusted using the Cochran-Mantel-Haenszel (CMH) method to take study differences in exposure into account. Again, it is unlikely that any of these AEs are drug related and hence adverse reactions from (b) (4)

**Adverse Events Occurring in 26-Week T2DM Trial with Frequency 5% or Greater and Higher with (b) (4)**

| | | NovoLog |
|---|---|---|
| | N=341 | N=341 |
| Nasopharyngitis | 5.0% | 7.0% |
| Urinary tract infection | 5.9% | 3.8% |

Common adverse reactions in the other trials were not remarkably different from the two 6-month trials and are not discussed in this review. Please see Dr. Kwon's review for details.

*Immunogenicity*
Dr. Bowen's review contains a discussion of the antibody analyses from study 3852. The 120-day safety update received on 4/04/2016 included immunogenicity data through the 52 week sampling timepoint. The two treatment arms were similar for insulin-aspart specific antibody incidence. Dr. Bowen states that *In general the antibody levels in patients from patients in each arm appear comparable as well as the insulin aspart specific and cross-reactive antibody responses. The Sponsor did not provide data on the frequency of treatment-boosted ADA in each treatment arm or the strategy for defining treatment-boosted ADA responses. This was communicated to the Sponsor in the 8-1-2016 IR, however the response was not reviewed in this cycle. Correlations between antibody levels and adverse events and HbA1c were analyzed. There appeared to be no correlation between the levels of ADA and AEs or changes in HbA1c.* It is noted, however, that these data should be reexamined when the deficiencies noted in section 3 of this review (related to assay validation) have been addressed. Dr. Kwon's review contains a summary of the Applicant's interpretation of the antibody data.

Immunogenicity was also evaluated using pre-defined MedDRA searches for identifying injection site reactions and immunogenicity-related AEs (i.e., allergic reactions). Events were few and no important imbalances were observed. No serious events occurred. If/when approved the labeling for (b) (4) should include the class labeling language for hypersensitivity, however, because the clinical development program may be too short in duration and/or too small to expect any severe hypersensitivity reactions to have occurred.

*Other safety issues*
Dr. Kwon found no major safety concerns with regard to lipodystrophy, vital signs, carcinogenicity (i.e. incidence of cancers), routine laboratory assessments, or electrocardiograms. This is not unexpected given the well characterized safety profile of NovoLog with regard to these issues. Please see her review for details.

(b) (4)

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## 9. Advisory Committee Meeting

No advisory committee meeting was convened for this sNDA.

## 10. Pediatrics

This application triggers the Pediatric Research Equity Act (PREA) because of the change in dosing regimen, and therefore, pediatric studies under PREA are recommended. The initial pediatric study plan (iPSP) was agreed on August 28, 2015. The PSP was discussed at the PeRC meeting on August 24, 2016, and the PeRC agreed with the sponsor's plan for a partial waiver in patients 0 to <1 years of age with T1DM and patients 0 to <10 years of age with T2DM because the studies are impossible or highly impractical and to the deferral in patients 1 to <18 years of

age with T1DM and patients 10 to <18 years of age with T2DM. A Phase 3 efficacy and safety study in children and adolescents with T1DM is recommended as postmarketing requirement.

## 11. Other Relevant Regulatory Issues

*Financial Disclosures*: Dr. Kwon reviewed financial disclosure information and found no potential concerns. I agree with her assessment.

*Site Inspections:* Clinical investigator site inspections were conducted at four domestic clinical sites as well as the applicant. The sites were chosen based on the OSI site selection tool, and there was enough domestic data to focus on domestic sites only. The site inspection of two clinical investigators revealed regulatory violations, and the remaining two clinical investigators revealed no regulatory violations. The regulatory deficiencies observed at two clinical sites are assessed to be unlikely to have a significant impact on the overall efficacy and safety data.

Please see the Clinical Inspection Summary dated August 15, 2016 by Dr. Cynthia Kleppinger for full details.

(b) (4)

*Support for IV administration*: In support of intravenous administration, the Sponsor submitted stability data of (b) (4) when diluted in two types of intravenous infusion fluids (0.9% NaCl and 5% glucose) at concentrations of 0.5 U/mL and 1.0 U/mL. (b) (4) is stable for 24 hours at room temperature post dilution.

The clinical pharmacology study NN1218-3949 investigated the pharmacokinetics and pharmacodynamics of (b) (4) following intravenous (IV) administration of a relatively low dose of NN1218 (0.02 U/kg). Any difference in the PD of (b) (4) vs. NovoLog following IV administration is not expected since the active ingredient is insulin aspart. However, there are no data establishing the safety of the drug product (including excipients) for longer-term IV infusion and at higher doses that are likely to be used in the clinical setting.

With regard to nonclinical data, the single-dose rabbit local tolerance study (#212147), which was the only study that included IV dosing, was adequate to assess toxicity of accidental exposure or very short-term exposure, but was not adequate to support long term repeated IV

exposure. The nonclinical study that the Applicant conducted to support clinical studies with SC dosing was a 4 week local tolerance study (#212251) in rats.

The Applicant should clarify how they plan to address the safety of longer-term infusion and higher doses of (b) (4) that are likely to occur in the clinical setting, specifically with regards to the excipients, nicotinamide and arginine.

# 12. Labeling

The Applicant's originally proposed tradename of Fiasp was believed to be misleading because it is an abbreviation for 'faster insulin aspart' and the DMEP did not believe that the data provided in the application conclusively demonstrated that the 'faster' time action profile translated into a clinically meaningful difference. The Applicant withdrew the original tradename request and resubmitted with the name (b) (4) The Division of Medication Error Prevention and Analysis (DMEPA) tentatively approved the applicant's proposed trade name (b) (4) on July 26, 2016.

Because a Complete Response action is recommended, further discussion of labeling is premature at this time.

# 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response (CR)

- Risk Benefit Assessment

A Complete Response is recommended because of deficiencies related to the reliability of the bioanalytical method used to assess PK samples in the Clinical Pharmacology program and because of deficiencies related to the anti-insulin antibody assay validation as identified by the Office of Biotechnology Products review.

With regard to safety and efficacy the submitted data are adequate to establish that (b) (4) is effective for glycemic control in patients with diabetes mellitus and to characterize the safety of the new product is similar when injected subcutaneously. The applicant has demonstrated in three adequate and well-controlled trials the glycemic efficacy of (b) (4) administered as bolus insulin either premeal/mealtime (0-2 minutes before meals) or post-meal (20 minutes after the meal). The table below from Dr. Kwon's review summarizes the efficacy findings in the phase 3 program.

| Treatment Group | N | Baseline Mean | End of Trial Mean | LS Mean Change from Baseline | Treatment Diff versus NovoLog (95% CI) |
|---|---|---|---|---|---|
| **Type 1 Diabetes Mellitus** | | | | | |
| ***Trial 3852:*** *26-week basal-bolus in combination with insulin detemir* | | | | | |
| Mealtime [(b) (4)] | 381 | 7.62 | 7.31 | -0.32 | -0.15 (-0.23, -0.07) |
| Postmeal [(b) (4)] | 382 | 7.63 | 7.51 | -0.13 | 0.04 (-0.04, 0.12) |
| Mealtime NovoLog | 380 | 7.58 | 7.42 | -0.17 | |
| **Type 2 Diabetes Mellitus** | | | | | |
| ***Trial 3853:*** *26-week basal-bolus in combination with insulin glargine and metformin* | | | | | |
| Mealtime [(b) (4)] | 345 | 7.96 | 6.63 | -1.38 | -0.02 (-0.15, 0.10) |
| Mealtime NovoLog | 344 | 7.89 | 6.59 | -1.36 | |
| ***Trial 4049:*** *18-week basal-bolus versus basal in combination with metformin* | | | | | |
| Mealtime [(b) (4)] +basal | 116 | 7.93 | 6.78 | -1.16 | -0.94 (-1.17, -0.72)* |
| Basal | 120 | 7.92 | 7.70 | -0.22 | |

*Treatment difference versus basal insulin

Active-control (vs. NovoLog) Trials 3852 (both [(b) (4)] treatment arms) and 3853 met the primary endpoints and demonstrated the non-inferiority of [(b) (4)] vs. NovoLog both given at mealtime (pre-specified non-inferiority margin of 0.4% for HbA1c). Superiority of [(b) (4)] plus basal insulin was superior to basal insulin alone in the T2DM population in trial 4049. Sensitivity analyses did not change the overall conclusions.

In Trial 3852, HbA1c lowering in the mealtime [(b) (4)] arm was superior to mealtime NovoLog. However, I agree with the conclusion of the statistical reviewer that a superiority claim vs. NovoLog for the primary endpoint for Study 3852 is not warranted since this finding was not replicated across both studies 3852 and 3853. Although only the T1DM trial had a postmeal treatment arm, it is acceptable to allow for postmeal use in T2DM because T2DM is the less insulin sensitive population and any adverse efficacy or safety findings would be more apparent in the T1DM population.

The exploratory analyses conducted by the Applicant of composite endpoints combining glycemic control and hypoglycemia risk, and the supporting PPG data derived from standardized meal test studies conducted as part of the phase 3 pivotal trial in T1DM seems to point towards [(b) (4)] administered at mealtime, to have better glucose lowering than mealtime NovoLog, and mealtime NovoLog in turn appears to be better than postmeal [(b) (4)] On the other hand, perhaps administering NovoLog 10 -15 minutes before the meal would have resulted in similar glycemic control to [(b) (4)] 0-2 minutes before the meal. While the optimal time of administration of bolus insulin may also be patient-dependent, i.e. vary based on the individual, it appears that the small increase in absorption may prove to be beneficial for patients with good insulin sensitivity such as T1DM patients by allowing for administration of the bolus insulin closer to mealtime. In the T2DM trial there was no apparent difference between premeal [(b) (4)] and premeal NovoLog, perhaps because insulin sensitivity is lower in these patients.

[(b) (4)]

[redacted]

The safety profile of [redacted] is similar to NovoLog and there are no additional safety concerns beyond what is known with bolus insulin products. The one exception to the similar safety profile is that hypoglycemia related to the bolus injection given at mealtime tends to occur earlier for [redacted] administered with the meal than with NovoLog administered with the meal. This finding likely reflects the specific time action profile of the two insulin products and does not affect the overall/risk benefit consideration.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

See Pediatrics above

- Recommended Comments to Applicant

Comments to the Applicant will be conveyed in a Complete Response Letter.

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

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/s/

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LISA B YANOFF
10/07/2016

JEAN-MARC P GUETTIER
10/07/2016

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 208751 |
| Priority or Standard | Standard |
| Submit Date(s) | December 8, 2015 |
| Received Date(s) | December 8, 2015 |
| PDUFA Goal Date | October 8, 2016 |
| Division / Office | Division of Metabolism and Endocrinology Products |
| Reviewer Name(s) | Hyon Kwon |
| Review Completion Date | October 3, 2016 |
| Established Name | Insulin aspart |
| (Proposed) Trade Name | (b) (4) |
| Therapeutic Class | Insulin |
| Applicant | Novo Nordisk |
| Formulation(s) | 100 units/mL in 10 mL vials and 3 mL FlexTouch |
| Dosing Regimen | Individualized |
| Indication(s) | To improve glycemic control in adults with diabetes mellitus |
| Intended Population(s) | Adults with diabetes mellitus |

# Table of Contents

# Table of Tables

# Table of Figures

# 1 Recommendations/Risk Benefit Assessment

Novo Nordisk submitted a 505 (b)(1) NDA for a new formulation of insulin aspart injection, 100 units/mL. The proposed trade name is (b) (4) The proposed indication for (b) (4) is to improve glycemic control in adults with diabetes mellitus. The already approved insulin aspart product is marketed under the Tradename NovoLog.

## 1.1 Recommendation on Regulatory Action

I recommend Complete Response of this NDA because of Clinical Pharmacology deficiencies and immunogenicity deficiencies identified by the Office of Biotechnology Products (OBP). The clinical review, however, identified no deficiencies precluding approval and the risk benefit assessment appears favorable. See section 1.2 below.

## 1.2 Risk Benefit Assessment

If (b) (4) is approved, it would offer another therapeutic option for patients with diabetes mellitus who would need prandial insulin therapy.

Compared to NovoLog, (b) (4) has two additional excipients, nicotinamide and L-arginine chloride, with the addition of nicotinamide intended to increase the rate of absorption of insulin aspart after subcutaneous injection to help with glycemic control after ingestion of a meal. This change appears to lead to an estimated 5 minutes earlier onset of action with (b) (4) compared to NovoLog, with similar total insulin aspart exposure, based on clinical pharmacology studies. It should be noted, however, that the Clinical Pharmacology results have been determined to be unreliable, as discussed in Dr. Shalini Wickramaratne Senarath Yapa's review dated September 8, 2016. Also, pharmacodynamic (PD) results with standardized meal test did not appear to show a meaningful difference in postprandial glucose reduction with (b) (4) compared to NovoLog, when both are given before a meal. In addition, when (b) (4) was administered postmeal, the mean plasma glucose profile was higher compared to mealtime NovoLog administration in Clinical Pharmacology studies. See section 4.4.2.

In both T1DM and T2DM Phase 3 trials (3852 and 3853) where subjects were treated with a basal-bolus regimen, mealtime (b) (4) was non-inferior (prespecified margin of 0.4%) in terms of change from baseline in HbA1c when compared to mealtime NovoLog after 26 weeks of treatment. A supportive trial in T2DM (4049) showed superiority of adding (b) (4) to basal insulin + metformin compared to basal insulin + metformin, with treatment difference of -0.94% in HbA1c (95% CI: -1.17, -0.72) after 18 weeks of treatment.

The change in 2-hour postprandial glucose (PPG) increment with standard meal after 26 weeks of treatment was a confirmatory secondary endpoint in both trials 3852 and 3853. In T1DM (trial 3852), treatment with mealtime (b) (4) led to statistically significant lower 2-hour PPG increment compared to mealtime NovoLog in the primary analysis, but sensitivity analyses failed to confirm this statistical significance. In subjects with T2DM (trial 3853), the 2-hour PPG increment with (b) (4) was lower compared to NovoLog after 26 weeks of treatment, but statistical significance was not found.

Postmeal dosing of (b) (4) (administered 20 minutes after start of a meal) was only investigated in T1DM in trial 3852 with results compared to mealtime NovoLog. For the comparison of postmeal (b) (4) to mealtime NovoLog, non-inferiority was met at the margin of 0.4% (estimated treatment difference of 0.04% [95% CI: -0.04, 0.12]). Also observed was a lower percentage of subjects in the postmeal (b) (4) achieving HbA1c target of <7% compared to mealtime NovoLog after 26 weeks (6% versus 10.3% for postmeal (b) (4) vs. mealtime NovoLog). In addition, the 2-hour PPG increment was increased with postmeal (b) (4) compared to mealtime NovoLog (difference not statistically significant), which is consistent with clinical pharmacology meal test study results.

A more rapidly absorbed insulin that allow injection immediately before starting a meal and/or postmeal may offer added convenience for diabetic patients, particularly in certain situations when dosing immediately before a meal is not possible or when meal consumption is unpredictable. Theoretically, an insulin product with a faster onset of action that could be better matched to carbohydrate intake by dosing after the meal could help lower postmeal glucose concentrations and improve postprandial glucose control, thereby contributing to overall improved glycemic control in diabetic patients. The difference in onset of action between (b) (4) and NovoLog (about 5 minutes) did not appear to translate into better postprandial glucose lowering with (b) (4) when given postmeal. However, the postmeal administration of (b) (4) was shown to be not inferior to mealtime administration of NovoLog based on HbA1c change at 26 weeks, thereby meeting the standard for approval.

The evaluation of risk focusing on reported adverse events, routine laboratory and immunogenicity assessments did not show any particular safety concerns. In both pivotal T1DM and T2DM trials (3852 and 3853 respectively), the most common serious adverse events and adverse events leading to study withdrawal were related to hypoglycemia. The immunogenicity assessment did not show any safety concerns; however, OBP has determined that the assay validation for insulin antibody testing is not adequate.

The most notable treatment difference with regard to hypoglycemia was an increase in the 'meal-related'[1] severe or blood glucose (BG) confirmed hypoglycemia[2] with

(b) (4) compared to NovoLog, both given at mealtime. In the T1DM (trial 3852), a statistically higher rate of severe or BG confirmed hypoglycemic episodes during the *first hour* after a meal was observed for mealtime (b) (4) compared to NovoLog (147.6 and 96.4 per 100 PYE with estimated treatment ratio of 1.48 [95% CI: 1.11, 1.96]). In T2DM (trial 3853), a statistically higher rate of severe or BG confirmed hypoglycemic episodes *within 2 hours* after a meal was observed with (b) (4) compared to NovoLog (226.5 and 148.5 per 100 PYE with estimated treatment ratio of 1.60 [95% CI: 1.13, 2.27]). This increased hypoglycemia rate within 1 and 2 hours after a meal in the mealtime (b) (4) group compared to NovoLog should be interpreted in light of the pharmacodynamic profile of (b) (4) where lower 1- and 2-hour postprandial glucose (PPG) was seen with mealtime (b) (4) compared to NovoLog.

In comparison, a numerically lower rate of severe or BG confirmed hypoglycemic episodes occurred with postmeal (b) (4) compared to NovoLog during the first hour after a meal in trial 3852 (22.5% or 0.7 PYE versus 28.4% or 1.0 PYE). This finding is also in keeping with the pharmcodynamic profile of postmeal (b) (4) where a higher 1- and 2-hour PPG was seen with postmeal (b) (4) compared to mealtime NovoLog.

(b) (4)

In conclusion, the pivotal trials demonstrated that (b) (4) achieved statistical noninferiority (clinically not unacceptably worse) in glycemic control compared to NovoLog when injected before a meal in patients with type 1 and type 2 diabetes mellitus meeting the regulatory standard approval. In fact, the point estimates of the change appeared similar. The data suggest that in T1DM (b) (4) may provide better

[1] Meal-related hypoglycemia was defined as occurring during first 1, 2, 4 and 6 hours after a meal
[2] BG confirmed hypoglycemia was defined as plasma glucose value <56 mg/dL with or without symptoms consistent with hypoglycemia

glycemic control when given premeal compared with NovoLog premeal, but given that there is only one Phase 3 study in T1DM a superiority claim is not verified. The results in T1DM subjects also showed that postmeal dosing of (b) (4) administered 20 minutes after start of a meal, led to non-inferior HbA1c reduction with a margin of 0.4%, although there was a larger 2-hour PPG increment and lower percentage of subjects achieved HbA1c targets with postmeal (b) (4) compared to mealtime NovoLog. The generalizability of the efficacy results and patient exposure was adequate in all trials, and the efficacy results across the pivotal trials can be reasonably applied to the U.S. population. Safety assessments were consistent with the known safety profile of insulin products. Therefore, the overall risk benefit for (b) (4) is favorable for approval.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended. There is no current Risk Evaluation and Mitigation Strategy (REMS) for NovoLog, and no safety concerns that would warrant REMS for (b) (4)

### 1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric study under Pediatric Research Equity Act (PREA) is recommended as this application triggers the PREA because of the change in dosing regimen.

The iPSP was agreed on August 28, 2015. The PSP was discussed at the PeRC meeting on August 24, 2016, and the PeRC agreed with the sponsor's plan for a partial waiver in patients 0 to <1 years of age with T1DM and patients 0 to <10 years of age with T2DM because the studies are impossible or highly impractical, and to the deferral in patients 1 to <18 years of age with T1DM and patients 10 to <18 years of age with T2DM. A Phase 3 efficacy and safety study in children and adolescents with T1DM is recommended as a postmarketing requirement.

Parenteral insulins are currently exempt from the requirement to conduct cardiovascular safety risk assessment studies. There is no safety concern based on the data in this application that suggests a cardiovascular risk with (b) (4)

## 2 Introduction and Regulatory Background

Novo Nordisk developed a new formulation of insulin aspart, with additional excipients that differs from the currently available insulin aspart formulation, NovoLog (U.S. trade name; global trade name is NovoRapid).

Division of Medication Error Prevention and Analysis (DMEPA) reviewed and concluded that the applicant's proposed trade name (b) (4) was conditionally acceptable on July 26, 2016. Therefore, in order to differentiate these two products with same active ingredient (i.e., insulin aspart), trade names will be used throughout this review to refer

to the currently available formulation (NovoLog) and new formulation of insulin aspart ((b) (4) It should be noted that the applicant referred to their insulin aspart as "faster aspart", and some of the applicant's tables and figures in this document may retain this name.

## 2.1 Product Information

Compared to the currently approved insulin aspart (NovoLog), this new formulation of insulin aspart ((b) (4) contains 2 addition excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride. Nicotinamide was added to increase the absorption of insulin aspart after administration, and L-arginine was added to stabilize the formulation.

Insulin aspart is an analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28, and is produced by recombinant DNA technology using *Saccharomyces cerevisiae* (baker's yeast).

The proposed indication for (b) (4) is to improve glycemic control in adults with diabetes mellitus (i.e., both T1DM and T2DM) and its intended use is for treatment of patients with diabetes mellitus both for basal-bolus therapy in combination with basal insulin (with or without OADs [oral antidiabetic drugs]) (b) (4) Also, (b) (4) is to be delivered intravenously by health care professionals. The applicant proposed that (b) (4) can be injected immediately before a meal and postmeal (within 20 minutes after starting a meal).

**Reviewer's comment: In support of intravenous administration, the applicant submitted stability data of (b) (4) when diluted in two types of intravenous infusion fluids (0.9% NaCl and 5% glucose) at concentrations of 0.5 U/mL and 1.0 U/mL (Section 1 of Module 3.2.P.8.3). OPQ concluded that (b) (4) is stable for 24 hours at room temperature post dilution.**

(b) (4) will be provided in a prefilled PDS290 pen-injector (3 mL) and in vials (10 mL) all with 100 U/ml insulin aspart. The prefilled device will have a dosage range of 1-80 units in increments of 1 unit.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The currently approved treatment of T1DM and T2DM include:

- Insulin and insulin analogs
- Sulfonylureas (SU)
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)

- Alpha-glucosidase inhibitors
- Glucagon-like peptide 1 (GLP-1) agonists
- Synthetic analogues of human amylin
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Bile acid sequestrant
- Dopamine agonists
- SGLT-2 inhibitors

## 2.3 Availability of Proposed Active Ingredient in the United States

NovoLog and (b) (4) have the same active ingredient, insulin aspart. NovoLog was approved for treatment of adult patients with diabetes mellitus on June 7, 2000, and subsequently approved for use in pediatric patients on September 13, 2005.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Two important safety issues arise with all insulin treatment: hypoglycemia and formation of insulin antibodies.

Hypoglycemia is the most common adverse event for insulin regimen. The severity of hypoglycemia can result in a range of impairment from temporary to permanent. The risk of hypoglycemia increases with increased intensive glycemic control. Refer to section 7.3.4 for discussion of hypoglycemia.

Exposure to insulin products may lead to formation of insulin antibodies. The formation of these antibodies may affect glycemic efficacy and require dose adjustment for glycemic control, or may affect safety and lead to increased incidence of allergic reactions. See section 7.4.6 for discussion of immunogenicity.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

| Date | Meeting |
|---|---|
| January 20, 2011 | IND Advice related to nonclinical and clinical development questions |
| March 2, 2011 | End of Phase 2 (EOP-2) Meeting (Meeting Minutes dated March 29, 2011): All aspects of clinical development program are discussed, including Phase 3 program; Agreement of non-inferiority margin of HbA1c at 0.4% was reached for post-prandial dosing of (b) (4) compared to premeal dosing of NovoLog; Agreement on the proposed number of exposed subjects (755 subjects) and duration of exposure (up to 6 months) in the proposed Phase 3a program to support the NDA submission |

| | |
|---|---|
| December 28, 2012 and April 25, 2013 | Follow-up correspondence to EOP-2: (b) (4) |
| September 12, 2013 | Type C Written Response to Cardiovascular Statistical Analysis Plan |
| December 11, 2013 | Type C Written Response to Pediatric Study Plan |
| July 17, 2014 | Type C Written Response regarding planned human factors and usability validation test protocol |
| July 28, 2014 | Type C Written Response regarding data standards for clinical and non-clinical data to be included in the NDA |
| December 16, 2014 | Type C Written Response regarding (b) (4) |
| May 1, 2015 | No agreement on the initial Pediatric Study Plan (iPSP) |
| June 22, 2015 | Pre-NDA Meeting (Meeting Minutes July 13, 2015), where the pooling strategy and presentation of safety data were agreed |
| July 24, 2015 | Follow-up advice on (b) (4) |
| July 28, 2015 | No agreement on the iPSP |
| August 28, 2015 | Agreement on the iPSP |

(b) (4)

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(b) (4)

## 2.6 Other Relevant Background Information

The applicant proposes to distinguish (b) (4) from NovoLog at the International Nonproprietary Names (INN), to ensure the safe use of these products because they believe that the unique PK and PD profiles of (b) (4) need differentiation in order to prevent prescribing errors and inadvertent substitution. Therefore, the applicant proposed the addition of a prefix to the INN insulin aspart, and proposed (b) (4) insulin aspart' as the proposed INN for (b) (4)

The nonproprietary name of (b) (4) and NovoLog reflects certain scientific characteristics of “insulin aspart”. A deviation from current nonproprietary naming for products approved under the FD&C Act is not warranted for (b) (4) at this time, and (b) (4) should be approved with the established name “insulin aspart” consistent with current nomenclature practices for products approved under the FD&C Act.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

The submission was well organized and information was easily found throughout the submission. The overall quality of submission was acceptable.

Clinical investigator site inspections were conducted at four domestic clinical sites as well as the applicant. The sites were chosen based on the OSI site selection tool, and there was enough domestic data to focus on domestic sites only. Two of the sites were chosen because they had never been previously inspected; Dr. Lucas was selected because she was the highest enroller in trial 3852 (32 subjects).

The site inspection of two clinical investigators revealed regulatory violations, and the remaining two clinical investigators revealed no regulatory violations. The regulatory deficiencies observed at two clinical sites (Drs. Lucas and Sandberg) are assessed to be unlikely to have a significant impact on the overall efficacy and safety data.

Please see the Clinical Inspection Summary dated August 15, 2016 by Dr. Cynthia Kleppinger for full details.

## 3.2 Compliance with Good Clinical Practices

The applicant stated that all trials were conducted according to Good Clinical Practice.

## 3.3 Financial Disclosures

Forms 3544 and 3545 for investigators involved in Phase 3 clinical trials used to establish (b) (4) efficacy were submitted in accordance with 21 CFR part 54 requirements.

Few investigators out of total investigators who participated in the Phase 3 programs had disclosable financial arrangements with the company as following:

- In trial 3852, 35 investigators had disclosable financial interests in FDA form 3455, and 3 investigators with certification of due diligence (FDA Form 3453, box 3);
- In trial 3853, 4 investigators had disclosable financial interests in FDA Form 3455, and 1 investigator with certification of due diligence (FDA Form 3453, box 3);
- In trial 4049, 3 investigators had disclosable financial interests in FDA Form 3455:
- (b) (4)
-

Bias was mitigated by conducting multi-center, multi-national trials. Some of these investigators contributed only a small proportion of total subjects for each trial. The potential for bias was further minimized through randomization, use of an objective endpoint (HbA1c), and use of all randomized and exposed population and the intent-to-treat principle for the primary analysis.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls (CMC)

For a detailed review of CMC, refer to review by the Office of Pharmaceutical Quality (OPQ) dated September 9, 2016 in Panorama which included the facility review/manufacturing inspection recommendation. OPQ recommends approval.

The divisions of CDRH-Devices, DMEPA and Human Factors also reviewed the pen injector device constituent as part of this application. (b) (4)

The drug substance is insulin aspart. The drug product is a clear and colorless solution containing the drug substance insulin aspart filled in 10 mL vial and in a 3 mL autoinjector cartridge assembled into prefilled pen injector. The prefilled pen injector has a range of 1 to 80 units adjustable in increments of 1 unit. Compared to NovoLog, two additional excipients, nicotinamide and L-arginine, are added. Both excipients are listed in the 'Inactive Ingredient Search for Approved Drug Products in products for injections' database from the US FDA. OPQ stated that the stability data provided in the application supported the compatibility of active ingredient with excipients and container closure components. The drug product is proposed for subcutaneous injection, (b) (4) or intravenous infusion.

The Drug Product Reviewer from OPQ reviewed the stability information available for the proposed product in vials and cartridges and granted an expiration period of 30 months when stored at 2-8 °C for the finished product in vials and in prefilled pen, with an in-use period of up to 28 days at room temperature (below 86 °F [30 °C]) after first use.


OPQ evaluated the submitted information regarding the compatibility of (b) (4) in intravenous (IV) infusion bags, and concluded that the product is table for 24 hours at room temperature after dilution.

All clinical trials in the development program used the final to-be-marketed formulation of (b) (4)

## 4.2 Clinical Microbiology

For detailed review of microbiology, refer to the review by Dr. Koushik Paul dated July 25, 2016 in Panorama. Dr. Paul recommended approval of this NDA. Based on her review of (b) (4), she concluded that the proposed (b) (4) level was adequate (b) (4). Microbiology issues related to CMC are also discussed in section 4.1.

## 4.3 Preclinical Pharmacology/Toxicology

For a detailed review of the Preclinical Pharmacology/Toxicology, refer to Dr. Miyun Tsai-Turton's review dated August 28, 2016 and September 20, 2016. Dr. Tsai-Turton recommends approval of this NDA.

The nonclinical development for (b) (4) relied upon the nonclinical program conducted to support NovoLog (NDA 020986) as well as literature review of two additional excipients (nicotinamide and L-arginine), pharmacokinetic studies of (b) (4) formulations in pigs, and local tolerance studies. No additional toxicity studies were conducted for (b) (4)

Local tolerance studies for (b) (4) was done in rat, rabbit, and minipigs models, and no safety concern was identified.

Dr. Tsai-Turton's concluded that her review of available literature supports the safe use of nicotinamide and L-arginine as excipients at the levels contained in (b) (4) formulation for chronic subcutaneous administration in humans. The drug substance-related impurity profiles were determined to be comparable between (b) (4) and NovoLog. One excipient-related impurity ( (b) (4) and two leachabels of (b) (4) were not determined to pose a safety risk to humans per ICH guidances.

Dr. Tsai-Turton further evaluated (b) (4)

## 4.4 Clinical Pharmacology

A detailed review of clinical pharmacology is being conducted by Dr. Shalini Wickramaratne Senarath Yapa. The Office of Clinical Pharmacology recommends a Complete Response for deficiencies related to inadequacy of the assay used in the Clinical Pharmacology studies. See her review dated September 8, 2016 for details.

### 4.4.1 Mechanism of Action

(b) (4) like endogenous insulin and other insulin analogues, acts through binding to insulin receptor to regulate glucose metabolism. (b) (4) lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and inhibits hepatic glucose production.

### 4.4.2 Pharmacodynamics

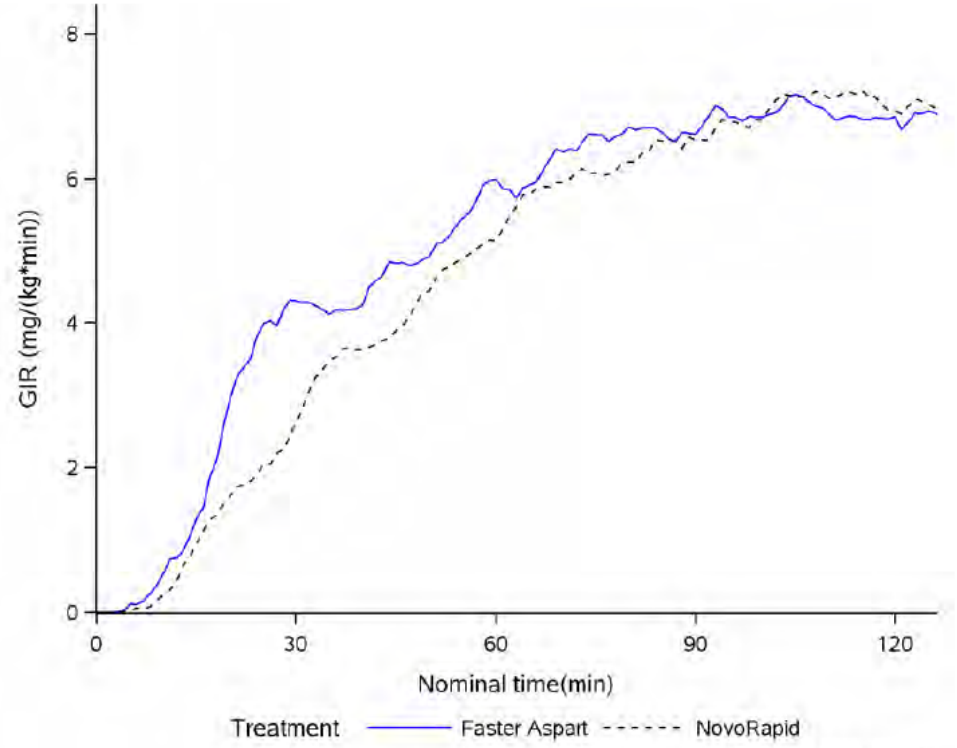
The information in this section is obtained from the applicant's summary.

<u>During Euglycemic Clamp</u>

The euglycemic clamp studies, with the exception of trial 3918, were all done at the same clinical research organization at Profil, Neuss, Germany.

The glucose infusion rate (GIR) was collected in trials 3887, 3891, and 3987. The mean GIR profiles for the first 2 hours in the pooled analysis are shown in Figure 1 below.

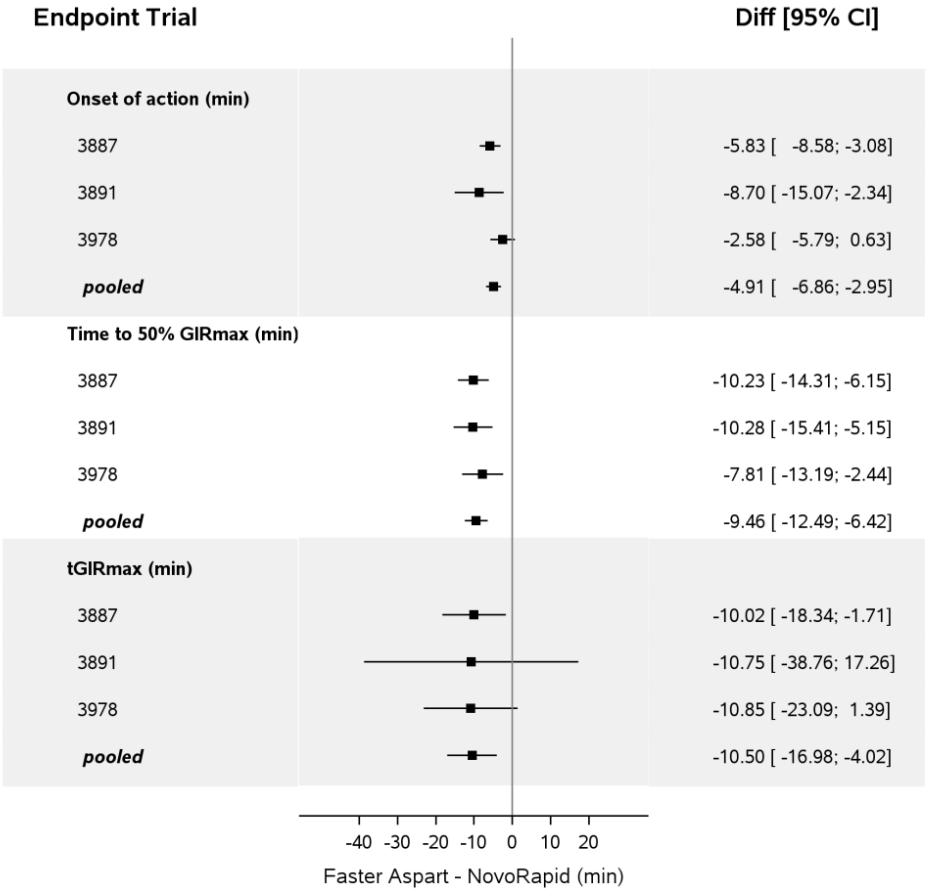
**Figure 1: Mean GIR Profiles (0-2 hours) in Adults with T1DM in the Pooled Analysis (0.2 U/kg, Trials 3887, 3891, and 3978)**




Source: Summary 2.7.2, Figure 3-12

In the pooled analysis, the estimated onset of action was about 5 minutes earlier and time to 50% $C_{max}$ was about 9.5 minutes earlier with (b) (4) compared to NovoLog (Figure 2).

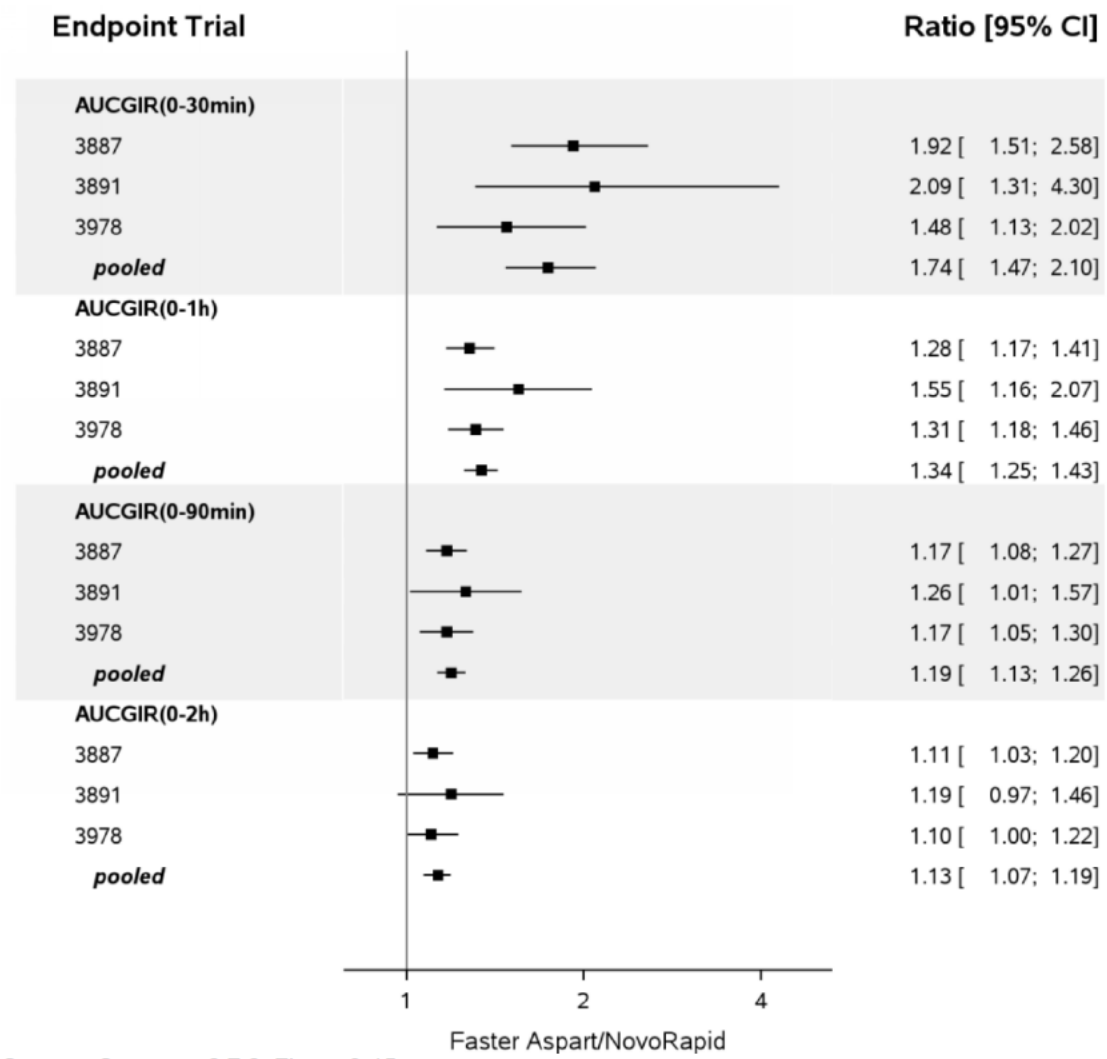
**Figure 2: Mean Treatment Difference and 95% CI for Onset of Glucose-Lowering Effect in Adults with T1DM in Individual Trials and Pooled Analysis (0.2 U/kg)**




Source: Summary 2.7.2, Figure 3-14

Similarly, the glucose-lowering effect with (b) (4) compared to NovoLog was most pronounced during the first 30 minutes, as shown in Figure 3.

**Figure 3: Mean Treatment Ratios and 95% CI for Early Glucose-Lowering Effect ($AUC_{GIR}$) in Adults with T1DM in Individual Trials and Pooled Analysis (0.2 U/kg)**




Source: Summary 2.7.2, Figure 3-15

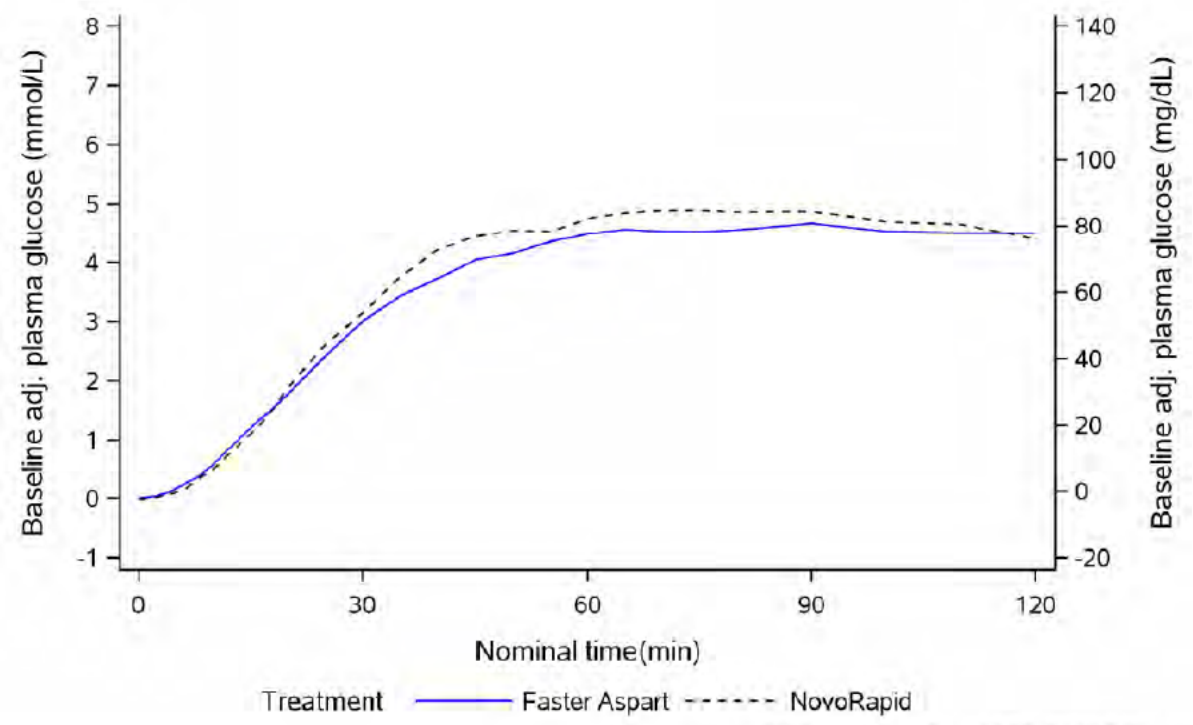
The total ($AUC_{GIR, 0\text{-}12h}$) and maximum glucose-lowering effect ($GIR_{max}$) were comparable between (b) (4) and NovoLog both in individual trials and in the pooled analysis.

Meal Test – Immediately before the meal

Trials 3889 (b) (4) evaluated the PD properties of (b) (4) and NovoLog after single subcutaneous injection (0.2 U/kg) immediately before a standardized meal in adults with T1DM. (b) (4)

In trial 3889, the plasma glucose parameters were not statistically different between (b) (4) and NovoLog (Figure 4). The estimated mean PPG increment during 2 hours after subcutaneous administration was 64.08 mg/dL for (b) (4) and 67.51 mg/dL for NovoLog.

**Figure 4: Trial 3889 – Mean Baseline-Adjusted Plasma Glucose Profiles (0-2 hours) in Adults with T1DM**




Source: Summary 2.7.2, Figure 3-17

(b) (4)

The pivotal Phase 3 trial 3852 also included a meal test in a standardized setting in which the dose (0.1 U/kg) and meal were standardized. See section 6.1.4.2 for postprandial glucose results after a standard meal in trial 3852.

**Reviewer's comments: These PD results during a meal test suggest that despite faster onset and greater early exposure with (b) (4) the PK differences may not translate into meaningful clinical differences in glucose effect with (b) (4) compared to NovoLog.**

Table 1 provides a summary of the treatment difference in post-prandial glucose in clinical pharmacology trials (b) (4), 3889), larger Phase 3 trial (3852) (b) (4) . The treatment differences in plasma glucose levels over 2 hours during a meal test were shown to statistically improve in trials 3852 (b) (4) but not in clinical pharmacology trials despite a trend favoring (b) (4).

**Table 1: Summary of Treatment Difference for Mean PPG Increment Over 1 and 2 Hours in Adults with T1DM During Meal Test in trials (b) (4) 3889, (b) (4) and 3852**

| Trial | Number of subjects | | Mean PPG increment over 1 hour | Mean PPG increment over 2 hours |
|---|---|---|---|---|
| | Faster aspart | NovoRapid® | Faster aspart – NovoRapid® | Faster aspart – NovoRapid® |
| (b) (4) | | | | |
| 3889 | 35 | 36 | -0.19 mmol/L [-0.57; 0.20]<br>-3.43 mg/dL [-10.29;3.61] | -0.19 mmol/L [-0.77; 0.39]<br>-3.43 mg/dL [-13.9; 7.04] |
| (b) (4) | | | | |
| 3852[a] | 353 | 350 | -1.18 mmol/L [-1.65; -0.71]<br>-21.3 mg/dL [-29.78;-12.82] | -0.67 mmol/L [-1.29; -0.04]<br>-12.09 mg/dL [-23.28; -0.72] |

**Note:** NovoRapid® is known as NovoLog® in the U.S. [a] For trial 3852, the change at 1 and 2 hours is the 1 and 2 hour PG increment

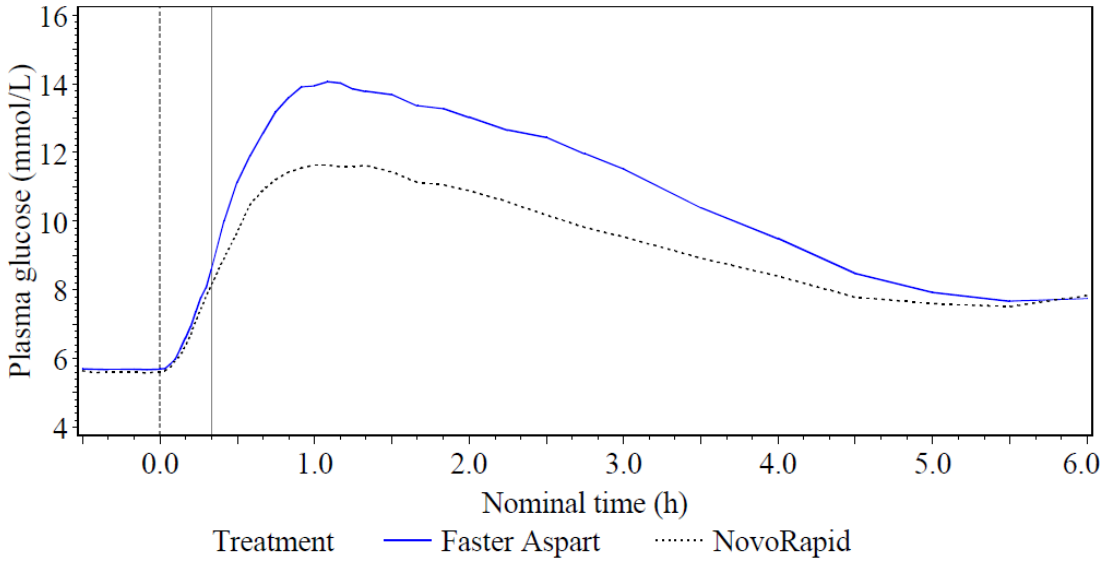
Source: Summary 2.7.2, Table 3-20

Meal Test – Postmeal

Trial 3921 compared the PK and PD properties of (b) (4) when given postmeal (i.e., 20 minutes after start of a standardized meal), compared to NovoLog when given premeal (i.e., immediately before a standardized meal) in adults with T1DM. The insulin dose was 0.2 U/kg.

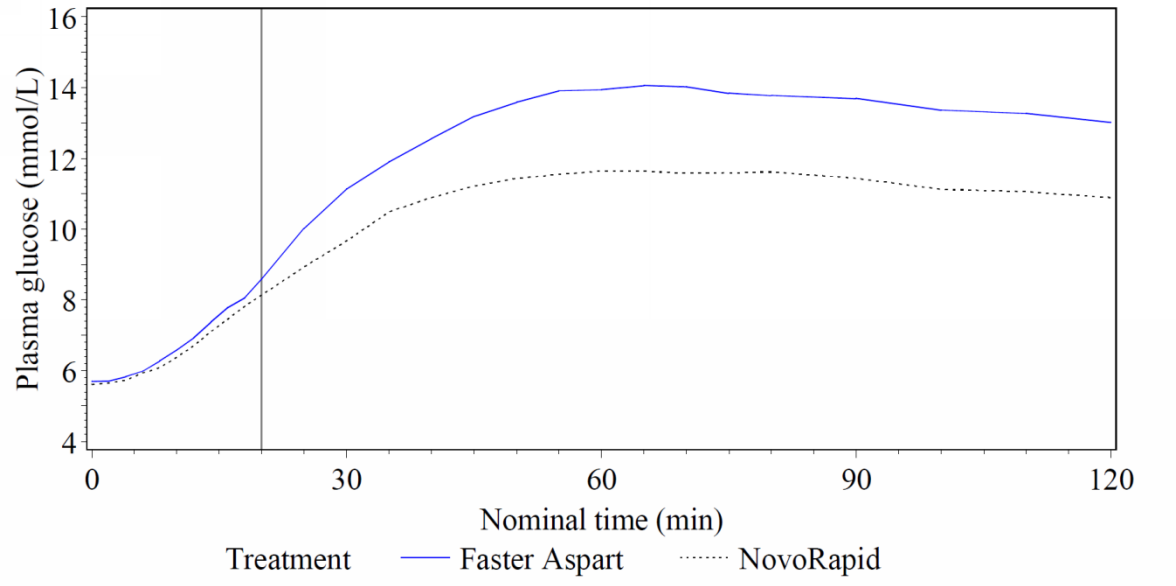
The mean plasma glucose profiles for postmeal (b) (4) was higher than premeal NovoLog for 0 to 6 hours (see Figure 5) and 0 to 2 hours (see Figure 6).

**Figure 5: Trial 3921 – The Plasma Glucose Mean Profiles (0-6 hours; mmol/L) with Last Observation Carried Forward – Full Analysis Set**




Source: CSR 3921, Figure 11-4

**Figure 6: Trial 3921 – The Plasma Glucose Mean Profiles (0-2 hours; mmol/L) with Last Observation Carried Forward – Full Analysis Set**

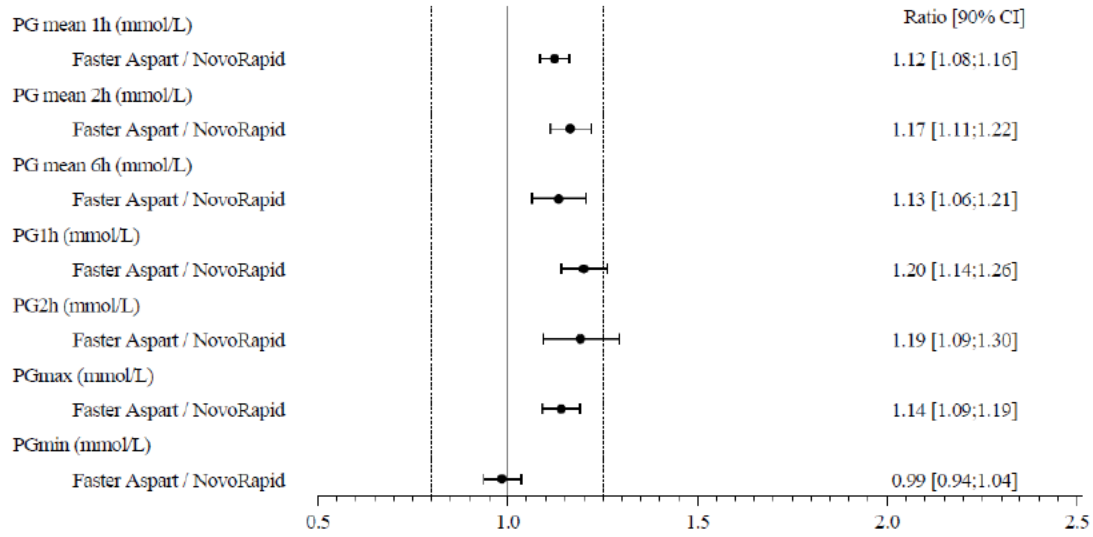



Source: CSR 3921, Figure 14.2.7

The glucose lowering effect was smaller for postmeal (b) (4) compared to premeal NovoLog during the 6 hour meal test. The mean plasma glucose concentration from 0-

6 hours after standardized meal was 13% higher with postmeal (b) (4) compared to premeal NovoLog (treatment ratio 1.13 [95% CI: 1.06;1.21]). Similar results are seen during the first hour and over 2 hours after standardized meal; see Figure 7 for summary of results.

**Figure 7: Trial 3921 – Plot of Results of Statistical Analyses of Pharmacodynamic Endpoints**




The vertical dashed lines indicate the levels 0.8 and 1.25

Source: CSR 3921, Figure 11-5

In trial 3852, the estimated treatment difference in the change from baseline in 1-hour PPG increment at Week 26 was statistically significant favoring mealtime NovoLog compared to postmeal dosing of (b) (4) (22.87 mg/dL versus 6.12 mg/dL; treatment difference of 16.75 mg/dL [95% CI: 8.26;25.24]). The results of trial 3852 are further described in section 6.1.4.2.

(b) (4)


### 4.4.3 Pharmacokinetics

Nicotinamide was included in this formulation of (b) (4) to increase the absorption leading to earlier exposure of insulin aspart.

Insulin aspart has a low binding affinity to plasma proteins (<10%). In the pooled analysis of clinical pharmacology trials, the mean terminal half-life of (b) (4) after subcutaneous administration was 57 minutes and was comparable to NovoLog. The median terminal half-life of (b) (4) after intravenous administration was about 10 minutes in trial 3949. The volume of distribution after IV administration was 0.22 L/kg in trial 3949, corresponding to extracellular fluid volume in the body.

Trial 3949 showed that the absolute bioavailability of insulin aspart after subcutaneous administration of (b) (4) in the abdomen, deltoid, and thigh was about 80%. The median onset was about 3 minutes and the median $t_{max}$ was 50-57.5 minutes after subcutaneous injection in abdomen, deltoid, and thigh. The total exposure was also comparable after subcutaneous injection in these three different regions; however, the maximum insulin aspart concentration ($C_{max}$) and the initial insulin exposure (AUC during 1st and 2nd hours) was comparable for abdomen and deltoid but slightly lower for thigh compared to both abdomen and deltoid. The mean glucose infusion rate (GIR) profiles were in similar range after subcutaneous administration of (b) (4) in the

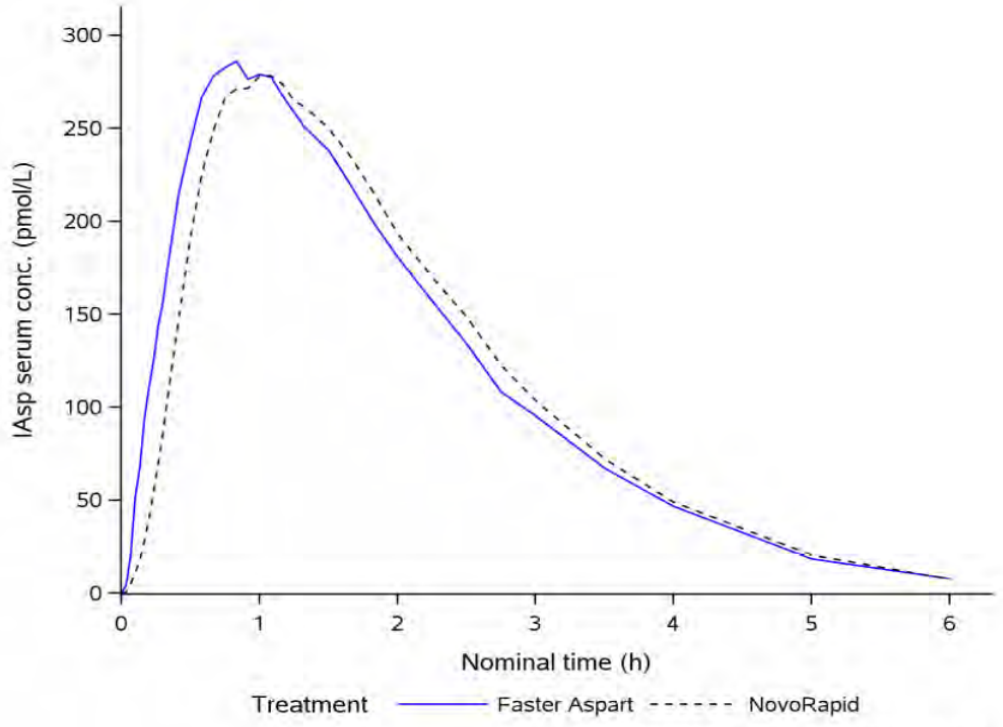
abdomen, deltoid, and thigh, although $GIR_{max}$ and $AUC_{GIR,0-12h}$ was slightly higher after abdomen administration.

**Reviewer's comments: The results of study 3949 support subcutaneous administration of (b) (4) in the abdomen, deltoid, or thigh.**

After single subcutaneous injection

The pooled PK analysis included clinical pharmacology trials 3887, (b) (4) 3889, 3891, 3921, and 3978. The pooled PK profile show left shift of (b) (4) compared to NovoLog, and crossing at about 60 minutes (Figure 9).

**Figure 9: Mean Insulin Aspart Profiles (0-6 hours) for Adults with T1DM in the Pooled Analysis (0.2 U/kg)**

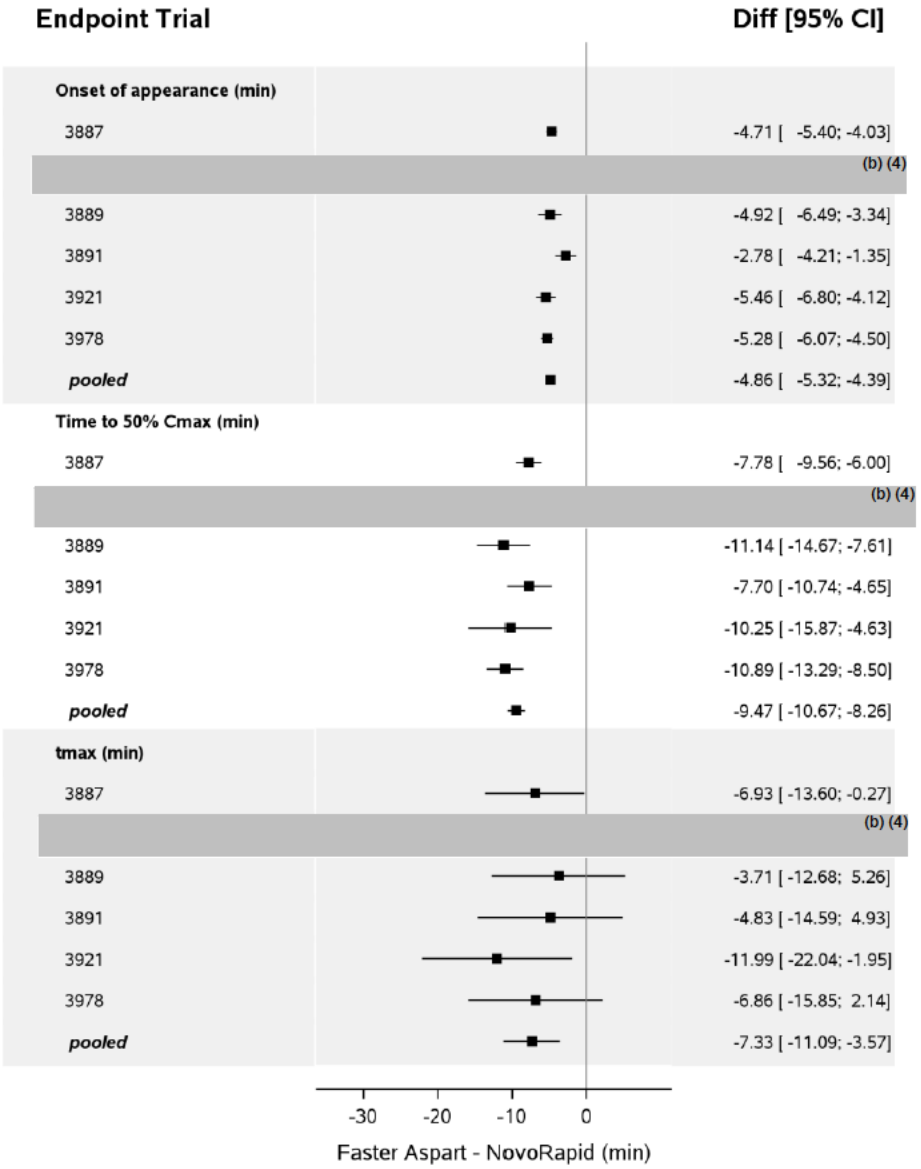



Source: Summary 2.7.2, Figure 3-3

The mean onset of insulin aspart ranged between 3.1 and 5.5 minutes with (b) (4) and between 5.9 and 12.3 minutes with NovoLog in individual trials. In the PK pooled analysis, insulin aspart appeared in the circulation about 4 minutes after administration of (b) (4) compared to about 9 minutes with NovoLog, and was **about 5 minutes earlier compared to NovoLog**.

The estimated time to reach 50% of the maximum serum insulin aspart concentration (time to 50% $C_{max}$) ranged between 18.9 and 26.3 minutes with (b) (4) and 26.6 and 37.0 minutes with NovoLog in individual trials. In the PK pool, **time to 50% $C_{max}$ was about 9.5 minutes earlier with** (b) (4) (22.6 minutes versus 32.1 minutes). The time to reach the maximum serum insulin aspart concentration ($t_{max}$) was 7.3 minutes earlier with (b) (4) (62.4 minutes) compared to NovoLog (69.8 minutes).

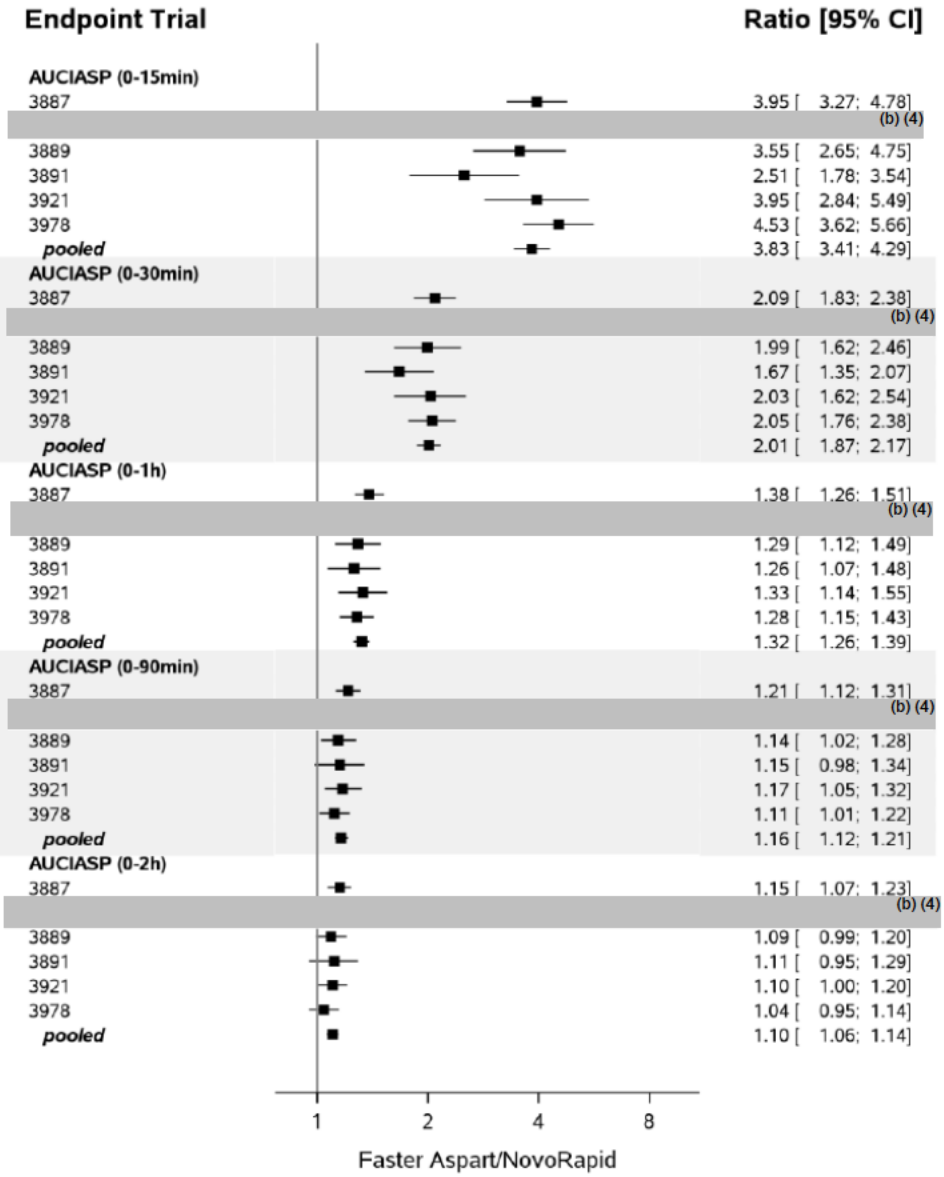
**Figure 10: Mean Treatment Difference and 95% CI for Onset of Insulin Exposure in Adults with T1DM in Individual Trials and Pooled Analysis (0.2 U/kg)**




Source: Summary 2.7.2, Figure 3-4

In the pooled analysis, the insulin aspart exposure during the first 30 minutes ($AUC_{IAsp, 0-30 min}$) was two times larger with (b) (4) compared to NovoLog; the estimated treatment ratio for $AUC_{IAsp, 0-30 min}$ was between 1.67 and 2.47 in the individual trials and 2.01 (95%CI: 1.87;2.17) in the pooled analysis. The largest insulin aspart exposure with (b) (4) compared to NovoLog was seen during the first 15 minutes and appeared to diminish after 1 hour, as shown in Figure 11.

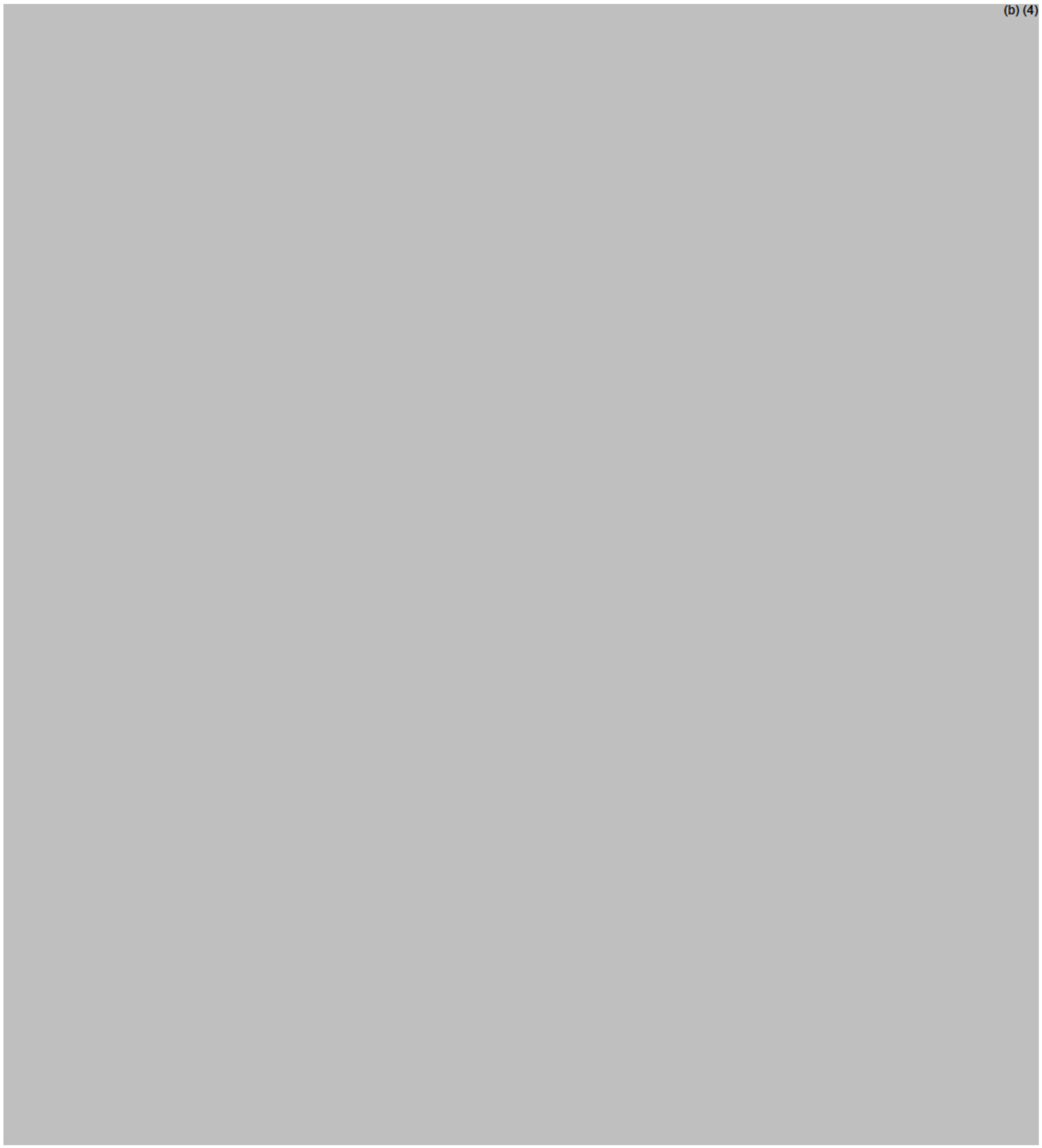
**Figure 11: Mean Treatment Ratios and 95% CI for Insulin Aspart Exposure ($AUC_{IAsp}$) in Adults with T1DM in Individual Trials and Pooled Analysis (0.2 U/kg)**




Source: Summary 2.7.2, Figure 3-5

The total insulin aspart exposure and maximum insulin levels were comparable between (b) (4) and NovoLog. The mean terminal half-life was similar between (b) (4) (57 minutes) and NovoLog (58 minutes).

(b) (4)



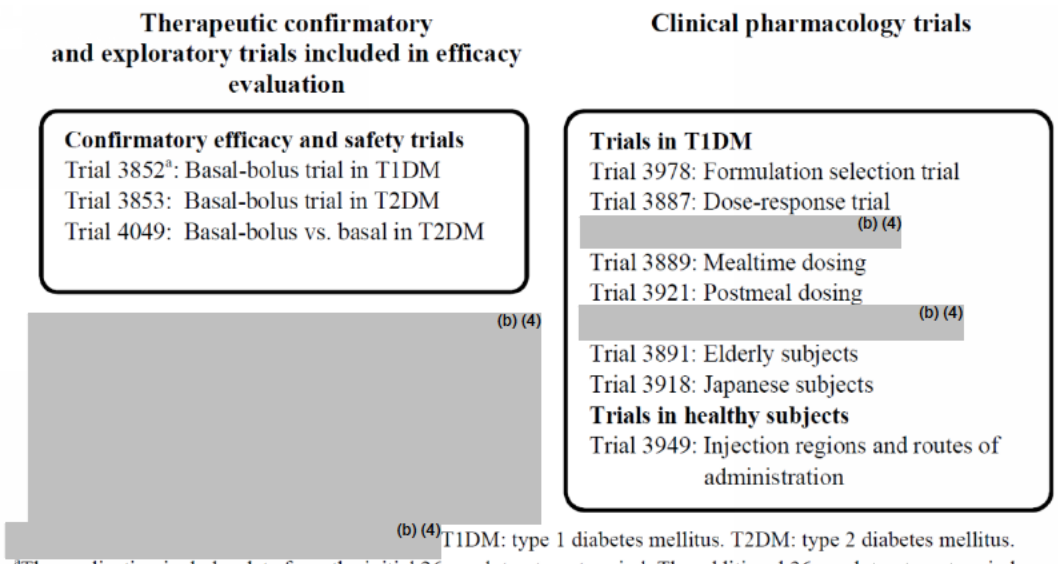
(b) (4)

# 5 Sources of Clinical Data

All trials were completed but the extension phase of the double-blind mealtime treatment groups from one Phase 3 trial (3852) was still ongoing. The data cut-off date for the NDA submission was March 10, 2015.

## 5.1 Tables of Studies/Clinical Trials

The clinical development program of this NDA included 9 clinical pharmacology trials, 3 Phase 3 trials (1 in T1DM and 2 in T2DM), and two CSII trials as following:




T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus.
[a]The application includes data from the initial 26-week treatment period. The additional 26-week treatment period was ongoing at the time of the cut-off date for the clinical trials (10th March 2015).

Source: SCE, Figure 1-1

All the clinical pharmacology studies were conducted with to-be-marketed formulation of (b) (4) Although study 3978 (b) (4) studied both the final formulation and an exploratory formulation of (b) (4) only results related to the final formulation will be discussed in this review.

In addition, the pivotal Phase 3 study 3852 included population PK analyses, and Phase 3 study 3852 (b) (4) included pharmacodynamic (PD) analyses during a standardized meal test.

It should be noted that T1DM trial 3852 assessed primary and secondary confirmatory endpoints after 26-weeks of treatment period, after which two treatment arms (mealtime (b) (4) and mealtime NovoLog) continued an additional 26 week treatment period for collection of longer-term safety data. The additional 26-week extension period was ongoing at the cut-off date for this application (March 10, 2015) and therefore not included in this application. Of note, the sponsor stated that all subjects in the mealtime (b) (4) and mealtime NovoLog arms consented to the full 52 weeks trial at the time of study entry.

**Reviewer's comment: At the EOP2 and pre-NDA Meetings, we agreed that the duration of exposure in the proposed 3a program of up to 6 months are sufficient to support NDA submission.**

## 5.2 Review Strategy

This review will mainly evaluate and discuss the efficacy findings from two pivotal Phase 3 trials (3852 in T1DM and 3853 in T2DM), one supportive Phase 3 trial (4049), (b) (4)

For efficacy review, the primary and confirmatory secondary endpoints are mainly discussed in section 6. Supportive secondary endpoints such as proportion of subjects reaching HbA1c targets, changes in insulin dose, FPG, and body weight are included in the efficacy section as they are clinically relevant secondary endpoints. Other secondary endpoints (e.g., SMPG profiles, interstitial glucose in continuous glucose monitoring, 1,5-anhydroglucitol) are not further discussed in this review as these results are considered exploratory.

(b) (4)

## 5.3 Discussion of Individual Studies/Clinical Trials

The clinical development program for (b) (4) included two confirmatory trials (3852 in T1DM and 3853 in T2DM), with the primary objective of confirming the glycemic efficacy and safety of (b) (4) compared to NovoLog in a basal-bolus regimen; trial 3852 also had an objective of comparing the glycemic efficacy of postmeal (b) (4) compared to

mealtime NovoLog. Trial 4049 compared the glycemic efficacy and safety of adding mealtime (b) (4) in basal-bolus therapy versus basal therapy alone, both in combination with metformin. (b) (4)

Study Drug and Devices: In three Phase 3 trials (i.e., 3852, 3853, and 4049), 100 U/mL solutions of (b) (4) and NovoLog were provided in identical disposable 3 mL PDS290 pen-injector devices and administered subcutaneously in the abdomen. The basal insulin in each trial was also 100 U/mL solution for subcutaneous injection provided in an appropriate 3 mL pen injection and administered in thigh or upper arm. The injection sites were different for basal and bolus administration to assess injection site reactions relevant for each insulin type.

(b) (4)

The to-be-marketed formulation of (b) (4) was used in all clinical trials.

Statistical Considerations applicable to all trials: Analysis Sets: The efficacy evaluations for all trials were done on the full analysis set (FAS), and completers analysis set and per protocol analysis set was used for sensitivity analyses. The analysis sets for trials were defined as following:

- **Full Analysis Set (FAS)** includes all randomized subjects, 'as randomized';
- **Per Protocol (PP) analysis set** includes all randomized subjects in FAS who did not violate any inclusion/exclusion criteria, did not participate in other clinical trials during trial, have an HbA1c measure at screening/randomization, have at least 12 weeks of actual exposure, and have at least one HbA1c measurement after 12 weeks of exposure, 'as treated' (note: for trial 4049, the minimal exposure requirement of "for more than 12 weeks" was removed because the treatment period of this trial was only 18 weeks);
- **Completer analysis set** includes all subjects who completed the trial, 'as randomized' for further sensitivity analysis of the primary endpoint;
- **Sensitivity analysis set** includes all subjects selected for sensitivity analysis for the meal test 'as randomized', who consumed the full amount of liquid meal in 12 minutes, were fasting, did not receive rescue medication during first 2 hours of meal test, did not experience a severe or BG confirmed hypoglycemic episodes on the same day as the meal test before start of the meal, continued study drug and did not receive non-trial insulin product, and the actual bolus dose did not deviate from the planned bolus dose by more than 1 U if the actual dose is ≤10 U or by more than 10% from the planned dose if actual bolus dose I >10 U;

- **Safety analysis set (SAS)** comprises all subjects receiving at least one dose of study drug, 'as treated'.

### 5.3.1 Trial 3852 – T1DM

Title: Efficacy and Safety of FIAsp Compared to NovoLog Both In Combination with Insulin Detemir in Adults with T1DM (Note: Applicant had used "FIAsp" as abbreviation for (b) (4)

Design: This was a 26-week (plus additional 26 weeks), randomized, multicenter, multinational, active-controlled, parallel group, basal bolus trial in 1143 adults with T1DM to compare the efficacy and safety of mealtime (b) (4) and mealtime NovoLog, both in combination with once or twice daily insulin detemir in a double-blind basal-bolus regimen. Mealtime (b) (4) and mealtime NovoLog were to be administered 0-2 minutes before main meals. The trial also included a 26-week open-label postmeal (b) (4) treatment arm (to be administered 20 minutes after start of the meal) with once or twice daily insulin detemir.

After screening, eligible subjects switched their basal insulin to insulin detemir and their bolus insulin to NovoLog, both on a unit-to-unit basis, and underwent 8-week run-in period. Subjects also received reinforced diabetes training on carbohydrate counting during the run-in period.

After the run-in period, subjects were randomized in 1:1:1 ratio to three treatment arms, to either blinded mealtime (b) (4) blinded mealtime NovoLog, or open-label postmeal (b) (4) all in combination with once or twice daily insulin detemir. Randomization was stratified based on method for adjusting bolus insulin (principles of flexible dosing based on meal carbohydrate content or using predefined bolus dosing algorithm), current basal treatment regimen (once or twice daily dosing), and whether the subject participated in the CGM and frequently sampled meal test subgroup (yes or no).

The primary efficacy and safety analyses were conducted after initial 26 weeks of treatment period, after which subjects in the two mealtime treatment arms (double-blind mealtime (b) (4) and mealtime NovoLog) continued for an additional 26 week treatment period for further collection of safety data. Of note, the 26 week extension period is still ongoing at the time of the cut-off date for this NDA submission.

Key Inclusion Criteria:
- Female or male adults with clinically diagnosed T1DM ≥12 months;
- BMI ≤35 kg/m$^2$;
- Currently treated with basal-bolus insulin regimen for ≥12 months and a basal insulin analogue (either insulin detemir or insulin glargine) for ≥4 months;
- HbA1c 7.0-9.5% both inclusive; one week before randomization, subjects must have HbA1c ≤9.5%.

Key Exclusion Criteria:

- Use of any anti-diabetic drug other than insulin for past 3 months;
- Anticipated change in concomitant drug known to interfere significantly with glucose metabolism (corticosteroids, beta blockers, monoamine oxidase inhibitors or anti-obesity drugs);
- Cardiovascular disease within past 6 months, systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg;
- Impaired liver function or impaired renal function (serum creatinine ≥2 mg/dL);
- Recurrent severe hypoglycemia (more than once past 12 months) or hypoglycemic unawareness, or hospitalization for diabetic ketoacidosis past 6 months;
- Proliferative retinopathy or maculopathy requiring treatment;
- Female of childbearing potential who is pregnant, breast-feeding, or intend to become pregnant, or is not using adequate contraception methods.

Insulin Dosing and Titration:

At the run-in visit, subjects were given a blood glucose (BG) meter and instructed on the use of glucometer device including regular calibration. Only the BG meter provided by the applicant was to be used to measure the values in the diary during the trial. The BG meter used test strips calibrated to plasma values, and these were values used for dose adjustments and recorded in the diary by the subject. The 4-point SMPG profiles were recorded for insulin titration purposes. The 7- and 9-point profile were used as part of supportive efficacy analysis; subjects were to do 7-9-7 point profile on 3 consecutive days before Baseline, Week 12, and Week 26 visits.

From the start of the 8-week run-in period, subjects were instructed to report the date and breakfast, lunch, and main evening meal insulin bolus doses on a daily basis in the diary they were given. The actual time from previous meal was also collected for extra insulin boluses along with the reason for the extra dose. Subjects reported the dose of basal insulin 3 consecutive days before scheduled visits/phone contacts along with the date and actual time point in the diary. For subjects using flexible principles of bolus dosing, the insulin:carbohydrate ratio and insulin sensitivity factor were collected.

*Basal insulin:* At the beginning of run-in period, subjects were switched unit-to-unit from their previous basal insulin analogue to insulin detemir (Levemir, 100 U/mL) at the dosing frequency (once or twice daily) used before study entry. Insulin detemir was to be injected subcutaneously in the thigh or upper arm (deltoid). During the run-in period, insulin detemir was titrated in a treat-to-target approach on a weekly basis to the pre-breakfast glycemic target of 71-90 mg/dL (and pre-dinner target of 71-108 mg/dL if on a twice daily regimen). Changing the dosing frequency of insulin detemir (once or twice daily) was allowed during the run-in period but not after randomization; after randomization, adjustment of basal dose could be made when needed (e.g., for safety)

but changing the dosing frequency of basal insulin after randomization was not allowed and was a reason for withdrawal.

*Bolus insulin:* At the beginning of run-in period, subjects switched to mealtime NovoLog (100 U/mL, injected subcutaneously into the abdominal wall) unit-to-unit from previous mealtime doses and continued to use the same method for adjustment of bolus insulin as they did before trial. No adjustment of bolus insulin dose was to be done during the run-in period unless for safety.

At randomization, subjects were switched on a unit-to-unit basis from NovoLog to the blinded bolus insulin treatment ((b) (4) or NovoLog) to be administered either mealtime (0-2 minutes before each main meal) or postmeal (20 minutes after start of the meal; (b) (4) only in the open-label arm). Additional bolus doses were allowed if necessary.

Subjects who were considered adequately trained during the run-in period to do flexible bolus adjustments based on the carbohydrate content of their meals were able to continue to do so after randomization. The subjects who were not proficient with carbohydrate counting used predefined bolus dosing algorithms to adjust their bolus doses twice a week during the treatment period. The bolus insulin was titrated to preprandial or bedtime SMPG target of 71-108 mg/dL at the subsequent meal or bedtime (for dinner dose) in a treat-to-target approach. Bolus dose titration was done twice weekly based on SMPG values measured during previous 3-4 days (-1 unit if ≥1 SMPGs below target; no change if 0-1 SMPG above target or no SMPGs below target; +1 unit if ≥2 SMPGs above target or no SMPGs below target).

Insulin titration was monitored and titration deviations were reviewed by the titration surveillance consultants from applicant in an unbiased manner.

Meal test: A standardized meal test was done at baseline (Week 0) and Week 26 for PPG measurement over 1, 2, 3, and 4 hours after meal ingestion. Fasting subjects received a standardized carbohydrate-rich liquid meal in the morning containing about 80 g of carbohydrates, which was to be consumed as quickly as possible and within 12 minutes.

At Week 0, all subjects received NovoLog 0-2 minutes before consumption of a meal. At Week 26, subjects received randomized treatment of either mealtime (b) (4) postmeal (b) (4) (20 minutes after start of a meal), or mealtime NovoLog. The bolus insulin administered was 0.1 U/kg body weight for all subjects at both meal tests.

Sites: A total of 169 sites screened subjects and 163 sites randomized subjects in 9 countries across North America and Europe.

Withdrawal Criteria: Subjects who withdrew or dropped out underwent a complete follow-up visit and were not followed any further. Subjects were withdrawn for following key criteria:

- Initiation or change of treatment with any anti-diabetic (other than study drug) or anti-obesity drugs, or any systemic treatment that could interfere with glucose metabolism;
- Change in insulin detemir dose frequency after randomization;
- Change in method of bolus insulin adjustment after randomization;
- Hypoglycemia or hyperglycemia during treatment period posing safety problem;
- Substantial and repeated non-compliance with study procedures;
- Pregnancy or intention of becoming pregnant;

Endpoints: The primary efficacy endpoint was the change in HbA1c from baseline to the end of treatment period (Week 26). The change from baseline in 2-hour PPG increment after the standardized meal was a confirmatory secondary endpoint. The change in body weight from baseline to end of treatment was another confirmatory secondary endpoint.

The number of treatment-emergent severe or BG confirmed hypoglycemic episodes (defined as subjects as unable to treat self and/or have a recorded plasma glucose value <56 mg/dL) during treatment period (0 to 26 weeks) was included as a confirmatory secondary endpoint as part of the stepwise hierarchical testing procedure (see below).

Statistical Methods: The primary objective was to establish the **non-inferiority** of **mealtime** (b) (4) compared to mealtime NovoLog, both in combination with basal insulin, by assessing the change from baseline to Week 26 in HbA1c with a margin of 0.4%. Therefore, non-inferiority was considered to be established if the upper bound of the 2-sided 95% CI for the estimated treatment difference for the mean change in HbA1c was ≤0.4%.

**Reviewer's comment: This was agreed upon at the End-of-Phase 2 Meeting.**

After the primary objective was met, a stepwise hierarchical testing procedure was used to control for type 1 error for confirmatory secondary endpoints as following, after 26 weeks of treatment period:

- Step 2: The **superiority** of **mealtime** (b) (4) versus mealtime NovoLog in the change from baseline in 2-hour PPG increment;
- Step 3: The **non-inferiority** of ***postmeal*** (b) (4) versus mealtime NovoLog in the change from baseline in HbA1c;
- Step 4: The superiority of **mealtime** (b) (4) versus mealtime NovoLog in the number of severe or BG confirmed hypoglycemic episodes;

- Step 5: The superiority of **mealtime** (b) (4) versus mealtime NovoLog in the change from baseline in body weight;
- Step 6: The superiority of ***postmeal*** (b) (4) versus mealtime NovoLog in the number of severe or BG confirmed hypoglycemic episodes.
- Step 7: The superiority of ***postmeal*** (b) (4) versus mealtime NovoLog in the change from baseline in body weight.

The primary endpoint was analyzed using mixed-effect model for repeated measurements (MMRM), a statistical model that assumes that the missing data is missing at random. Continuous endpoints which were measured at visits between baseline and end of treatment were analyzed using MMRM model, which included treatment, region, and strata as fixed effects, subjects as a random effect, baseline measure as a covariate and interactions between all fixed effects and visit and between covariate and visit.

Continuous endpoints that only measured at baseline and end of treatment only such as change in 1-4h PPG increment, were analyzed using an analysis of variance (ANCOVA) model including treatment, region and strata as factors and with endpoint at baseline as a covariate. Dichotomous endpoints were analyzed using logistic regression model using treatment, region and strata as factors, and endpoint at baseline as a covariate.

The number of treatment-emergent severe or BG confirmed hypoglycemic episodes from baseline to end of treatment was analyzed using a negative binomial regression model with a log-link function, and the logarithm of time period in which a hypoglycemic episode was considered treatment-emergent as offset, including treatment, region and strata as factors.

Descriptive statistics of basal and bolus insulin doses was based on the safety analysis set.

### 5.3.2 Trial 3853 – T2DM

Title: Efficacy and Safety of FIAsp Compared to Insulin Aspart in Combination with Insulin Glargine and Metformin in Adults with Type 2 Diabetes

Design: This was a 26-week, randomized, double-blind, parallel-group, active-controlled basal-bolus trial in 689 subjects with T2DM on a pretrial basal + OAD regimen for ≥6 months. The trial compared the efficacy and safety of mealtime (b) (4) versus mealtime NovoLog, both administered immediately before (0-2 minutes) main meals, and both in combination with once daily insulin glargine and metformin in a basal-bolus regimen.

After screening, eligible subjects underwent an 8-week run-in period where all OADs other than metformin were discontinued and basal insulin treatment was optimized

using a treat-to-target approach (pre-breakfast SMPG glycemic target of 71-90 mg/dL) on a weekly basis.

After the run-in period, subjects were randomized in a 1:1 ratio to either mealtime (b) (4) or mealtime NovoLog for 26 weeks of double-blind treatment period where the bolus insulin was titrated, in combination with insulin glargine and metformin.

Key Inclusion Criteria:

- Female or male adults with type 2 diabetes (clinical diagnosis) ≥6 months;
- Treated with basal insulin for at least 6 months;
- Current once daily treatment with insulin NPH, insulin detemir or glargine for at least 3 months;
- Current treatment with either 1) metformin with unchanged dose for at least 3 months (≥ dose of 1000 mg), or 2) metformin in combination with sulfonylurea or glinide or DPP-4 inhibitors and/or alpha-glucosidase inhibitors with unchanged dosing for at least 3 months;
- HbA1c 7-9.5% inclusive in the metformin group, or 7-9% inclusive in the metformin +other OAD combination group; A week before randomization, HbA1c 7-9.5%;
- BMI ≤40 kg/$m^2$;
- Not currently using real time CGM system and/or willing not to use a real time CGM system during the trial other than the blinded one provided if selected to the CGM subgroup.

Key Exclusion Criteria:

- Any use of bolus insulin, except short-term use (≤14 days) due to intermittent illness and not during past 3 months;
- Use of GLP-1 agonists and/or TZDs during past 3 months;
- Anticipated change in concomitant drug known to interfere significantly with glucose metabolism (corticosteroids, beta blockers, monoamine oxidase inhibitors or anti-obesity drugs);
- Cardiovascular disease within past 6 months, systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg;
- Impaired liver function or impaired renal function (serum creatinine ≥1.5 mg/dL for males and ≥1.2 mg/dL for females);
- Recurrent severe hypoglycemia (more than once past 12 months) or hypoglycemic unawareness, or hospitalization for diabetic ketoacidosis past 6 months;
- Proliferative retinopathy or maculopathy requiring treatment;
- Female of childbearing potential who is pregnant, breast-feeding, or intend to become pregnant, or is not using adequate contraception methods.

Insulin Dosing and Titration: At the start of run-in period, all OADs other than metformin were discontinued and subjects were switched from their previous basal insulin to once-daily insulin glargine at their pre-trial dose. All subjects continued their pre-trial

metformin treatment without changing the frequency or dose during the trial duration. From the beginning of 8-week run-in period, subjects were instructed to report the date, dose and time point for their basal insulin doses on 3 consecutive days before scheduled visits/phone contact in the provided diary. During the run-in period, the basal insulin was titrated on a weekly basis using a treat-to-target approach with a protocol specified pre-breakfast SMPG target of 71-90 mg/dL.

At randomization, subjects started on 4 units of bolus insulin before each main meal with either (b) (4) or NovoLog, both taken 0-2 minutes before each of three main meals. Thereafter the bolus insulin dose was titrated daily to preprandial or bedtime SMPG glycemic target of 71-108 mg/dL at subsequent meal or bedtime in a treat-to-target approach. Titration of bolus dose was done daily based on SMPG values measured the previous day (-1 unit if below target; +1 unit if above target). Additional bolus doses were allowed if necessary. Adjustment of basal dose could be made when needed (e.g., safety), but changing the dose frequency was not allowed.

From randomization, subjects also reported the date and breakfast, lunch, and main evening meal insulin bolus doses and time points on a daily basis in the diary. The actual time from previous meal was also collected for extra insulin boluses along with the reason for the extra dose.

Insulin titration was monitored and titration deviations were reviewed by the titration surveillance consultants from applicant, which was done centrally in an unbiased manner.

Meal test: A standardized meal test was done at baseline and Week 26 for PPG measurement over 1, 2, 3, and 4 hours after meal ingestion. Fasting subjects received a standardized carbohydrate-rich liquid meal in the morning containing about 80 g of carbohydrates, which was to be consumed as quickly as possible and within 12 minutes.

At baseline meal test, no bolus insulin dose was given (representing baseline before bolus intensification). At Week 26 visit, the bolus insulin dose was administered subcutaneously 0-2 minutes before the start of the meal in the abdomen. The bolus insulin dose was calculated by dividing the carbohydrate content of the meal (80 g) by the insulin:carbohydrate ratio. The ratio was calculated as 500 divided by the last available total daily dose of both basal and bolus insulin, rounded to the nearest whole unit. The total daily dose of insulin was based on last available doses before the meal test.

Sites: A total of 135 sites screened subjects and 123 sites randomized subjects in 9 countries across North America, Europe, and Asia (India).

Endpoints: The primary efficacy endpoint was the change in HbA1c from baseline to the end of treatment period (Week 26). The change from baseline in 2-hour PPG increment after the standardized meal was a confirmatory secondary endpoint. The change in body weight from baseline to end of treatment was another confirmatory secondary endpoint.

The number of treatment-emergent severe or BG confirmed hypoglycemic episodes (defined as subjects as unable to treat self and/or have a recorded plasma glucose <56 mg/dL) during treatment period (0 to 26 weeks) was included as a confirmatory secondary endpoint as part of the stepwise hierarchical testing procedure (see below).

Statistical Methods: The primary objective was to confirm the **non-inferiority** of mealtime (b) (4) compared to mealtime NovoLog, both in combination with basal insulin, by assessing the change from baseline to Week 26 in HbA1c with a margin of 0.4%.

**Reviewer's comment: This non-inferiority margin (0.4%) was agreed upon at the EOP2 meeting.**

After the primary objective was met, a stepwise hierarchical testing procedure was used for confirmatory secondary endpoints to control for type 1 error, in the following order:

- The superiority of (b) (4) versus NovoLog in the change from baseline in 2-hour PPG increment;
- The superiority of (b) (4) versus NovoLog in the number of severe or BG confirmed hypoglycemic episodes;
- The superiority of (b) (4) versus NovoLog in the change from baseline in body weight.

The primary endpoint was analyzed using MMRM. Continuous endpoints which were measured at visits between baseline and end of treatment were analyzed using MMRM model, which included treatment, region, and strata as fixed effects, subjects as a random effect, baseline measure as a covariate and interactions between all fixed effects and visit and between covariate and visit.

Continuous endpoints that only measured at baseline and end of treatment only such as change in 1-4h PPG increment, were analyzed using an ANCOVA model including treatment, region and strata as factors and with endpoint at baseline as a covariate. Dichotomous endpoints were analyzed using logistic regression model using treatment, region and strata as factors, and endpoint at baseline as a covariate.

The number of treatment-emergent severe or BG confirmed hypoglycemic episodes from baseline to end of treatment was analyzed using a negative binomial regression model with a log-link function, and the logarithm of time period in which a hypoglycemic

episode was considered treatment-emergent as offset, including treatment, region and strata as factors.

The evaluation of efficacy was based on the FAS comprising all randomized subjects as randomized. Sensitivity analyses were done in completers analysis set (subjects who completed the trial, as randomized) and per protocol analysis set (as treated).

Descriptive statistics of basal and bolus insulin doses was based on the safety analysis set.

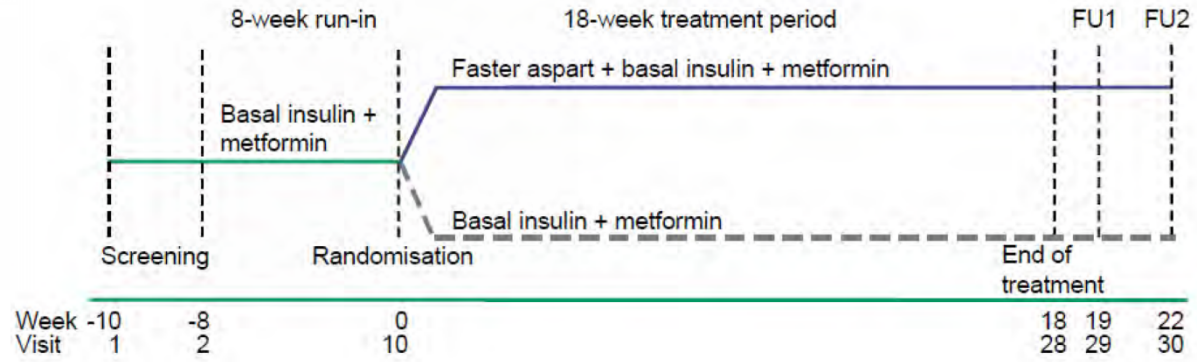
### 5.3.3 Trial 4049 – T2DM

Title: Efficacy and Safety of FIAsp in a Basal-bolus Regimen Versus Basal Insulin Therapy, Both in Combination with Metformin in Adult Subjects with Type 2 Diabetes

Design: This was a multicenter, multinational, 18-week, randomized, open-label, parallel group trial in subjects with T2DM on a pre-trial basal + OAD regimen for ≥6 months. This trial compared the efficacy and safety of mealtime (b) (4) in a basal-bolus regimen versus basal insulin regimen alone, in combination with metformin treatment. In both treatment arms, the basal insulin was the subject's pretrial basal insulin (once daily insulin detemir, insulin glargine or human NPH insulin).

The trial design is shown in Figure 13.

**Figure 13: Trial 4049 Design Overview**




Source: CSR 4049, Figure 9-1

At the beginning of the 8-week run-in period, subjects discontinued all other OADs other than metformin. Subjects continued their pretrial metformin regimen and once-daily basal insulin at the same dose level as before the trial. During the run-in period, the once daily basal insulin treatment was optimized using a treat-to-target approach (pre-breakfast SMPG glycemic target of 71-108 mg/dL).

After the run-in period, subjects were randomized 1:1 ratio to either basal-bolus insulin treatment arm or basal insulin treatment arm, both in combination with metformin. Randomization was stratified by type of once daily basal insulin (insulin detemir, insulin glargine, or NPH insulin).

Change in total daily dose of metformin, unless due to safety concerns, was a reason for subject withdrawal; change in metformin dose for a maximum of 3 consecutive days due to safety reasons was permitted. Initiation or change of treatment with any anti-diabetic drug other than trial products or anti-obesity medications also led to subject withdrawal from the study.

At randomization, subjects in the basal-bolus insulin treatment arm started to inject (b) (4) 0-2 minutes before each main meal in addition to their basal insulin and metformin treatment, and subjects in the basal insulin treatment arm continued on the basal insulin and metformin treatment. During the 18 week treatment period, the dose of (b) (4) in the basal-bolus treatment arm was adjusted daily based on premeal and bedtime SMPGs according to titration guideline.

Key Inclusion Criteria:

- Clinical diagnosis with T2DM ≥6 months before screening; BMI ≤40 kg/m$^2$;
- Current treatment with once daily insulin detemir, insulin glargine or NPH for at least 3 months;
- Current treatment with either 1) metformin with unchanged dosing for at least 3 months before screening, or 2) metformin in combination with other OADs (SU or glinide or DPP-4 inhibitors and/or alpha-glucosidase inhibitor) with unchanged dosing for at least 3 months before screening; metformin dose must be at least 1000 mg;
- HbA1c 7.5-9.5% inclusive in the metformin group and 7.5-9% in the metformin plus other OAD group; a week before randomization, HbA1c 7-9% inclusive.

Exclusion Criteria:

- Any use of bolus insulin except short-term use due to intermittent illness and no within 3 months before screening;
- Use of GLP-1 agonists and/or TZDs within 3 months;
- Anticipated change in concomitant drug known to interfere significantly with glucose metabolism (e.g., systemic corticosteroids, beta-blockers, anti-obesity);
- Cardiovascular disease within 6 months;
- Systolic blood pressure ≥180 mmHg and/or diastolic blood pressure≥100 mmHg;
- Impaired liver function (ALT ≥2.5x ULN), impaired renal function (serum creatinine >1.5 mg/dL for males, >1.2 mg/dL for females, or estimated creatinine clearance <60 mL/min);
- Recurrent severe hypoglycemia or hypoglycemic unawareness, or hospitalization for diabetic ketoacidosis during previous 6 months;

- Proliferative retinopathy or maculopathy requiring treatment;
- Pregnant, breastfeeding, intend to become pregnant, or not using adequate contraception.

Insulin Dosing and Titration: Basal insulin was to be administered subcutaneously in thigh or upper arm (deltoid area). (b) (4) was to be injected into the abdominal wall. Rotation of injection site within a given region is recommended.

Basal insulin was to be given daily in the evening at about the same time each day. (b) (4) was to be given three times daily 0-2 minutes before three main meals.

From beginning of 8-week run-in period, subjects were instructed to report the date, dose and time point for their basal insulin doses on 3 consecutive days before each scheduled visit/phone contact in the provided diary. The basal insulin dose was titrated and optimized weekly based on the mean of 3 pre-breakfast SMPG values measured during 3 consecutive days before weekly visit/contact with mean pre-breakfast SMPG target of 71-108 mg/dL. After the run-in period, basal insulin dose adjustment can be made if needed (e.g., safety), but changing the dose frequency was not allowed.

At randomization, (b) (4) was initiated with a start bolus dose of 4 units taken 0-2 minutes before each of three main meals, and titrated daily to preprandial or bedtime SMPG glycemic target of 71-108 mg/dL. Titration of bolus dose was done daily based on SMPG values measured the previous day (-1 unit if below target; +1 unit if above target). Additional bolus doses were allowed if necessary, and the investigator reviewed and adjusted treatment at weekly contacts. Subjects randomized to bolus treatment were instructed to report the date, dose, and time point of their bolus insulin in the diary each day.

If a fourth meal is eaten, subject can use an extra (b) (4) dose ($4^{th}$ dose) just before this meal at the investigators recommendation, but no dose adjustment recommendations was provided for (b) (4) dosing outside three main meals. The $4^{th}$ dose was to be entered in the diary as “extra bolus insulin”.

Sites: A total of 51 sites screened subjects and 45 sites randomized subjects in 6 countries across North and South America, Europe, and India.

Endpoints: The primary efficacy endpoint was the change in HbA1c from baseline to the end of treatment period (0 to 18 weeks). There was no confirmatory secondary endpoint in this trial.

Statistical Methods: The primary objective was to confirm the superiority of mealtime (b) (4) in a full basal-bolus regimen versus basal insulin therapy, both in combination with metformin, in the change from baseline to Week 18 in HbA1c. The primary

endpoint was analyzed using MMRM where all calculated changes in HbA1c from baseline at Visits 16, 22, and 28 were included in the analysis.

The evaluation of efficacy was based on the FAS. Sensitivity analyses were done in completers analysis set and per protocol analysis set. Descriptive statistics of basal and bolus insulin doses was based on the safety analysis set.

(b) (4)

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(b) (4)

# 6 Review of Efficacy

## ***Efficacy Summary***

Overall, the applicant has demonstrated the glycemic efficacy of (b) (4) as bolus insulin in patients with type 1 and type 2 diabetes mellitus for duration of up to 26 weeks, when used in combination with basal insulin.

The applicant demonstrated that (b) (4) is non-inferior to NovoLog in terms of glycemic control, as measured by the change from baseline in HbA1c at the end of

treatment period in all three Phase 3 trials with a non-inferiority margin of 0.4% (i.e., the upper bound of the two-sided 95% CI of treatment difference was <0.4%). In two pivotal trials, 3852 in T1DM and 3852 in T2DM, (b) (4) was compared to NovoLog as mealtime insulin and was injected 0-2 minutes before main meals and established non-inferiority. See Table 2 for treatment differences and summary results for three Phase 3 trials.

**Table 2: Summary of Change in HbA1c for Phase 3 Trials 3852, 3853, and 4049**

| Treatment Group | N | Baseline Mean | End of Trial Mean | LS Mean Change from Baseline | Treatment Diff versus NovoLog (95% CI) |
|---|---|---|---|---|---|
| **Type 1 Diabetes Mellitus** | | | | | |
| ***Trial 3852:*** *26-week basal-bolus in combination with insulin detemir* | | | | | |
| Mealtime (b) (4) | 381 | 7.62 | 7.31 | -0.32 | -0.15 (-0.23, -0.07) |
| Postmeal (b) (4) | 382 | 7.63 | 7.51 | -0.13 | 0.04 (-0.04, 0.12) |
| Mealtime NovoLog | 380 | 7.58 | 7.42 | -0.17 | |
| **Type 2 Diabetes Mellitus** | | | | | |
| ***Trial 3853:*** *26-week basal-bolus in combination with insulin glargine and metformin* | | | | | |
| Mealtime (b) (4) | 345 | 7.96 | 6.63 | -1.38 | -0.02 (-0.15, 0.10) |
| Mealtime NovoLog | 344 | 7.89 | 6.59 | -1.36 | |
| ***Trial 4049:*** *18-week basal-bolus versus basal in combination with metformin* | | | | | |
| Mealtime (b) (4) +basal | 116 | 7.93 | 6.78 | -1.16 | -0.94 (-1.17, -0.72)* |
| Basal | 120 | 7.92 | 7.70 | -0.22 | |

*Treatment difference versus basal insulin

Postmeal dosing (administered 20 minutes after start of a meal) was only evaluated in trial 3852 in patients with T1DM, where (b) (4) was administered after main meals in an open-label treatment arm and was compared to mealtime NovoLog treatment arm. Although numerically the HbA1c reduction was slightly less with postmeal (b) (4) compared to mealtime NovoLog, non-inferiority criterion was met at the margin of 0.4% (Table 2).

A higher percentage of subjects in the mealtime (b) (4) achieved HbA1c target of <7% (15.7%) compared to NovoLog (10.3%), and a lower percentage of subjects in the postmeal (b) (4) achieved HbA1c target of <7% (6%) compared to NovoLog after 26 weeks of treatment in trial 3852. None of these treatment differences were considered statistically significant. However, the estimated odds of achieving HbA1c target of ≤6.5% was statistically significantly lower with postmeal (b) (4) compared to NovoLog (4.8% versus 7.4%; estimated odds ratio of 0.52 [95% CI: 0.30, 0.91]).

In comparison to trial 3852, the percentage of subjects achieving HbA1c target increased substantially in both treatment groups in trial 3853 due to intensification of insulin therapy from basal therapy to basal-bolus therapy during the treatment period. After 26 weeks of treatment, similar proportion of subjects in both treatment arms

achieved HbA1c target <7% after 26 weeks of treatment (additional 69% of subjects in each treatment group).

Treatment with mealtime (b) (4) led to statistically larger decrease in 2-hour PPG increment after 26 weeks compared to NovoLog in patients with T1DM in trial 3852 (treatment difference of -12.01 mg/dL [95% CI: -23.33, -0.70]), but sensitivity analyses did not confirm this statistical significance. The 2-hour PPG increment was numerically increased with postmeal (b) (4) compared to NovoLog with treatment difference of 5.32 mg/dL (95% CI: -6.05, 16.68). As discussed in the safety section 7, there was no statistically significant difference in the overall estimated severe or BG confirmed hypoglycemic episodes between (b) (4) and NovoLog treatment groups.

Although numerically there was a larger decrease in the 2-hour PPG increment in the (b) (4) group compared to NovoLog group in patients with T2DM (trial 3853), this decrease was not statistically significant (treatment difference of -6.57 mg/dL [95% CI: -14.54, 1.41]).

In trial 3852, although the mealtime (b) (4) appeared to have received slightly more bolus insulin dose compared to mealtime NovoLog at the end of trial, this did not appear to have occurred until the last 2-3 weeks of trial (reason unknown), which would not have a large impact on the primary endpoint (HbA1c). In trial 3853, both treatment groups appeared to have received similar dose of (b) (4) and NovoLog. In both trials (3852 and 3853), the basal insulin appeared to have remained stable and comparable between treatment groups after randomization.

The mean weight gain after 26 weeks of treatment was similar between treatment groups in trials 3852 (mean weight gain of 0.7 kg) and 3853 (mean weight gain of 2.7 kg). The magnitude of change from baseline in FPG after 26 weeks of treatment was also small and comparable between treatment arms in trials 3852 and 3853.

In the 18-week trial in subjects with T2DM (trial 4049) where the efficacy and safety of adding (b) (4) to basal insulin +metformin was compared to basal insulin +metformin, adding (b) (4) led to statistically superior HbA1c reduction (Table 2). The estimated increase in the body weight was greater in the (b) (4) treatment group (1.83 kg) compared to basal group (0.17 kg) with statistically significant treatment difference (1.66 kg [95% CI: 0.89, 2.43]), which is expected since insulin is associated with weight gain.

In trial 3852, insulin detemir once or twice daily was the basal insulin used in each treatment arm. In trial 3853, once daily insulin glargine was the basal insulin used with metformin. Therefore, the clinical development for (b) (4) included experience with both insulin detemir and glargine as basal insulin products. In trial 4049, once daily basal insulin allowed were insulin detemir, insulin glargine, or NPH, and subjects continued their pre-trial basal insulin treatment.

(b) (4)

## 6.1 Indication

The applicant is seeking approval for (b) (4) to improve glycemic control in adults with diabetes mellitus (e.g., both type 1 and type 2).

### 6.1.1 Methods

The individual trial designs are discussed in Section 5.2. In this efficacy section of review, each trial is discussed individually for demographics, patient disposition, and efficacy endpoints.

### 6.1.2 Demographics

Trial 3852 – T1DM

The demographics and baseline characteristics are summarized in Table 3, Table 4, and Table 5.

The mean age of subjects was 44 years (range 18 to 83 years), and the majority of subjects (93%) were 18 to 64 years of age with the remaining (7.5%) 65 years of age or

older. 59% of subjects were male. About half of subjects (53%) were from the United States, majority of subjects (93%) were White, and very small proportion of subjects were African-American (2.3%) or Asian (1.2%).

The mean BMI at baseline was 26.7 kg/m$^2$ with a range of 17 to 37.9 kg/m$^2$. The mean duration of diabetes in this patient population was about 20 years (range 1.2 to 65.4 years) with mean HbA1c at baseline of 7.6% (range 5.6 to 9.8%). About 42.5% of randomized subjects reported one or more diabetes complications with diabetic retinopathy (28.4%) and diabetic neuropathy (20.1%) most frequently reported (not shown; see Table 14.1.10 in CSR 3852).

**Table 3: Trial 3852 – Summary of Baseline Diabetes Characteristics (FAS)**

| | Faster aspart (meal) | Faster aspart (post) | NovoRapid (meal) | Total |
|---|---|---|---|---|
| Number of subjects | 381 | 382 | 380 | 1143 |
| Age (yrs) | | | | |
| Mean (SD) | 46.1 (13.8) | 43.5 (13.7) | 43.7 (14.0) | 44.4 (13.9) |
| Median | 47.0 | 44.0 | 43.0 | 44.0 |
| Min ; Max | 18.0 ; 83.0 | 18.0 ; 77.0 | 19.0 ; 78.0 | 18.0 ; 83.0 |
| Body weight (kg) | | | | |
| Mean (SD) | 78.56 (14.89) | 80.49 (15.93) | 80.15 (15.21) | 79.73 (15.36) |
| Median | 77.80 | 79.70 | 78.79 | 78.70 |
| Min ; Max | 45.3 ; 131.6 | 46.0 ; 140.0 | 41.0 ; 124.3 | 41.0 ; 140.0 |
| BMI (kg/m^2) | | | | |
| Mean (SD) | 26.4 ( 3.8) | 26.9 ( 4.1) | 26.7 ( 3.7) | 26.7 ( 3.9) |
| Median | 26.2 | 26.6 | 26.4 | 26.4 |
| Min ; Max | 18.1 ; 35.8 | 17.0 ; 37.9 | 17.1 ; 36.8 | 17.0 ; 37.9 |
| Duration of diabetes (yrs) | | | | |
| Mean (SD) | 20.9 (12.9) | 19.5 (12.1) | 19.3 (11.8) | 19.9 (12.3) |
| Median | 19.6 | 17.3 | 16.7 | 17.7 |
| Min ; Max | 1.3 ; 65.4 | 1.2 ; 59.2 | 1.2 ; 57.4 | 1.2 ; 65.4 |
| HbA1c (%) | | | | |
| Mean (SD) | 7.62 ( 0.71) | 7.63 ( 0.72) | 7.58 ( 0.68) | 7.61 ( 0.70) |
| Median | 7.60 | 7.55 | 7.50 | 7.50 |
| Min ; Max | 6.0 ; 9.8 | 6.1 ; 9.8 | 5.6 ; 9.6 | 5.6 ; 9.8 |
| FPG (mmol/L) | | | | |
| Mean (SD) | 8.40 ( 3.09) | 8.08 ( 3.16) | 7.87 ( 2.79) | 8.12 ( 3.02) |
| Median | 7.95 | 7.65 | 7.50 | 7.60 |
| Min ; Max | 2.3 ; 22.2 | 1.0 ; 25.2 | 2.9 ; 18.0 | 1.0 ; 25.2 |

Source: CSR 3852, Table 10-2

**Table 4: Trial 3852 – Summary of Demographics and Baseline Characteristics (FAS)**

| | Faster aspart (meal) N | (%) | Faster aspart (post) N | (%) | NovoRapid (meal) N | (%) | Total N | (%) |
|---|---|---|---|---|---|---|---|---|
| Number of subjects | 381 | | 382 | | 380 | | 1143 | |
| Age group | | | | | | | | |
| 18-64 years | 346 | ( 90.8) | 359 | ( 94.0) | 352 | ( 92.6) | 1057 | ( 92.5) |
| >= 65 years | 35 | ( 9.2) | 23 | ( 6.0) | 28 | ( 7.4) | 86 | ( 7.5) |
| BMI group | | | | | | | | |
| < 18.5 kg/m2 | 1 | ( 0.3) | 7 | ( 1.8) | 1 | ( 0.3) | 9 | ( 0.8) |
| 18.5 - 24.9 kg/m2 | 143 | ( 37.5) | 123 | ( 32.2) | 128 | ( 33.7) | 394 | ( 34.5) |
| 25.0 - 29.9 kg/m2 | 168 | ( 44.1) | 156 | ( 40.8) | 174 | ( 45.8) | 498 | ( 43.6) |
| >= 30.0 kg/m2 | 69 | ( 18.1) | 96 | ( 25.1) | 77 | ( 20.3) | 242 | ( 21.2) |
| Sex | | | | | | | | |
| Female | 166 | ( 43.6) | 163 | ( 42.7) | 142 | ( 37.4) | 471 | ( 41.2) |
| Male | 215 | ( 56.4) | 219 | ( 57.3) | 238 | ( 62.6) | 672 | ( 58.8) |
| Country of residence | | | | | | | | |
| Belgium | 7 | ( 1.8) | 9 | ( 2.4) | 11 | ( 2.9) | 27 | ( 2.4) |
| Canada | 23 | ( 6.0) | 19 | ( 5.0) | 30 | ( 7.9) | 72 | ( 6.3) |
| Czech Republic | 17 | ( 4.5) | 16 | ( 4.2) | 15 | ( 3.9) | 48 | ( 4.2) |
| Finland | 8 | ( 2.1) | 10 | ( 2.6) | 10 | ( 2.6) | 28 | ( 2.4) |
| Germany | 69 | ( 18.1) | 58 | ( 15.2) | 66 | ( 17.4) | 193 | ( 16.9) |
| Hungary | 17 | ( 4.5) | 14 | ( 3.7) | 15 | ( 3.9) | 46 | ( 4.0) |
| Poland | 24 | ( 6.3) | 24 | ( 6.3) | 18 | ( 4.7) | 66 | ( 5.8) |
| United Kingdom | 23 | ( 6.0) | 19 | ( 5.0) | 18 | ( 4.7) | 60 | ( 5.2) |
| United States | 193 | ( 50.7) | 213 | ( 55.8) | 197 | ( 51.8) | 603 | ( 52.8) |
| Ethnicity | | | | | | | | |
| Hispanic or Latino | 33 | ( 8.7) | 30 | ( 7.9) | 16 | ( 4.2) | 79 | ( 6.9) |
| Not Hispanic or Latino | 348 | ( 91.3) | 352 | ( 92.1) | 364 | ( 95.8) | 1064 | ( 93.1) |
| Race | | | | | | | | |
| White | 363 | ( 95.3) | 355 | ( 92.9) | 348 | ( 91.6) | 1066 | ( 93.3) |
| Black or African American | 5 | ( 1.3) | 12 | ( 3.1) | 9 | ( 2.4) | 26 | ( 2.3) |
| Asian | 5 | ( 1.3) | 2 | ( 0.5) | 7 | ( 1.8) | 14 | ( 1.2) |
| Native Hawaiian or Other Pacific Islander | 0 | | 1 | ( 0.3) | 2 | ( 0.5) | 3 | ( 0.3) |
| American Indian or Alaska Native | 1 | ( 0.3) | 0 | | 0 | | 1 | ( 0.1) |
| Other | 0 | | 3 | ( 0.8) | 3 | ( 0.8) | 6 | ( 0.5) |
| NA | 7 | ( 1.8) | 9 | ( 2.4) | 11 | ( 2.9) | 27 | ( 2.4) |
| Smoking | | | | | | | | |
| Current smoker | 66 | ( 17.3) | 60 | ( 15.7) | 64 | ( 16.8) | 190 | ( 16.6) |
| Never smoked | 229 | ( 60.1) | 236 | ( 61.8) | 237 | ( 62.4) | 702 | ( 61.4) |
| Previous smoker | 86 | ( 22.6) | 85 | ( 22.3) | 78 | ( 20.5) | 249 | ( 21.8) |
| Missing | 0 | | 1 | ( 0.3) | 1 | ( 0.3) | 2 | ( 0.2) |

Source: CSR 3852, Table 10-3

The majority of randomized subjects were previously on insulin glargine (70%) or insulin detemir (29%) as basal insulin and insulin aspart (48%) or insulin lispro (42%) as bolus insulin before entering the study (Table 5).

**Table 5: Trial 3852 – Summary of Anti-Diabetic Treatment Regimen at Screening (FAS)**

| | Faster aspart (meal) N (%) | Faster aspart (post) N (%) | NovoRapid (meal) N (%) | Total N (%) |
|---|---|---|---|---|
| Number of subjects | 381 | 382 | 380 | 1143 |
| Basal + Bolus | 381 (100.0) | 382 (100.0) | 380 (100.0) | 1143 (100.0) |
| Basal insulin | 381 (100.0) | 381 ( 99.7) | 380 (100.0) | 1142 ( 99.9) |
| IGlar | 269 ( 70.6) | 259 ( 67.8) | 277 ( 72.9) | 805 ( 70.4) |
| IDet | 111 ( 29.1) | 118 ( 30.9) | 101 ( 26.6) | 330 ( 28.9) |
| NPH | 0 | 4 ( 1.0) | 1 ( 0.3) | 5 ( 0.4) |
| IDet+IGlar | 1 ( 0.3) | 0 | 1 ( 0.3) | 2 ( 0.2) |
| Bolus insulin | 381 (100.0) | 382 (100.0) | 379 ( 99.7) | 1142 ( 99.9) |
| IAsp | 185 ( 48.6) | 195 ( 51.0) | 172 ( 45.3) | 552 ( 48.3) |
| ILis | 159 ( 41.7) | 157 ( 41.1) | 166 ( 43.7) | 482 ( 42.2) |
| IGlu | 27 ( 7.1) | 22 ( 5.8) | 30 ( 7.9) | 79 ( 6.9) |
| HI | 9 ( 2.4) | 8 ( 2.1) | 10 ( 2.6) | 27 ( 2.4) |
| HI+IAsp | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |
| IGlu+ILis | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Premix insulin | 0 | 1 ( 0.3) | 1 ( 0.3) | 2 ( 0.2) |
| NPH/HI | 0 | 1 ( 0.3) | 1 ( 0.3) | 2 ( 0.2) |

N: Number of subjects, %: Percentage of subjects, IGlar: Insulin Glargine, IDet: Insulin Detemir, NPH: Neutral Protamine Hagedorn, ILis: Insulin Lispro, IGlu: Insulin Glulisine, HI: Human Insulin, IAsp: Insulin Aspart

Source: CSR 3852, 14.1.9

**Reviewer's comments: The study population reasonably represents the general population with type 1 diabetes. Overall, there were no notable differences in the baseline characteristics between treatment groups.**

Trial 3853 – T2DM

The baseline characteristics and demographics are summarized in Table 6 and Table 7. The mean age was 59.5 years (range 21 to 83 years) with the majority of subjects (71%) being 18-64 years of age. About 51% of subjects enrolled were women, and the majority of subjects were White (81%) and not Hispanic or Latino (93.6%).

The mean HbA1c was 7.9% (range 5.3-10%) and the mean FPG was 122.2 mg/dL (range 45.1 to 293.7 mg/dL) at baseline. The mean duration of diabetes was 12.7 years (range 1-9 years).

**Table 6: Trial 3853 – Baseline Characteristics of Study Population**

| | Faster aspart | NovoRapid | Total |
|---|---|---|---|
| Number of subjects | 345 | 344 | 689 |
| Age (yrs) | | | |
| N | 345 | 344 | 689 |
| Mean (SD) | 59.6 (9.3) | 59.4 (9.6) | 59.5 (9.4) |
| Median | 60.0 | 61.0 | 60.0 |
| Min ; Max | 33.0 ; 82.0 | 21.0 ; 83.0 | 21.0 ; 83.0 |
| Height (m) | | | |
| N | 345 | 344 | 689 |
| Mean (SD) | 1.7 (0.1) | 1.7 (0.1) | 1.7 (0.1) |
| Median | 1.7 | 1.7 | 1.7 |
| Min ; Max | 1.4 ; 2.0 | 1.4 ; 2.0 | 1.4 ; 2.0 |
| Body weight (kg) | | | |
| N | 345 | 344 | 689 |
| Mean (SD) | 89.0 (16.9) | 88.3 (16.7) | 88.7 (16.8) |
| Median | 87.3 | 87.0 | 87.3 |
| Min ; Max | 54.9 ; 139.1 | 53.1 ; 147.6 | 53.1 ; 147.6 |
| Body weight (lb) | | | |
| N | 345 | 344 | 689 |
| Mean (SD) | 196.28 (37.28) | 194.65 (36.87) | 195.47 (37.06) |
| Median | 192.50 | 191.79 | 192.40 |
| Min ; Max | 121.0 ; 306.6 | 117.0 ; 325.4 | 117.0 ; 325.4 |
| BMI (kg/m^2) | | | |
| N | 345 | 344 | 689 |
| Mean (SD) | 31.5 (4.7) | 31.0 (4.5) | 31.2 (4.6) |
| Median | 31.6 | 31.1 | 31.2 |
| Min ; Max | 20.6 ; 42.4 | 20.6 ; 40.9 | 20.6 ; 42.4 |
| Duration of diabetes (yrs) | | | |
| N | 345 | 344 | 689 |
| Mean (SD) | 13.2 (6.7) | 12.3 (6.3) | 12.7 (6.5) |
| Median | 13.0 | 11.0 | 12.0 |
| Min ; Max | 2.0 ; 39.0 | 1.0 ; 38.0 | 1.0 ; 39.0 |
| HbA1c (%) | | | |
| N | 345 | 344 | 689 |
| Mean (SD) | 7.96 (0.68) | 7.89 (0.71) | 7.92 (0.70) |
| Median | 7.90 | 7.80 | 7.80 |
| Min ; Max | 6.7 ; 10.6 | 5.3 ; 10.0 | 5.3 ; 10.6 |
| FPG (mmol/L) | | | |
| N | 340 | 339 | 679 |
| Mean (SD) | 6.76 (1.82) | 6.81 (1.95) | 6.78 (1.88) |
| Median | 6.60 | 6.60 | 6.60 |
| Min ; Max | 2.5 ; 14.1 | 3.1 ; 16.3 | 2.5 ; 16.3 |
| FPG (mg/dL) | | | |
| N | 340 | 339 | 679 |
| Mean (SD) | 121.73 (32.71) | 122.72 (35.09) | 122.22 (33.90) |
| Median | 118.93 | 118.93 | 118.93 |
| Min ; Max | 45.1 ; 254.1 | 55.9 ; 293.7 | 45.1 ; 293.7 |

Source: CSR 3853, Table 10-3

**Table 7: Trial 3853 – Baseline Demographics of Study Population**

| | Faster aspart N (%) | NovoRapid N (%) | Total N (%) |
|---|---|---|---|
| Number of subjects | 345 | 344 | 689 |
| Age group | | | |
| N | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| 18-64 years | 241 ( 69.9) | 248 ( 72.1) | 489 ( 71.0) |
| >= 65 years | 104 ( 30.1) | 96 ( 27.9) | 200 ( 29.0) |
| BMI group | | | |
| N | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| 18.5 - 24.9 kg/m2 | 32 ( 9.3) | 36 ( 10.5) | 68 ( 9.9) |
| 25.0 - 29.9 kg/m2 | 109 ( 31.6) | 108 ( 31.4) | 217 ( 31.5) |
| >= 30.0 kg/m2 | 204 ( 59.1) | 200 ( 58.1) | 404 ( 58.6) |
| Sex | | | |
| N | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| Female | 182 ( 52.8) | 171 ( 49.7) | 353 ( 51.2) |
| Male | 163 ( 47.2) | 173 ( 50.3) | 336 ( 48.8) |
| Country of residence | | | |
| N | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| Canada | 8 ( 2.3) | 15 ( 4.4) | 23 ( 3.3) |
| Croatia | 7 ( 2.0) | 9 ( 2.6) | 16 ( 2.3) |
| India | 36 ( 10.4) | 38 ( 11.0) | 74 ( 10.7) |
| Israel | 14 ( 4.1) | 20 ( 5.8) | 34 ( 4.9) |
| Russia | 50 ( 14.5) | 57 ( 16.6) | 107 ( 15.5) |
| Serbia | 45 ( 13.0) | 50 ( 14.5) | 95 ( 13.8) |
| Slovakia | 30 ( 8.7) | 24 ( 7.0) | 54 ( 7.8) |
| United Kingdom | 11 ( 3.2) | 13 ( 3.8) | 24 ( 3.5) |
| United States | 144 ( 41.7) | 118 ( 34.3) | 262 ( 38.0) |
| Ethnicity | | | |
| N | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| Hispanic or latino | 26 ( 7.5) | 18 ( 5.2) | 44 ( 6.4) |
| Not hispanic or latino | 319 ( 92.5) | 326 ( 94.8) | 645 ( 93.6) |
| Race | | | |
| N | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| White | 277 ( 80.3) | 281 ( 81.7) | 558 ( 81.0) |
| Asian | 40 ( 11.6) | 42 ( 12.2) | 82 ( 11.9) |
| Black or african american | 22 ( 6.4) | 18 ( 5.2) | 40 ( 5.8) |
| American indian or alaska native | 3 ( 0.9) | 0 | 3 ( 0.4) |
| Native hawaiian or other pacific islander | 2 ( 0.6) | 0 | 2 ( 0.3) |
| Other | 1 ( 0.3) | 3 ( 0.9) | 4 ( 0.6) |
| Smoking | | | |
| N | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| Current smoker | 37 ( 10.7) | 48 ( 14.0) | 85 ( 12.3) |
| Never smoked | 224 ( 64.9) | 226 ( 65.7) | 450 ( 65.3) |
| Previous smoker | 83 ( 24.1) | 70 ( 20.3) | 153 ( 22.2) |
| Missing | 1 ( 0.3) | 0 | 1 ( 0.1) |

N: Number of subjects, %: Percentage of subjects, BMI: Body mass index.
Baseline is at randomisation (visit 10 - week 0).
Source: CSR 3853, Table 10-4

All subjects were to be on basal insulin before study at screening. In addition to basal insulin, about 53.8% of subjects were also treated with metformin, and 43.7% of subjects were treated with metformin and another OAD. Table 8 provides a summary of

oral anti-diabetic regimen at screening. Overall, the proportion of subjects on one or two anti-diabetic drugs along with basal insulin appeared to be well-balanced between treatment groups.

**Table 8: Trial 3853 – Summary of Oral Anti-Diabetic Regimen at Screening in Trial Population – FAS**

| | Faster aspart N (%) | NovoRapid N (%) | Total N (%) |
|---|---|---|---|
| Number of subjects | 345 | 344 | 689 |
| 1 Anti-diabetic treatment | 187 ( 54.2) | 184 ( 53.5) | 371 ( 53.8) |
| Biguanide | 187 ( 54.2) | 184 ( 53.5) | 371 ( 53.8) |
| 2 Anti-diabetic treatments | 149 ( 43.2) | 152 ( 44.2) | 301 ( 43.7) |
| Biguanide + alpha-glucosidase inhibitor | 1 ( 0.3) | 1 ( 0.3) | 2 ( 0.3) |
| Biguanide + dpp-4 inhibitor | 15 ( 4.3) | 28 ( 8.1) | 43 ( 6.2) |
| Biguanide + glinide | 8 ( 2.3) | 9 ( 2.6) | 17 ( 2.5) |
| Biguanide + sglt2-inhibitor | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Biguanide + sulphonylurea | 125 ( 36.2) | 113 ( 32.8) | 238 ( 34.5) |
| >2 Anti-diabetic treatments | 9 ( 2.6) | 8 ( 2.3) | 17 ( 2.5) |
| Biguanide + alpha-glucosidase inhibitor + sulphonylurea | 1 ( 0.3) | 0 | 1 ( 0.1) |
| Biguanide + dpp-4 inhibitor + glinide | 2 ( 0.6) | 1 ( 0.3) | 3 ( 0.4) |
| Biguanide + dpp-4 inhibitor + glinide + sulphonylurea | 1 ( 0.3) | 0 | 1 ( 0.1) |
| Biguanide + dpp-4 inhibitor + sulphonylurea | 5 ( 1.4) | 7 ( 2.0) | 12 ( 1.7) |

N: Number of subjects, %: Percentage of subjects

Source: CSR 3853, 14.1.10

**Reviewer's comments: No notable differences in the baseline characteristics or demographics between treatment groups were seen in trial 3853.**

**As expected, T2DM subjects participating in trial 3853 in comparison to T1DM subjects from trial 3852 were slightly older, had higher baseline BMI, and enrolled slightly larger proportion of Asian and African-American subjects.**

**Trial 4049 – T2DM**

The baseline characteristics and demographics are summarized in Table 9 and Table 10. Overall, there were no notable differences in the baseline characteristics or demographics between treatment groups.

The mean age was 57.4 years (range 27 to 77 years), where 75% of subjects were 18-64 years of age and 25% were ≥65 years of age. Slightly more than half of subjects were female (51.7%). The majority of subjects were White (69.9%) and not Hispanic or Latino (62.7%), and about 26% were Asian.

The mean duration of diabetes was 11.3 years (range 1 to 33 years) with mean baseline HbA1c of 7.9% (range 6.4 to 11.4%). At screening, about 65% of subjects were on being treated with insulin glargine, 21% with NPH insulin and 14% with insulin detemir.

**Table 9: Trial 4049 – Summary of Baseline Characteristics (FAS)**

| | Faster aspart + Basal | Basal | Total |
|---|---|---|---|
| Number of subjects | 116 | 120 | 236 |
| Age (yrs) | | | |
| N | 116 | 120 | 236 |
| Mean (SD) | 57.5 ( 9.9) | 57.4 ( 8.5) | 57.4 ( 9.2) |
| Median | 58.0 | 58.0 | 58.0 |
| Min ; Max | 27.0 ; 77.0 | 36.0 ; 77.0 | 27.0 ; 77.0 |
| Body weight (kg) | | | |
| N | 116 | 120 | 236 |
| Mean (SD) | 82.2 ( 16.2) | 85.1 ( 17.3) | 83.7 ( 16.8) |
| Median | 81.0 | 81.7 | 81.5 |
| Min ; Max | 49.6 ; 133.1 | 52.3 ; 133.2 | 49.6 ; 133.2 |
| BMI[a] (kg/m^2) | | | |
| N | 116 | 120 | 236 |
| Mean (SD) | 30.4 ( 5.0) | 31.1 ( 4.7) | 30.8 ( 4.8) |
| Median | 30.1 | 30.6 | 30.2 |
| Min ; Max | 19.9 ; 40.9 | 21.2 ; 40.5 | 19.9 ; 40.9 |
| Duration of diabetes (yrs) | | | |
| N | 115 | 120 | 235 |
| Mean (SD) | 10.9 ( 6.1) | 11.8 ( 7.4) | 11.3 ( 6.8) |
| Median | 10.0 | 11.0 | 10.0 |
| Min ; Max | 2.0 ; 29.0 | 1.0 ; 33.0 | 1.0 ; 33.0 |
| $HbA_{1c}$[b] (%) | | | |
| N | 116 | 120 | 236 |
| Mean (SD) | 7.93 ( 0.69) | 7.92 ( 0.68) | 7.93 ( 0.69) |
| Median | 7.90 | 7.80 | 7.90 |
| Min ; Max | 6.4 ; 11.4 | 6.4 ; 10.2 | 6.4 ; 11.4 |
| FPG (mmol/L) | | | |
| N | 116 | 119 | 235 |
| Mean (SD) | 7.4 ( 2.4) | 7.7 ( 2.9) | 7.5 ( 2.6) |
| Median | 7.1 | 7.0 | 7.0 |
| Min ; Max | 3.7 ; 16.9 | 2.7 ; 18.0 | 2.7 ; 18.0 |

[a] Screening based on inclusion criterion, BMI ≤ 40.0 $kg/m^2$, occurred at visit 1. Subjects with BMI > 40.0 $kg/m^2$ at visit 10 were not excluded.
[b] The randomisation criterion, $HbA_{1c}$ 7.0–9.0%, was based on $HbA_{1c}$ at visit 9. Subjects with $HbA_{1c}$ < 7.0% or > 9.0% at visit 10 were not excluded.
N: Number of subjects, BMI: Body mass index, FPG: Fasting plasma glucose
Max: Maximum, Min: Minimum, SD: Standard deviation, yrs: Years
Baseline is at randomisation (Visit 10 - Week 0).
Source: CSR 4049, Table 10-2

**Table 10: Trial 4049 – Demographics and Baseline Characteristics (FAS)**

| | Faster aspart + Basal | Basal | Total |
|---|---|---|---|
| Number of subjects | 116 | 120 | 236 |
| Age group | | | |
| N | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| 18-64 years | 86 ( 74.1) | 91 ( 75.8) | 177 ( 75.0) |
| >= 65 years | 30 ( 25.9) | 29 ( 24.2) | 59 ( 25.0) |
| BMI group | | | |
| N | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| 18.5 - 24.9 kg/m2 | 19 ( 16.4) | 10 ( 8.3) | 29 ( 12.3) |
| 25.0 - 29.9 kg/m2 | 36 ( 31.0) | 46 ( 38.3) | 82 ( 34.7) |
| >= 30.0 kg/m2 | 61 ( 52.6) | 64 ( 53.3) | 125 ( 53.0) |
| Sex | | | |
| N | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Female | 61 ( 52.6) | 61 ( 50.8) | 122 ( 51.7) |
| Male | 55 ( 47.4) | 59 ( 49.2) | 114 ( 48.3) |
| Country of residence | | | |
| N | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Argentina | 16 ( 13.8) | 28 ( 23.3) | 44 ( 18.6) |
| India | 31 ( 26.7) | 30 ( 25.0) | 61 ( 25.8) |
| Mexico | 17 ( 14.7) | 14 ( 11.7) | 31 ( 13.1) |
| Romania | 16 ( 13.8) | 12 ( 10.0) | 28 ( 11.9) |
| Slovenia | 18 ( 15.5) | 14 ( 11.7) | 32 ( 13.6) |
| United States | 18 ( 15.5) | 22 ( 18.3) | 40 ( 16.9) |
| Ethnicity | | | |
| N | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Hispanic or Latino | 40 ( 34.5) | 48 ( 40.0) | 88 ( 37.3) |
| Not Hispanic or Latino | 76 ( 65.5) | 72 ( 60.0) | 148 ( 62.7) |
| Race | | | |
| N | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Asian | 31 ( 26.7) | 31 ( 25.8) | 62 ( 26.3) |
| Black or African American | 5 ( 4.3) | 4 ( 3.3) | 9 ( 3.8) |
| White | 80 ( 69.0) | 85 ( 70.8) | 165 ( 69.9) |
| Smoking | | | |
| N | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Never smoked | 90 ( 77.6) | 89 ( 74.2) | 179 ( 75.8) |
| Previous smoker | 18 ( 15.5) | 25 ( 20.8) | 43 ( 18.2) |
| Current smoker | 8 ( 6.9) | 6 ( 5.0) | 14 ( 5.9) |
| Basal insulin type | | | |
| N | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Insulin glargine | 76 ( 65.5) | 77 ( 64.2) | 153 ( 64.8) |
| Insulin detemir | 16 ( 13.8) | 17 ( 14.2) | 33 ( 14.0) |
| NPH | 24 ( 20.7) | 26 ( 21.7) | 50 ( 21.2) |

N: Number of subjects, %: Percentage of subjects, BMI: Body mass index
NPH: Neutral Protamine Hagedorn
Baseline is at randomisation (Visit 10 - Week 0).

Source: CSR 4049, Table 10-3

At screening, the majority of randomized subjects (59.3%) were receiving basal insulin plus one OAD (i.e., metformin), and over one-third (38.6%) were receiving basal insulin plus 2 OADs (mostly metformin+SU). Only a small proportion of enrolled subjects were receiving basal insulin plus more than 2 OADs (2.1%). There was no notable difference in previous anti-diabetic treatment across treatment groups at screening.

**Reviewer's comment: Trial 4049 had a higher proportion of Hispanic or Latino subjects (37%) compared to trial 3853 (6.4%) or 3852 (6.9%). This reflected the differences in countries and regions where trials were conducted as trial 4049 enrolled a sizeable proportion of subjects from Argentina (18.6%) and Mexico (25.8%).**

**Although the participation of minorities were overall low, trial in T1DM (3852) had a lower proportion of subjects who are African-American and Asian compared to trials in T2DM (3853 and 4049), most likely because the majority of patients with T1DM are Caucasians and also due to the some differences in countries where trials were conducted.**

**Overall, the patient demographics suggest appropriate randomization.**

(b) (4)

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### 6.1.3 Subject Disposition

The subjects' disposition for each trial is discussed below. Discontinuations due to adverse events are discussed in section 7.3.3. See the Statistical Review for evaluating the impact of missing data for efficacy analyses.

Trial 3852 – T1DM

A total of 1692 subjects were screened, of which 402 were screen failures, mostly due to not meeting the HbA1c inclusion criteria. A total of 1290 subjects entered the run-in period, and 147 subjects were run-in failures, mostly due to withdrawal by subjects (64 subjects) and meeting withdrawal criteria (46 subjects; mostly for non-compliance with trial procedures [22 subjects] and included in trial in violation to criteria [16 subjects]).

Of 1143 subjects randomized, 81 subjects (7.1%) were withdrawn from the trial after randomization, with a slightly higher proportion of subjects in the (b) (4) groups (30 subjects [7.9%] in the mealtime (b) (4) group and 27 subjects [7.1%] in the postmeal (b) (4) group) compared to the NovoLog group (24 subjects [6.3%]) not completing the trial. The most common reason for withdrawal was by subject request, in 17 subjects (4.5%) from the mealtime (b) (4) group, 7 subjects (1.8%) from the postmeal (b) (4) group, and 10 subjects (2.6%) from the NovoLog group.

Seven subjects in the mealtime (b) (4) group, 10 subjects in the postmeal (b) (4) group, and 8 subjects in the NovoLog group withdrew due to withdrawal criteria. The most common reason was for 'substantial and repeated non-compliance with trial

procedures' in 3 subjects in the mealtime (b) (4) group, 2 subjects in the postmeal (b) (4) group, and 3 subjects in the NovoLog group.

Three subjects withdrew for 'other' reason: 2 subjects (one subject each from mealtime (b) (4) and postmeal (b) (4) groups) withdrew at Weeks 10 and 6 respectively because "sponsor and principal investigator decided to close the site", and 1 subject in the postmeal (b) (4) group withdrew at Week 19 because "sponsor withdrew subject due to extended period in between visits".

Three subjects in the postmeal (b) (4) group and 2 subjects in the mealtime NovoLog group withdrew due to hypoglycemia (withdrawal criterion #4). These subjects are discussed in section 7.3.3 (Table 55).

Subject disposition is summarized in Table 14.

**Table 14: Trial 3852 – Summary of Subject Disposition – All Subjects**

| | Faster aspart (meal) N (%) | Faster aspart (post) N (%) | NovoRapid (meal) N (%) | Total N (%) |
|---|---|---|---|---|
| Screened | | | | 1692 |
| Screening failures | | | | 402 |
| Run-in failures | | | | 147 |
| Randomised | 381 (100.0) | 382 (100.0) | 380 (100.0) | 1143 (100.0) |
| Exposed* | 386 | 377 | 380 | 1143 |
| Withdrawn at/after randomisation | 30 ( 7.9) | 27 ( 7.1) | 24 ( 6.3) | 81 ( 7.1) |
| Adverse event | 5 ( 1.3) | 4 ( 1.0) | 2 ( 0.5) | 11 ( 1.0) |
| Withdrawal criteria | | | | |
| #1: change in other anti-diabetes or anti-obesity medications | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |
| #2: change of basal insulin dose frequency | 0 | 1 ( 0.3) | 1 ( 0.3) | 2 ( 0.2) |
| #4: hypoglycaemia posing a safety problem | 0 | 3 ( 0.8) | 2 ( 0.5) | 5 ( 0.4) |
| #6: medication interfering with glucose metabolism | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |
| #8: non-compliance with trial procedures | 3 ( 0.8) | 2 ( 0.5) | 3 ( 0.8) | 8 ( 0.7) |
| #11: included in trial in contravention to criteria | 1 ( 0.3) | 3 ( 0.8) | 2 ( 0.5) | 6 ( 0.5) |
| #13: participating in other clinical trials | 1 ( 0.3) | 1 ( 0.3) | 0 | 2 ( 0.2) |
| Lost to follow-up | 0 | 3 ( 0.8) | 2 ( 0.5) | 5 ( 0.4) |
| Pregnancy | 0 | 1 ( 0.3) | 2 ( 0.5) | 3 ( 0.3) |
| Withdrawal by subject | 17 ( 4.5) | 7 ( 1.8) | 10 ( 2.6) | 34 ( 3.0) |
| Other | 1 ( 0.3) | 2 ( 0.5) | 0 | 3 ( 0.3) |
| Completed trial | 351 ( 92.1) | 355 ( 92.9) | 356 ( 93.7) | 1062 ( 92.9) |

N: Number of subjects, %: Percentage of randomised subjects
*: Includes subjects 'as treated'

Source: CSR 3852, Table 10-1

**Reviewer's comment: The overall discontinuation was low with an overall rate of 7%. Although there was a slight imbalance between treatment groups for withdrawal criteria, the numbers were small and unlikely to have a significant impact on the efficacy findings.**

All analysis sets in trial 3852 are summarized in Table 15. For definitions of these analysis sets, see section 5.3.1.

**Table 15: Trial 3852 Analysis Sets**

| | Faster aspart (meal) N (%) | Faster aspart (post) N (%) | NovoRapid (meal) N (%) | Total N (%) |
|---|---|---|---|---|
| Randomised | 381 (100.0) | 382 (100.0) | 380 (100.0) | 1143 (100.0) |
| Full analysis set | 381 (100.0) | 382 (100.0) | 380 (100.0) | 1143 (100.0) |
| Per protocol analysis set* | 367 | 357 | 375 | 1099 |
| Safety analysis set* | 386 | 377 | 380 | 1143 |
| Sensitivity analysis set | 284 ( 74.5) | 285 ( 74.6) | 310 ( 81.6) | 879 ( 76.9) |
| Completed trial | 351 ( 92.1) | 355 ( 92.9) | 356 ( 93.7) | 1062 ( 92.9) |

N: Number of subjects, %: Percentage of randomised subjects
*: Includes subjects 'as treated'
Source: CSR 3852, Table 10-6

Five subjects were randomized to postmeal (b) (4) group but injected their bolus insulin before meal consistently during the trial. These subjects were included 'as randomized' in the FAS and 'as treated' in the PP analysis set and safety analysis set.

Forty-four subjects were excluded from the PP analysis set, the majority (30 subjects) due to having less than 12 weeks of actual treatment exposure.

Trial 3853 – T2DM

A total of 1367 subjects were screened, of which 486 subjects were screening failures with the majority due to not meeting the HbA1c inclusion criteria (339 subjects). Of 881 subjects that entered the run-in period, 192 were run-in failures with the most common reason for not meeting the HbA1c randomization criteria (124 subjects) at Visit 9 (a week before randomization).

Of 689 subjects randomized, 83 subjects (12%) withdrew or were withdrawn from the trial after randomization, 44 subjects from the (b) (4) group and 39 subjects from NovoLog group. The most common reason for withdrawal was by subject request, where 30 subjects (15 subjects from each treatment group) requested to be withdrawn. Eleven subjects and 6 subjects from the (b) (4) and NovoLog group respectively withdrew due to non-compliance with trial procedures.

Two subjects in the (b) (4) group and 5 subjects in the NovoLog group withdrew due to adverse events.

Three subjects withdrew for 'other' reasons, as following:

- Subject (b) (6) moved out of country and unable to attend scheduled visits (After 8 weeks from NovoLog group);

- Subject (b) (6) advised to stop study drug because subject wanted HbA1c to be >7% and study goal was to lower it <7% (After 5 weeks from (b) (4) group);
- Subject (b) (6) discontinued due to weight gain and an increasing number of hypoglycemic events (After 10 weeks from (b) (4) group).

Subject (b) (6) should be considered withdrawal due to adverse events, as s/he experienced adverse reactions (weight gain and hypoglycemia) that led to study discontinuation. Also, another subject from (b) (4) group (subject (b) (6) withdrew due to withdrawal criterion #5 (hypoglycemia posing a safety problem). These subjects are discussed in section 7.3.3.

See Table 16 for a summary of subject disposition for trial 3853.

**Table 16: Trial 3853 – Summary of Subject Disposition – All Subjects**

| | Faster aspart N (%) | NovoRapid N (%) | Total N (%) |
|---|---|---|---|
| Screened | | | 1367 |
| Screening failures | | | 486 |
| Run-in failures | | | 192 |
| Randomised | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| Exposed | 341 ( 98.8) | 341 ( 99.1) | 682 ( 99.0) |
| Withdrawn at/after Randomisation | 44 ( 12.8) | 39 ( 11.3) | 83 ( 12.0) |
| Adverse event | 2 ( 0.6) | 5 ( 1.5) | 7 ( 1.0) |
| Lack of efficacy | 0 ( 0.0) | 1 ( 0.3) | 1 ( 0.1) |
| Withdrawal criteria | | | |
| # 2: change of basal insulin dose frequency | 0 ( 0.0) | 1 ( 0.3) | 1 ( 0.1) |
| # 3: bolus insulin dose <6 units daily | 0 ( 0.0) | 1 ( 0.3) | 1 ( 0.1) |
| # 4: bolus insulin injections <3 daily | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.1) |
| # 5: hypoglycaemia posing a safety problem | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.1) |
| # 7: medication interfering with glucose metabolism | 1 ( 0.3) | 1 ( 0.3) | 2 ( 0.3) |
| # 8: change in metformin dose | 1 ( 0.3) | 0 ( 0.0) | 1 ( 0.1) |
| # 9: protocol deviation influencing efficacy or safety | 0 ( 0.0) | 1 ( 0.3) | 1 ( 0.1) |
| #10: non-compliance with trial procedures | 11 ( 3.2) | 6 ( 1.7) | 17 ( 2.5) |
| #13: included in trial in contravention to criteria | 4 ( 1.2) | 4 ( 1.2) | 8 ( 1.2) |
| #15: participating in other clinical trials | 1 ( 0.3) | 1 ( 0.3) | 2 ( 0.3) |
| Other | 2 ( 0.6) | 1 ( 0.3) | 3 ( 0.4) |
| Withdrawal by subject | 15 ( 4.3) | 15 ( 4.4) | 30 ( 4.4) |
| Lost to follow-up | 5 ( 1.4) | 2 ( 0.6) | 7 ( 1.0) |
| Completed trial | 301 ( 87.2) | 305 ( 88.7) | 606 ( 88.0) |

N: Number of subjects, %: Percentage of randomised subjects, #1-15: Withdrawal criterion no 1-15
Source, CSR 3853, Table 10-1

Subjects in all analysis sets are summarized in Table 17. For definitions of these analysis sets, see section 5.3.2.

**Table 17: Trial 3853 – Analysis Sets**

| | Faster aspart N (%) | NovoRapid N (%) | Total N (%) |
|---|---|---|---|
| Randomised | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| Full analysis set | 345 (100.0) | 344 (100.0) | 689 (100.0) |
| Per protocol analysis set | 307 ( 89.0) | 314 ( 91.3) | 621 ( 90.1) |
| Safety analysis set | 341 ( 98.8) | 341 ( 99.1) | 682 ( 99.0) |
| Sensitivity analysis set | 255 ( 73.9) | 266 ( 77.3) | 521 ( 75.6) |

N: Number of subjects, %: Percentage of randomised subjects

Source: CSR 3853, Table 10-7

Sixty-eight subjects were excluded from the PP analysis set. The majority of subjects (45 subjects) were excluded because they received less than 12 weeks of treatment.

Trial 4049

A total of 555 subjects were screened, of which 232 subjects were screen failures, mostly due to not meeting the HbA1c inclusion criteria. A total of 323 subjects entered the run-in period, and 87 subjects were run-in failures, with the most subjects (62 subjects) not meeting the randomization HbA1c criterion (7-9%) the week before randomization.

Of 236 subjects randomized, 9 subjects (7.8%) from basal-bolus treatment arm and 5 subjects (4.2%) from basal treatment arm were withdrawn from the trial at or after randomization (Table 18). Therefore, the completion rate was slightly higher in the basal only group; 107 subjects (92%) in the basal-bolus insulin arm and 115 subjects (96%) in the basal insulin arm.

Two subjects from basal-bolus arm (one of which was a SAE) and one subject from basal arm withdrew due to AE.

One subject withdrew from basal arm due to 'other' (incarcerated and unable to attend study visit).

**Table 18: Trial 4049 – Summary of Subject Disposition – All Subjects**

| | Faster aspart + Basal N (%) | Basal N (%) | Total N (%) |
|---|---|---|---|
| Screened | | | 555 |
| Screening failures | | | 232 |
| Run-in failures | | | 87 |
| Randomised | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Exposed | 115 ( 99.1) | 120 (100.0) | 235 ( 99.6) |
| Withdrawn at/after randomisation | 9 ( 7.8) | 5 ( 4.2) | 14 ( 5.9) |
| Adverse event | 2 ( 1.7) | 1 ( 0.8) | 3 ( 1.3) |
| Protocol violation | | | |
| #4: bolus insulin injections <3 daily | 1 ( 0.9) | 0 ( 0.0) | 1 ( 0.4) |
| #7: medication interfering with glucose metabolism | 0 ( 0.0) | 1 ( 0.8) | 1 ( 0.4) |
| #10: non-compliance with trial procedures | 2 ( 1.7) | 0 ( 0.0) | 2 ( 0.8) |
| #13: included in trial in contravention to criteria | 1 ( 0.9) | 0 ( 0.0) | 1 ( 0.4) |
| Lost to follow-up | 0 ( 0.0) | 1 ( 0.8) | 1 ( 0.4) |
| Withdrawal by subject | 3 ( 2.6) | 1 ( 0.8) | 4 ( 1.7) |
| Other | 0 ( 0.0) | 1 ( 0.8) | 1 ( 0.4) |
| Completed trial | 107 ( 92.2) | 115 ( 95.8) | 222 ( 94.1) |

N: Number of subjects, %: Percentage of randomised subjects
Source: CSR 4049, Table 10-1

The number of subjects in all analysis sets for trial 4049 is summarized in Table 19.

**Table 19: Trial 4049 – Analysis Sets**

| | Faster aspart + Basal N (%) | Basal N (%) | Total N (%) |
|---|---|---|---|
| Randomised | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Full analysis set | 116 (100.0) | 120 (100.0) | 236 (100.0) |
| Per protocol analysis set | 114 ( 98.3) | 118 ( 98.3) | 232 ( 98.3) |
| Safety analysis set | 115 ( 99.1) | 120 (100.0) | 235 ( 99.6) |
| Completer analysis set | 107 ( 92.2) | 115 ( 95.8) | 222 ( 94.1) |

N: Number of subjects, %: Percentage of randomised subjects
Source: CSR 4049, Table 10-7

Four subjects were excluded from PP analysis set, 2 subjects from each treatment group for the following reasons:

- Two subjects, both in basal-bolus arm were taking a combination of OADs not allowed per inclusion criteria;
- One subject from basal arm was started on an exclusionary drug during the trial; another subject from basal arm was withdrawn from the trial and there was no HbA1c result for this subject after randomization.

One randomized subject was not included in the safety analysis set because s/he was withdrawn from the trial before being exposed to the study drug.

(b) (4)

### 6.1.4 Trial 3852 – T1DM

Please refer to Dr. Alex Cambon for his statistical analysis of the primary endpoint for all trials. The results discussed here are the applicant's analyses provided in the Complete Study Reports (CSR) for trial 3852.

#### 6.1.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. In addition to the change in HbA1c, HbA1c responders and insulin doses are discussed in this section.

Although the primary efficacy endpoint was primarily for non-inferiority testing between mealtime (b) (4) and mealtime NovoLog, and non-inferiority between postmeal (b) (4) and mealtime NovoLog was confirmatory secondary endpoints, both results related to HbA1c are discussed here. Table 20 provides an overall summary of change in HbA1c from baseline to Week 26 for all treatment arms.

**Table 20: Trial 3852 – Summary of Change in HbA1c (%) From Baseline to Week 26 (FAS)**

| Treatment | Mealtime (b) (4) (N=381) | Postmeal (b) (4) (N=382) | Mealtime NovoLog (N=380) |
|---|---|---|---|
| Baseline mean | 7.62 | 7.63 | 7.58 |
| Week 26 mean | 7.31 | 7.51 | 7.42 |
| Adjusted change from baseline | -0.32 | -0.13 | -0.17 |
| Diff vs NovoLog (95% CI) | -0.15 (-0.23; -0.07) | 0.04 (-0.04; 0.12) | |

Note: Analyzed using a mixed-effect model for repeated measures; model included treatment, region, and strata as fixed effects, subjects as random effect, baseline HbA1c as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR NN1218-3852, Adapted from Table 14.2.34, Table 14.2.35

*Mealtime (b) (4) versus Mealtime NovoLog (Step 1):* The change from baseline in HbA1c after 26 weeks of treatment was -0.32% with mealtime (b) (4) compared to

-0.17% with mealtime NovoLog, and the treatment difference between mealtime (b) (4) versus mealtime NovoLog was -0.15% with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: -0.23;-0.07). Therefore, the non-inferiority of mealtime (b) (4) compared to mealtime NovoLog was established with a margin of 0.4%.

**Reviewer's comment: The treatment difference in HbA1c reduction between mealtime (b) (4) and mealtime NovoLog was statistically significantly larger with upper limit of 95% CI <0. However, this statistical analysis was not part of pre-specified hierarchical testing and the result is considered exploratory.**

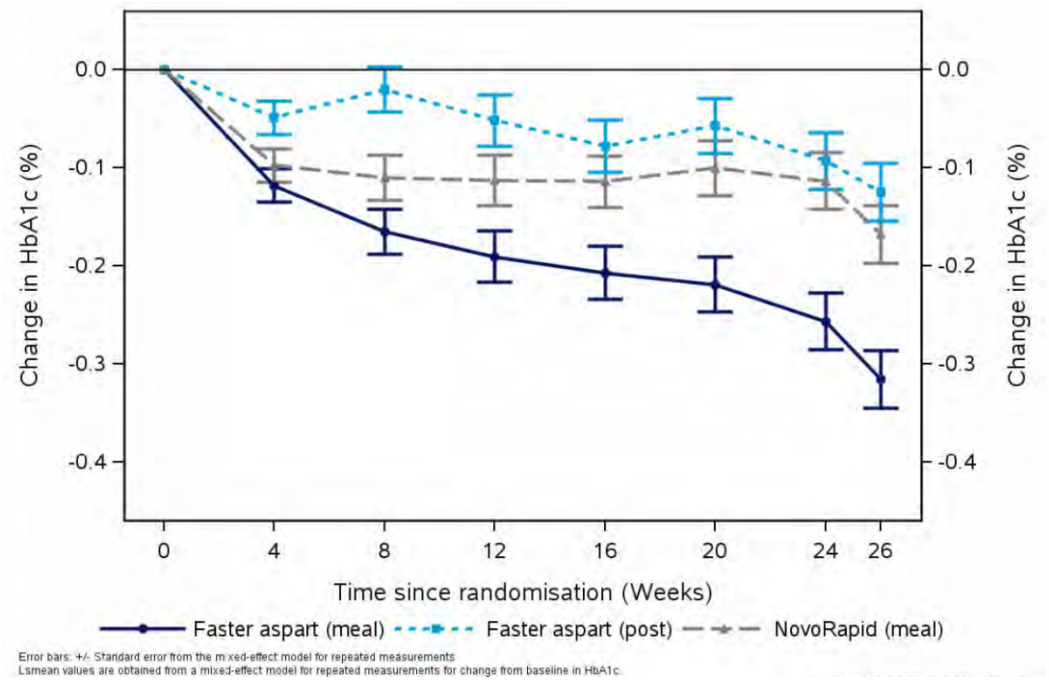
*Postmeal (b) (4) versus Mealtime NovoLog (Step 3)*: The change from baseline in HbA1c after 26 weeks of treatment was -0.13% with postmeal (b) (4) versus -0.17% with mealtime NovoLog, and the treatment difference between postmeal (b) (4) versus mealtime NovoLog was 0.04% with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: -0.04;0.12). Therefore, the non-inferiority of postmeal (b) (4) compared to mealtime NovoLog was established with a margin of 0.4%.

**Reviewer's comment: Although the primary analysis established non-inferiority between postmeal (b) (4) and mealtime NovoLog within a margin of 0.4%, it should be noted that numerically, the decrease in HbA1c with the mealtime NovoLog group compared to the postmeal (b) (4) group is slightly larger, albeit very small (-0.04% more with NovoLog).**

The sensitivity analyses of the primary endpoint to evaluate the impact of missing data supported the results of the primary analysis (not shown). See Statistical Review for further discussion of sensitivity analyses.

The estimated adjusted mean changes in HbA1c from baseline by treatment week over 26 weeks between treatment arms are depicted in Figure 15. In comparison to mealtime NovoLog and postmeal (b) (4) treatment groups where the HbA1c did not show much decline over 26 weeks, HbA1c levels continued to decline over 26 weeks in subjects who received mealtime (b) (4)

**Figure 15: Trial 3852 – Adjusted Mean Change in HbA1c (%) From Baseline By Treatment Week (FAS)**




Source: CSR NN1218-3852, Figure 14.2.39

**HbA1c responders**

The results of HbA1c responders are summarized in Table 21. Overall, the proportion of subjects achieving HbA1c goals of <7% and ≤6.5% after 26 weeks of treatment was highest in the mealtime (b) (4) treatment group, followed by mealtime NovoLog treatment group, with the lowest number of responders seen in subjects in the postmeal (b) (4) treatment group.

A higher proportion of subjects achieved HbA1c <7% in the **mealtime** (b) (4) group (15.7%) compared to mealtime NovoLog group (10.3%) over 26 weeks of treatment period, with the estimated odds of achieving HbA1c <7% statistically significantly higher (1.47 [95% CI: 1.02, 2.13]).

With **postmeal** (b) (4) the estimated odds of achieving HbA1c <7% without severe hypoglycemia was statistically significantly **lower** compared to mealtime NovoLog after 26 weeks of treatment (0.66 [95% CI: 0.44; 0.96]). In addition, the estimated odds of achieving HbA1c ≤6.5% (0.52 [95% CI: 0.30, 0.91]), achieving HbA1c ≤6.5% without severe hypoglycemia (0.48 [95% CI: 0.27, 0.85]), and achieving HbA1c ≤6.5% without severe hypoglycemia and with minimal weight gain (0.41 [95% CI: 0.21, 0.79]) were all statistically significantly lower with postmeal (b) (4) compared to mealtime NovoLog.

**Table 21: Trial 3852 – HbA1c Responders After 26 Weeks (FAS)**

| Treatment | Mealtime (b) (4) (N=381) | Postmeal (b) (4) (N=382) | Mealtime NovoLog (N=380) |
|---|---|---|---|
| **HbA1c <7%** | | | |
| Baseline | 17.6% | 17.3% | 17.9% |
| Week 26 | 33.3% | 23.3% | 28.2% |
| Diff (Week 26 – Baseline) | 15.7% | 6.0% | 10.3% |
| Odds Ratio versus NovoLog (95% CI) | **1.47 (1.02; 2.13)** | 0.73 (0.49; 1.07) | |
| **HbA1c <7% without severe hypoglycemia** | | | |
| Week 26 | 30.7% | 20.4% | 26.6% |
| Odds Ratio versus NovoLog (95% CI) | 1.36 (0.95; 1.96) | **0.66 (0.44; 0.96)** | |
| **HbA1c <7% without severe hypoglycemia and with minimal weight gain*** | | | |
| Week 26 | 21.3% | 14.9% | 19.7% |
| Odds Ratio versus NovoLog (95% CI) | 1.14 (0.77; 1.69) | 0.68 (0.44; 1.03) | |
| **HbA1c ≤6.5%** | | | |
| Baseline | 4.5% | 3.1% | 5.0% |
| Week 26 | 14.4% | 7.9% | 12.4% |
| Diff (Week 26 – Baseline) | 9.9% | 4.8% | 7.4% |
| Odds Ratio versus NovoLog (95% CI) | 1.26 (0.78; 2.03) | **0.52 (0.30; 0.91)** | |
| **HbA1c ≤6.5% without severe hypoglycemia** | | | |
| Week 26 | 13.4% | 6.5% | 11.3% |
| Odds Ratio versus NovoLog (95% CI) | 1.27 (0.78; 2.08) | **0.48 (0.27; 0.85)** | |
| **HbA1c ≤6.5% without severe hypoglycemia and with minimal weight gain*** | | | |
| Week 26 | 8.7% | 4.5% | 8.9% |
| Odds Ratio versus NovoLog (95% CI) | 0.97 (0.56; 1.69) | **0.41 (0.21; 0.79)** | |

*Minimal weight gain was defined as weight gain of <3%.
Source: CSR 3852, Adapted from Table 11-3, Table 11-4

**Mean daily insulin dosage (basal, bolus, total)**

In order to determine whether there was a difference between treatment groups in terms of insulin titration that may explain this difference in the change in HbA1c during treatment period between groups, the mean daily insulin doses between treatment groups were evaluated.

Table 22 summarizes the mean observed daily doses of bolus and basal insulin doses a week before randomization, baseline, and at the end of trial, as well as total insulin dose at the end of 26 weeks of treatment period.

**Table 22: Trial 3852 – Mean Daily Insulin Doses (Units & Units/kg) at Baseline and After 26 Weeks (SAS)**

| Type of insulin | Mealtime (b) (4) (N=381) | Postmeal (b) (4) (N=382) | Mealtime NovoLog (N=380) |
|---|---|---|---|
| Bolus insulin | | | |
| 7 days before randomization* (Week -1) | 29.8 U<br>0.37 U/kg | 31.5 U<br>0.39 U/kg | 32.0 U<br>0.39 U/kg |
| Baseline (Week 0) | 29.5 U<br>0.37 U/kg | 30.9 U<br>0.38 U/kg | 32.2 U<br>0.39 U/kg |
| End of Trial (EOT) | 36.8 U<br>0.46 U/kg | 36.6 U<br>0.45 U/kg | 37.7 U<br>0.45 U/kg |
| *Change from baseline to EOT* | *7.3 U*<br>*0.09 U/kg* | *6.0 U*<br>*0.07 U/kg* | *5.5 U*<br>*0.06 U/kg* |
| Basal insulin | | | |
| 7 days before randomization (Week -1) | 35.0 U<br>0.44 U/kg | 37.8 U<br>0.46 U/kg | 37.0 U<br>0.46 U/kg |
| Baseline (Week 0) | 36.0 U<br>0.45 U/kg | 38.7 U<br>0.47 U/kg | 37.7 U<br>0.47 U/kg |
| End of Trial (EOT) | 36.1 U<br>0.45 U/kg | 40.0 U<br>0.48 U/kg | 38.5 U<br>0.47 U/kg |
| *Change from baseline to EOT* | *0.1 U*<br>*None per U/kg* | *1.3 U*<br>*0.01 U/kg* | *0.8 U*<br>*None per U/kg* |
| Total insulin | | | |
| End of Trial | 72.9 U<br>0.91 U/kg | 76.6 U<br>0.93 U/kg | 76.2 U<br>0.92 U/kg |

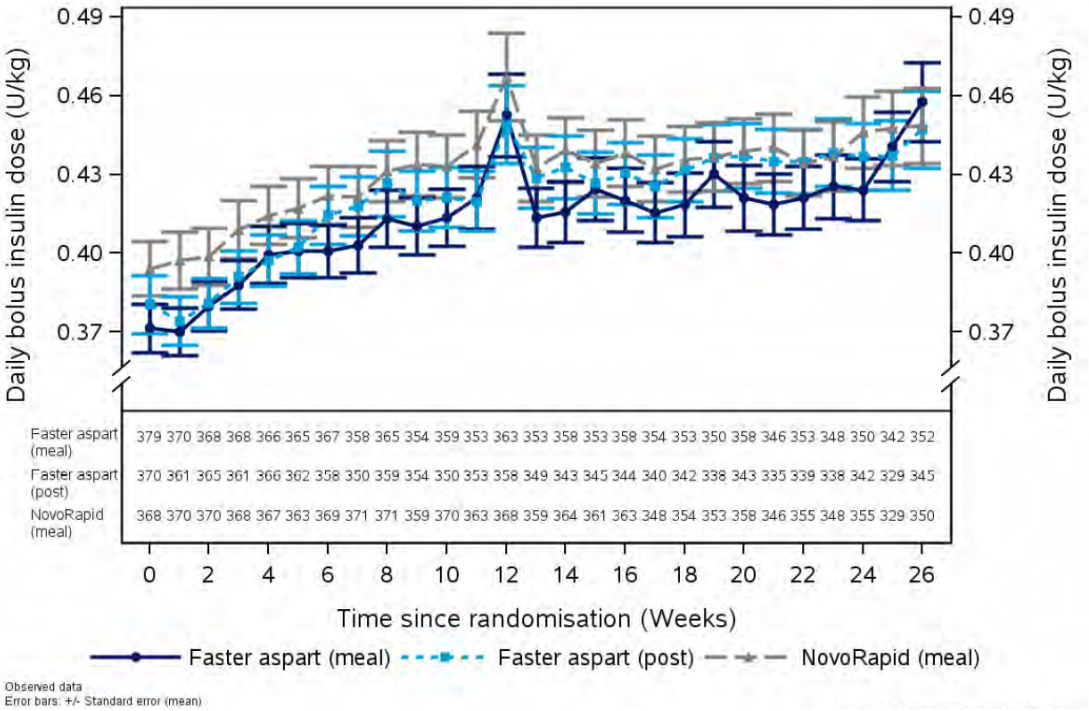
End of trial contains last available measurement.
Source: CSR 3852, Adapted from Tables 14.2.9-14.2.12, 14.2.25-14.2.28, 14.2.29-14.2.30

The basal insulin dose was to be mainly adjusted during the run-in period using treat-to-target approach and not to be changed unless necessary. During the 26 weeks of treatment period, the dose of basal insulin dose appear to be stable in all three treatment groups after randomization, as the basal insulin dose did not change very much from baseline (Week 0) to end of treatment period. The total insulin dose after 26 weeks of treatment period appeared to correlate with the added dose of bolus and basal insulin dose.

After randomization, bolus insulin dose was adjusted either using a pre-defined titration algorithm or using the principles of flexible dosing based on the meal carbohydrate content. Thus the mean daily bolus insulin dose increased during 26 weeks of treatment period in all three treatment groups. The mean change in bolus insulin dose from baseline to end of treatment period was slightly larger in the mealtime (b) (4) treatment arm (7.3 U or 0.09 U/kg dose) compared to mealtime NovoLog (5.5 U or 0.06 U/kg dose); mealtime (b) (4) group received about 0.03 U/kg additional dose compared to NovoLog treatment group. The mean change in bolus insulin dose from baseline to end of treatment was very similar between postmeal (b) (4) (6.0 U or 0.07 U/kg) and mealtime NovoLog (5.2 U or 0.06 U/kg).

A plot of mean daily bolus insulin dose in units/kg by treatment over study is displayed in Figure 16. There was a sharp increase in the mean daily bolus dose at 12 and 26 weeks for all treatment groups. The applicant stated that this was not related to actual doses but caused by a data entry error due to an inconsistency in the subject diaries for Week 12 and Week 26, where the field for entering the carbohydrate content of the meal and field for entering the bolus dose had swapped places compared to the diaries for the other visits.

**Figure 16: Trial 3852 – Mean Daily Bolus Insulin Dose in Units/kg by Treatment Week (SAS)**




Source: CSR 3852, Figure 14.2.19

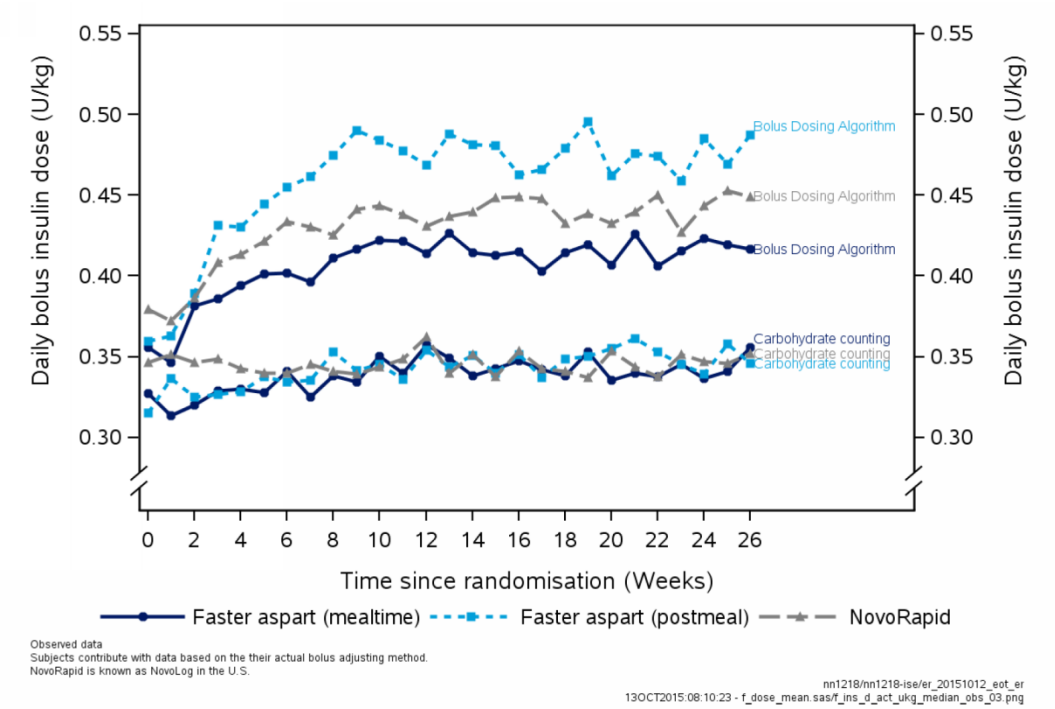
**Reviewer's comment: Based on Figure 16, the mean bolus insulin dose in NovoLog treatment group appeared to have been slightly larger compared to mealtime (b) (4) from baseline (Week 0), and this trend remained for the most of treatment period except during the last 2-3 weeks where the mean bolus dose appeared to have increased more in the mealtime (b) (4) group compared to the NovoLog group. The reason for this is not provided, and remains unexplained. However, given that the HbA1c levels generally reflect glycemic control during previous 8-12 weeks, I do not believe that this change in bolus dose during last 2-3 weeks of trial had much impact on the primary endpoint.**

For subjects who used flexible bolus dosing, the mean insulin:carbohydrate ratios decreased from a baseline level of about 9 g/U to around 8 g/U after 26 weeks of

treatment in both (b) (4) and NovoLog groups, and the mean sensitivity factor remained fairly stable during the trial at around 2 mmol/L per unit in all treatment groups (not shown here; see Table 14.2.16 and 14.2.17 in CSR 3852).

Subjects using the dosing algorithm got higher median bolus dose compared to subjects using flexible dosing with carbohydrate counting (Figure 17). The basal insulin doses remained stable for both titration methods over 26 weeks of treatment period (not shown; see ISE Appendix 6.5, Tables 74 to 77 and 80 to 83).

**Figure 17: Median Daily Bolus Insulin Dose (Actual in Units/kg) By Treatment Week By Titration Method in Trial 3852 (SAS)**




Source: ISE, Appendix 6.5, Figure 71

In addition, the change in HbA1c from baseline at Week 26 was somewhat similar for both titration method in the mealtime (b) (4) group (0.36% with algorithm versus 0.26% with carbohydrate counting) whereas there was less HbA1c reduction with carbohydrate counting in the NovoLog group (0.30% with algorithm versus 0.06% with carbohydrate counting), see Table 23.

**Table 23: HbA1c at Baseline and End of 26 Weeks By Method of Insulin Bolus Dose Adjustment in Trial 3852 (FAS)**

| Trial<br>Method of insulin dose adjustment | Baseline | | | End of 26 weeks | | | Change | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | (SD) | N | Mean | (SD) | N | Mean | (SD) |
| 3852 | | | | | | | | | |
| Bolus dosing algorithm | | | | | | | | | |
| Faster aspart (mealtime) | 159 | 7.58 | ( 0.69) | 159 | 7.22 | ( 0.76) | 159 | -0.36 | ( 0.59) |
| NovoRapid | 156 | 7.63 | ( 0.67) | 156 | 7.34 | ( 0.74) | 156 | -0.30 | ( 0.56) |
| Faster aspart (postmeal) | 159 | 7.65 | ( 0.73) | 159 | 7.48 | ( 0.78) | 159 | -0.17 | ( 0.62) |
| Carbohydrate counting | | | | | | | | | |
| Faster aspart (mealtime) | 222 | 7.64 | ( 0.72) | 222 | 7.38 | ( 0.77) | 222 | -0.26 | ( 0.56) |
| NovoRapid | 224 | 7.54 | ( 0.69) | 224 | 7.47 | ( 0.80) | 224 | -0.06 | ( 0.67) |
| Faster aspart (postmeal) | 223 | 7.62 | ( 0.71) | 223 | 7.53 | ( 0.77) | 223 | -0.09 | ( 0.56) |

Source: ISE Appendix 6.4, Table 27

**Reviewer's comment: It appears that subjects who titrated bolus insulin dose using algorithm received larger dose, and also had more HbA1c reduction compared to subjects who titrated using carbohydrate counting in all treatment groups. The primary efficacy analysis for HbA1c reduction adjusted for method of adjusting bolus insulin at randomization, and the proportion of subjects using each method was balanced across treatment groups.**

Since trial 3852 allowed extra bolus insulin doses at the Investigator's recommendation, data regarding extra insulin doses were also reviewed to assess whether there was a difference between treatment arms with regard to the amount of additional insulin doses that treatment groups received during the trial. An Information Request related to additional/extra bolus insulin doses was sent on June 10, 2016 (Question 6) and the applicant provided their response on June 23, 2016. The applicant summarized that 79.5% of subjects in the mealtime (b) (4) group, 79.8% of subjects in the postmeal (b) (4) group, and 82.6% of subjects in the NovoLog group received additional bolus doses mostly due to either high blood sugar level or snack, and about 10% of subjects received extra bolus doses in all treatment groups.

**Table 24: Trial 3852 – Subjects with Additional Bolus Doses and Number of Bolus Doses by Treatment (Safety Analysis Set)**

| | Faster Aspart (Meal time) N (%) E | Faster Aspart (Post-meal) N (%) E | Novorapid N (%) E |
|---|---|---|---|
| Number of subjects | 386 | 377 | 380 |
| Subjects with additional bolus doses | 307 ( 79.5) 19847 | 301 ( 79.8) 19438 | 314 ( 82.6) 20736 |
| High blood sugar level | 301 ( 78.0) 11872 | 293 ( 77.7) 12563 | 304 ( 80.0) 13194 |
| Snack | 219 ( 56.7) 7930 | 223 ( 59.2) 6785 | 223 ( 58.7) 7495 |
| Not categorized | 18 ( 4.7) 45 | 40 ( 10.6) 90 | 33 ( 8.7) 47 |

| | Faster Aspart (Meal time) E (%) | Faster Aspart (Post-meal) E (%) | Novorapid E (%) |
|---|---|---|---|
| Number of subjects | 386 | 377 | 380 |
| Total number of bolus doses | 197507 (100.0) | 190762 (100.0) | 199461 (100.0) |
| Before Breakfast | 58725 ( 29.7) | 56494 ( 29.6) | 58895 ( 29.5) |
| Before Lunch | 58727 ( 29.7) | 56650 ( 29.7) | 59346 ( 29.8) |
| Before Main evening meal | 60208 ( 30.5) | 58180 ( 30.5) | 60484 ( 30.3) |
| Additional bolus doses | 19847 ( 10.0) | 19438 ( 10.2) | 20736 ( 10.4) |
| High blood sugar level | 11872 ( 6.0) | 12563 ( 6.6) | 13194 ( 6.6) |
| Snack | 7930 ( 4.0) | 6785 ( 3.6) | 7495 ( 3.8) |
| Not categorized | 45 ( 0.0) | 90 ( 0.0) | 47 ( 0.0) |

N=number of subjects, %=proportion of subjects, E=number of additional bolus doses
Source: Response to Information Request, June 22, 2016, Appendix 3, Tables 1 and 2

Table 25 summarize the mean and median bolus dose at breakfast, lunch and main evening meal, which increased over 26 weeks of treatment period in all three treatment groups at a similar level across treatment groups. No apparent difference between treatment arms was seen with the 'Other' bolus doses (i.e., extra bolus doses).

**Table 25: Trial 3852 – Daily Bolus Insulin Dose by Meal at Week 1 and After 26 Weeks**

| Week | Treatment | Safety analysis set | N | Descriptive statistics Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|---|---|
| *Continued from previous page* | | | | | | | | |
| **Doses in U/kg** | | | | | | | | |
| **Main evening meal** | | | | | | | | |
| Week 1 | Faster aspart (meal) | 386 | 377 | 0.133 | 0.072 | 0.116 | 0.02 | 0.55 |
| | Faster aspart (post) | 377 | 367 | 0.133 | 0.071 | 0.120 | 0.01 | 0.63 |
| | NovoRapid (meal) | 380 | 379 | 0.139 | 0.078 | 0.122 | 0.02 | 0.53 |
| End of trial | Faster aspart (meal) | 386 | 386 | 0.172 | 0.132 | 0.139 | 0.02 | 1.04 |
| | Faster aspart (post) | 377 | 377 | 0.166 | 0.115 | 0.141 | 0.02 | 1.09 |
| | NovoRapid (meal) | 380 | 380 | 0.169 | 0.111 | 0.137 | 0.03 | 0.77 |
| **Other** | | | | | | | | |
| Week 1 | Faster aspart (meal) | 386 | 380 | 0.022 | 0.042 | 0.000 | 0.00 | 0.42 |
| | Faster aspart (post) | 377 | 370 | 0.023 | 0.036 | 0.000 | 0.00 | 0.17 |
| | NovoRapid (meal) | 380 | 379 | 0.025 | 0.045 | 0.000 | 0.00 | 0.29 |
| End of trial | Faster aspart (meal) | 386 | 386 | 0.018 | 0.035 | 0.000 | 0.00 | 0.23 |
| | Faster aspart (post) | 377 | 377 | 0.016 | 0.039 | 0.000 | 0.00 | 0.37 |
| | NovoRapid (meal) | 380 | 380 | 0.018 | 0.039 | 0.000 | 0.00 | 0.27 |

Safety analysis set. End of trial contains last available measurement.
N: Number of subjects, SD: Standard deviation.
Source: CSR 3852, Table 11-8

### 6.1.4.2 Secondary Efficacy Endpoints

The following were identified as confirmatory secondary endpoints in trial 3852 and were part of hierarchical testing for hypothesis testing to evaluate for superiority of **mealtime** (b) (4) compared to mealtime NovoLog:

- Step 2: The change from baseline in 2-hour PPG increment (meal test) after 26;
- Step 4: The number of treatment-emergent severe or BG confirmed hypoglycemic events from baseline until Week 26;
- Step 5: The change from baseline in body weight after 26 weeks of randomized treatment.

And the following were also confirmatory secondary endpoints to test for superiority of **postmeal** (b) (4) compared to mealtime NovoLog:

- Step 6: The number of treatment-emergent severe or BG confirmed hypoglycemic events from baseline until Week 26;
- Step 7: The change from baseline in body weight after 26 weeks of randomized treatment.

The confirmatory secondary endpoint was stopped in Step 4, because the number of treatment-emergent severe or BG confirmed hypoglycemic episodes from baseline until

Week 26 was not superior with mealtime (b) (4) compared to mealtime NovoLog. Hypoglycemic episodes are further discussed in safety section 7.3.4.

In this section, the changes in PPG increment and PPG after standardized meal test and changes in body weight will be summarized and discussed. Treatment-emergent severe or BG confirmed hypoglycemic events are summarized in section 7.3.4.

**Postprandial Glucose in Standardized Meal Test**

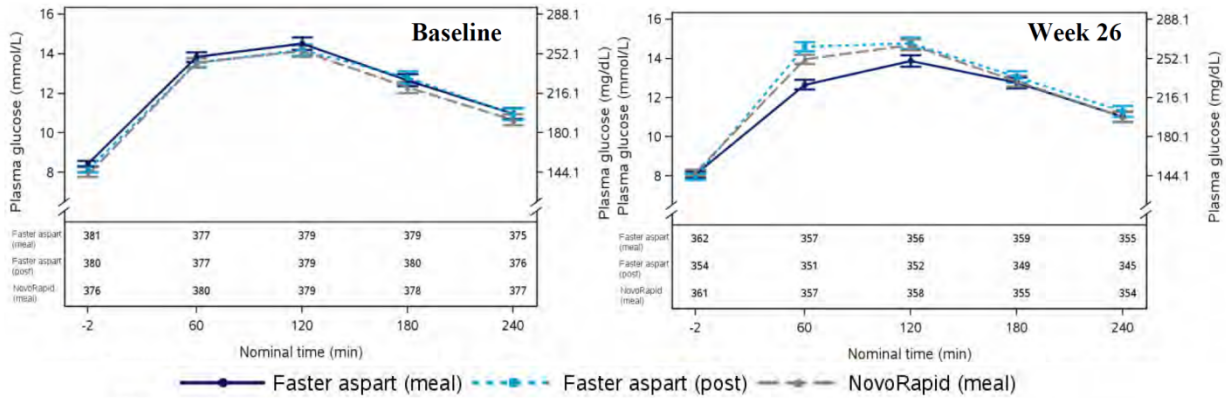
The changes from baseline in PPG and PPG increment after 26 week of treatment measured as part of a standardized meal test are described here.

At baseline and after 26 weeks of treatment, the PPG was measured 60 minutes (1-hour), 120 minutes (2-hour), 180 minutes (3-hour) and 240 minutes (4-hours) after starting the standardized liquid meal. The 1, 2, 3 and 4-hour PPG increments were derived separately by subtracting each PPG measurement from the plasma glucose measured before the meal test (-2 minutes).

Postprandial Glucose (PPG):

The mean plasma glucose (central laboratory-measured) levels are plotted at baseline and at Week 26 in Figure 18. The mean plasma glucose level peaked at 120 minutes after meal consumption and decreased in all treatment groups. The Figure show that the PPG levels at 60 and 120 minutes after meal consumption were lower in the mealtime (b) (4) treatment group compared to NovoLog treatment group after 26 weeks of treatment.

**Figure 18: Trial 3852 Meal Test – Mean Plot of Postprandial Glucose at Baseline and Week 26 (FAS)**




Full analysis set. Error bars: ± standard error (mean). Observed data, except for the cases where glucose or glucagon is administered, in which case the last measurement before rescue intervention is carried forward. Numbers under graph are number of subjects.

Source: CSR 3852, Figure 11-3

The estimated change from baseline after 26 weeks of treatment in postprandial glucose with meal test at 60, 120, 180, and 240 minutes are summarized in Table 26. The **decrease** in postprandial glucose **with mealtime** (b) (4) in comparison to NovoLog was statistically significant **at 60 minutes** (treatment difference of -25.44 mg/dL [95% CI: -36.12; -14.76 mg/dL]) and **at 120 minutes** (treatment difference of -16.73 mg/dL [95% CI: -29.26; -4.20 mg/dL]). In comparison, the **increase** in postprandial glucose **with postmeal** (b) (4) in comparison to mealtime NovoLog treatment was statistically significant **at 60 minutes** (treatment difference of 12.38 mg/dL [95% CI: 1.65; 23.11 mg/dL]). No statistical significance was seen between treatments at 180 and 240 minutes after start of the meal.

**Table 26: Trial 3852 Meal Test – Change from Baseline in Postprandial Glucose (mg/dL) after 26 Weeks of Treatment (FAS)**

| | Meal (b) (4) | Postmeal (b) (4) | Meal NovoLog |
|---|---|---|---|
| PPG at 60 min, N | 353 | 346 | 357 |
| Change from baseline at Wk 26, mg/dL | -17.96 | 19.86 | 7.48 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -25.44 (-36.12; -14.76) | 12.38 (1.65; 23.11) | |
| PPG at 120 min, N | 354 | 349 | 357 |
| Change from baseline at Wk 26, mg/dL | -7.94 | 9.87 | 8.78 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -16.73 (-29.26; -4.20) | 1.08 (-11.49; 13.66) | |
| PPG at 180 min, N | 357 | 347 | 353 |
| Change from baseline at Wk 26, mg/dL | 3.36 | 8.30 | 7.12 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -3.76 (-16.16; 8.61) | 1.18 (-11.28; 13.64) | |
| PPG at 240 min, N | 350 | 341 | 352 |
| Change from baseline at Wk 26, mg/dL | 3.14 | 7.17 | 4.76 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -1.62 (-13.21; 9.97) | 2.41 (-9.26; 14.07) | |

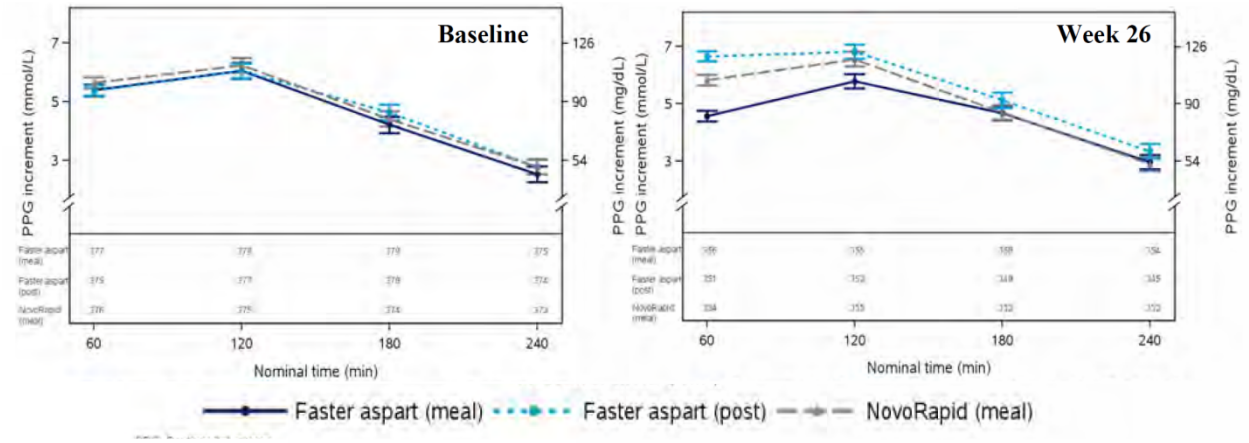
Change from baseline in postprandial glucose (meal test) is analyzed using an ANOVA model with treatment, region and strata as factors and baseline postprandial glucose (meal test) as covariate.
Source: CSR 3852, Table 14.2.52

The sensitivity analysis using the sensitivity analysis set showed similar results as FAS.

Postprandial Glucose (PPG) Increment:

The corresponding PPG increment was derived separately using each PPG measurement minus the pre-prandial PG. The mean increments in plasma glucose during the 4-hour meal test (PPG increments) at baseline and at Week 26 are displayed in Figure 19. The PPG appear to peak at around 2 hour and decrease at subsequent time points.

**Figure 19: Trial 3852 Meal Test – Mean Plot of Postprandial Glucose Increment at Baseline and Week 26 (FAS)**




Full analysis set. Error bars: ±standard error. Observed data, except for the cases where glucose or glucagon is administered, in which case the last measurement before rescue intervention is carried forward. Numbers under graph are number of subjects.

PPG: postprandial glucose.

Source: CSR 3852, Figure 11-4

The estimated change from baseline after 26 weeks of treatment in PPG increment with meal test at 60, 120, 180, and 240 minutes are summarized in Table 27. The **decrease** in PPG increment **with mealtime** (b) (4) in comparison to mealtime NovoLog was **statistically significant at 60 minutes** (treatment difference of -21.21 mg/dL [95% CI: -29.65; -12.77 mg/dL]) **and at 120 minutes** (treatment difference of -12.01 mg/dL [95% CI: -23.33; -0.70 mg/dL]). In comparison, the **increase** in postprandial glucose **with postmeal** (b) (4) in comparison to mealtime NovoLog treatment was **statistically significant at 60 minutes** (treatment difference of 16.75 mg/dL [95% CI: 8.26; 25.24 mg/dL]). No statistical significance was seen between treatments at 180 and 240 minutes after start of the meal.

**Table 27: Trial 3852 Meal Test – Change from Baseline in Postprandial Glucose Increment (mg/dL) after 26 Weeks of Treatment (FAS)**

| | Meal (b) (4) | Postmeal (b) (4) | Meal NovoLog |
|---|---|---|---|
| PPG increment at 60 min, N | 352 | 344 | 350 |
| Change from baseline at Wk 26 | -15.10 | 22.87 | 6.12 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | **-21.21 (-29.65; -12.77)** | **16.75 (8.26; 25.24)** | |
| PPG increment at 120 min, N | 353 | 347 | 350 |
| Change from baseline at Wk 26 | -5.19 | 12.14 | 6.83 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | **-12.01 (-23.33; -0.70)** | 5.32 (-6.05; 16.68) | |
| PPG increment at 180 min, N | 356 | 345 | 346 |
| Change from baseline at Wk 26 | 5.88 | 11.23 | 4.60 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | 1.29 (-10.60; 13.17) | 6.63 (-5.35; 18.61) | |
| PPG increment at 240 min, N | 340 | 339 | 346 |
| Change from baseline at Wk 26 | 6.22 | 10.38 | 2.84 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | 3.38 (-8.05; 14.80) | 7.54 (-3.97; 19.04) | |

Change from baseline in postprandial glucose (meal test) is analyzed using an ANOVA model with treatment, region and strata as factors and baseline postprandial glucose (meal test) as covariate.
Source: CSR 3852, Table 14.2.53

Although the estimated treatment difference was of the same direction, the sensitivity analysis did not confirm the statistical significance in the change from baseline in 2-hour PPG increment between mealtime (b) (4) and NovoLog. The magnitude of the treatment difference was slightly smaller and 95% CI crossed 0 (treatment difference of -10.22 mg/dL [95% CI: -22.77; 2.33]). These may be due to relatively small proportion of subjects being included in the sensitivity analysis set (77%).

**Reviewer's comment: There was a reduction in the mean 2-hour PPG increment and 1-hour PPG increment with mealtime (b) (4) whereas there was an increase in both postmeal (b) (4) and mealtime NovoLog treatment groups. The 1-hour and 2-hour PPG increment achieved statistical significance in the primary analysis comparing treatment difference between mealtime (b) (4) and NovoLog; the 2-hour PPG increment, which was a confirmatory secondary endpoint, was not confirmed in the sensitivity analysis. There was an increase in all PPG increment with postmeal (b) (4) compared to NovoLog, and the increase in PPG increment with postmeal (b) (4) versus NovoLog reached statistical significance at 1-hour.**

**I recommend not labeling PPG results from this trial given that the impact of missing data on sensitivity analysis did not confirm the 2-hour PPG benefit, and given that any treatment difference in postprandial glucose would be expected to be captured in the observed change in HbA1c (primary endpoint). Although 2-hour PPG increment was a pre-specified confirmatory secondary endpoint, a**

**larger treatment difference was observed with 1-hour PPG increment, and it is unclear which PPG measure is more clinically relevant and reliable measure.**

**Change from Baseline in Body Weight**

The weight change from baseline was similar between treatment arms without any statistically significant treatment difference, as shown in Table 28.

**Table 28: Trial 3852 Mean (SD) Change in Body Weight (kg) After 26 Weeks (FAS)**

| | Meal (b) (4) (N=381) | Postmeal (b) (4) (N=382) | Meal NovoLog (N=380) |
|---|---|---|---|
| Baseline | 78.56 (14.89) | 80.49 (15.93) | 80.21 (15.21) |
| Week 26 | 79.47 (15.34) | 81.28 (16.59) | 80.83 (15.40) |
| Adjusted change from baseline* | 0.67 | 0.70 | 0.55 |
| Treatment difference versus NovoLog (95% CI)* | 0.12 (-0.30; 0.55) | 0.16 (-0.27; 0.58) | |

*Change from baseline in body weight is analyzed using MMRM including Week 12 and Week 26 visits; model includes treatment, region, strata as fixed effects, subject as random effect, baseline body weight as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 3852, Table 14.2.104 and 14.2.105

### 6.1.4.3 Other Endpoints

An additional secondary efficacy endpoint that may have the most clinical relevance, the change from baseline in FPG, is described here.

**Change from Baseline in FPG**

The magnitude of change from baseline in FPG after 26 weeks of treatment was small in each treatment arm, and the treatment difference did not reach any statistical significance.

**Table 29: Trial 3852 – Mean Change in Fasting Plasma Glucose After 26 Weeks (FAS)**

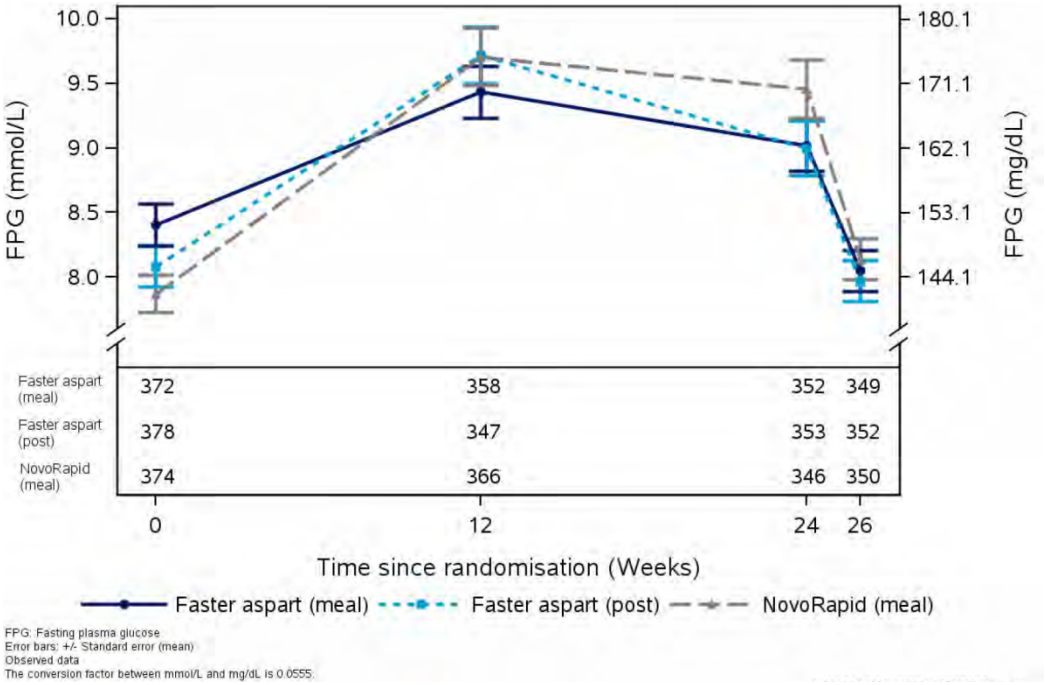
| | Meal (b) (4) (N=381) | Postmeal (b) (4) (N=382) | Meal NovoLog (N=380) |
|---|---|---|---|
| Baseline | 151.41 | 145.63 | 141.76 |
| Week 26 | 145.02 | 143.56 | 146.64 |
| Adjusted change from baseline* | -3.08 | -2.69 | 1.43 |
| Treatment difference versus NovoLog (95% CI)* | -4.51 (-12.28; 3.26) | -4.12 (-11.83; 3.59) | |

*Change from baseline is analyzed using MMRM including Week 12, 24, and 26 visit measures; model includes treatment, region, strata as fixed effects, subject as random effect, baseline body weight as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 3852, Table 14.2.92 and 14.2.93

The mean FPG by treatment week is shown in Figure 20, and appeared to show slight increase from baseline to Week 12, with subsequent decline from Week 12 to Week 24 and sharply declined from Week 24 to Week 26.

The applicant stated that the fasting state of the subjects was more strictly enforced at Week 0 and 26 because the standardized meal tests were being done for all subjects at these visits. If a subject was not fasting at these meal test visits, or if the fasting SMPG was outside the range of 71-160 mg/dL, then the meal test was rescheduled. Therefore, the observed increase in FPG at Weeks 12 and 24 compared to baseline is likely to be unreliable.

**Figure 20: Trial 3852 – Mean Fasting Plasma Glucose by Treatment Week (FAS)**



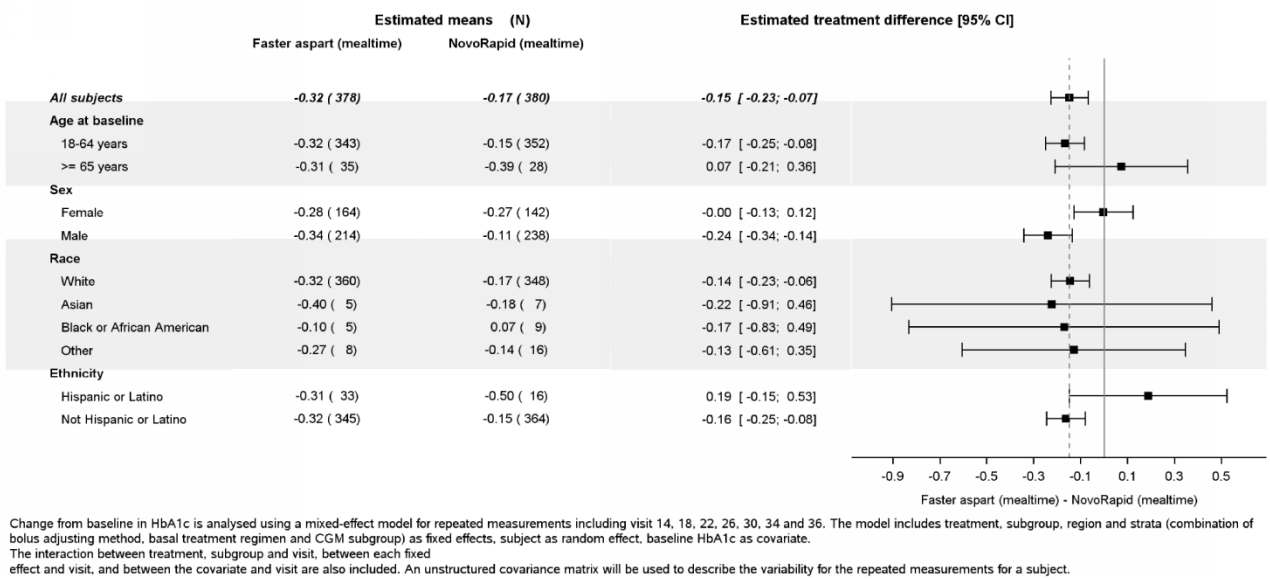

Source: CSR 3852, Figure 14.2.94

### 6.1.4.4 Subpopulations

The subgroup analyses on primary efficacy endpoint (i.e., change in HbA1c from baseline to Week 26) by demographics and disease factors in mealtime (b) (4) compared to mealtime NovoLog are shown in Figure 21 and Figure 23 respectively. The subgroup analyses in postmeal (b) (4) compared to NovoLog by demographics and disease factors are shown in Figure 22 and Figure 24 respectively. Subgroup analysis by region is not shown since the efficacy response was similar across two regions where the trial was conducted, North America and Europe (see Figure 35 and 45 in ISE, Appendix 6.4).

The applicant's analysis of treatment effect (mean change in HbA1c from baseline to Week 26) in mealtime (b) (4) or postmeal (b) (4) compared to NovoLog was overall consistent across different subgroups. The only notable finding was that the efficacy of (b) (4) appeared to be lower in the Hispanic or Latino group, but this finding is inconclusive given the small number of subjects in this subgroup.

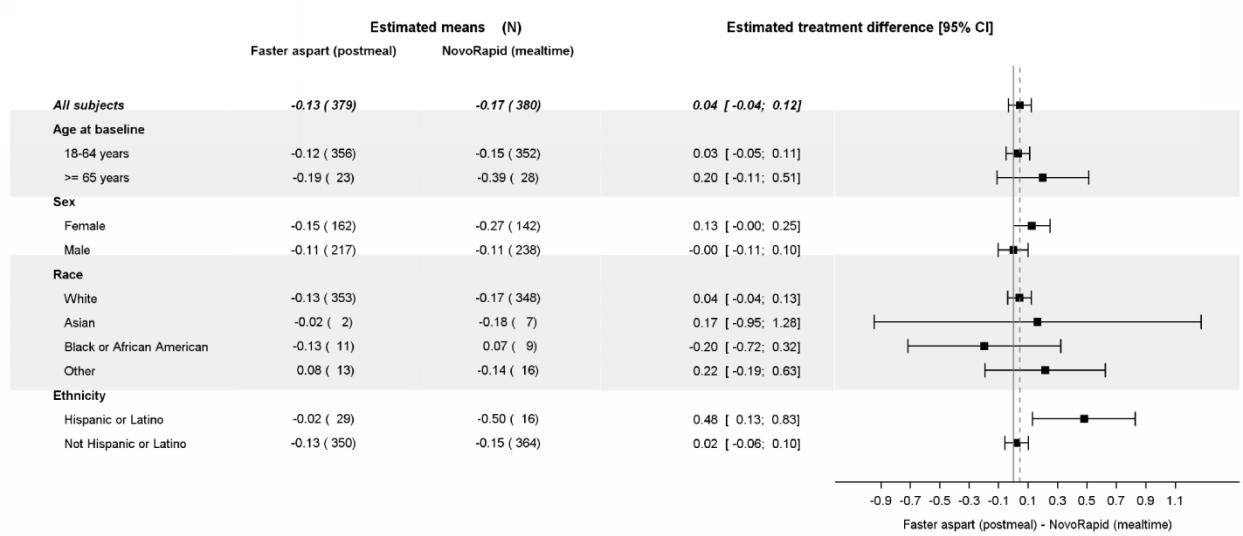
**Figure 21: Forest Plot of Estimated Treatment Difference for Change From Baseline in HbA1c (%) by Demographic Factors for Subjects in Trial 3852 - Mealtime (b) (4) versus NovoLog (FAS)**




Change from baseline in HbA1c is analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30, 34 and 36. The model includes treatment, subgroup, region and strata (combination of bolus adjusting method, basal treatment regimen and CGM subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate.
The interaction between treatment, subgroup and visit, between each fixed
effect and visit, and between the covariate and visit are also included. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject.

Source: ISE, Appendix 6.4, Figure 29

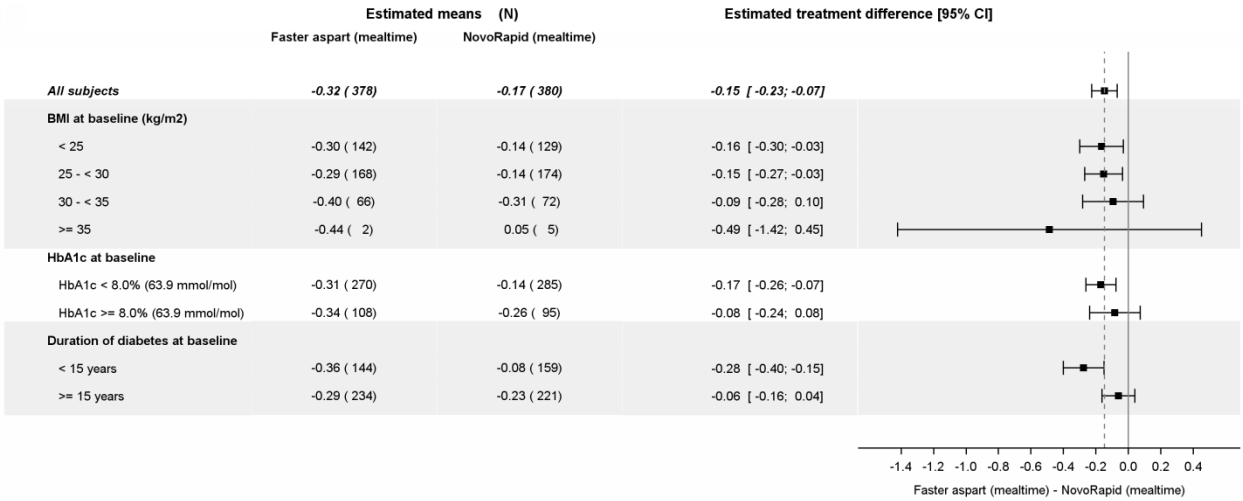
**Figure 22: Forest Plot of Estimated Treatment Difference for Change From Baseline in HbA1c (%) by Demographic Factors for Subjects in Trial 3852 - Postmeal (b) (4) versus NovoLog (FAS)**




Change from baseline in HbA1c is analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30, 34 and 36. The model includes treatment, subgroup, region and strata (combination of bolus adjusting method, basal treatment regimen and CGM subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate. The interaction between treatment, subgroup and visit, between each fixed effect and visit, and between the covariate and visit are also included. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject.

Source: ISE, Appendix 6.4, Figure 39

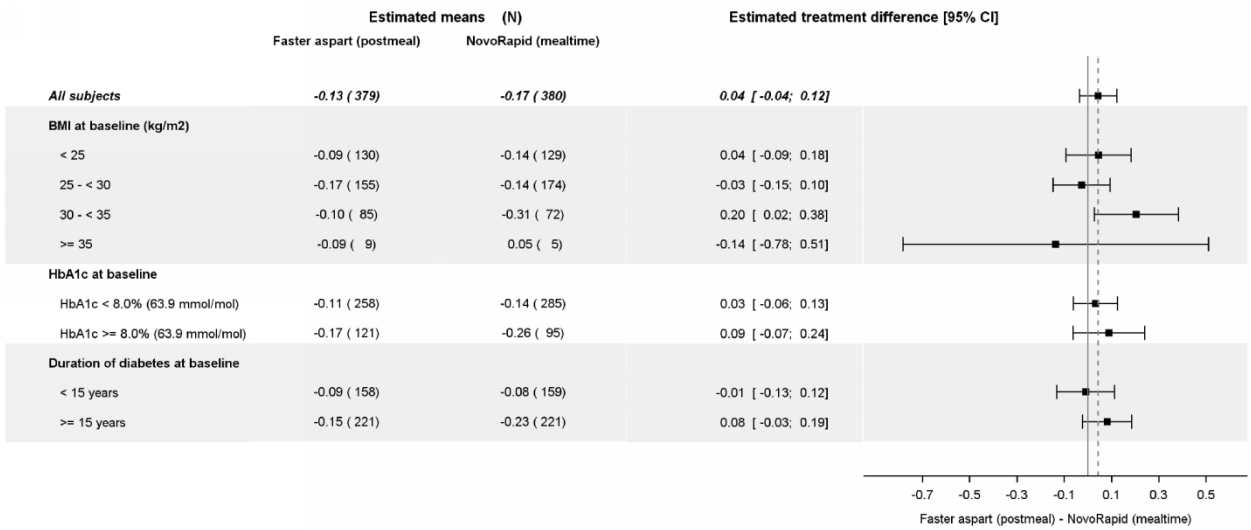
**Figure 23: Forest Plot of Estimated Treatment Difference for Change From Baseline in HbA1c (%) by Diabetes Factors for Subjects in Trial 3852 -Mealtime (b) (4) versus NovoLog (FAS)**




Change from baseline in HbA1c is analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30, 34 and 36. The model includes treatment, subgroup, region and strata (combination of bolus adjusting method, basal treatment regimen and CGM subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate.
The interaction between treatment, subgroup and visit, between each fixed
effect and visit, and between the covariate and visit are also included. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject.
NovoRapid is known as NovoLog in the U.S.

Source: ISE, Appendix 6.4, Figure 31

**Figure 24: Forest Plot of Estimated Treatment Difference for Change From Baseline in HbA1c (%) by Diabetes Factors for Subjects in Trial 3852 -Postmeal (b) (4) versus NovoLog (FAS)**




Change from baseline in HbA1c is analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30, 34 and 36. The model includes treatment, subgroup, region and strata (combination of bolus adjusting method, basal treatment regimen and CGM subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate. The interaction between treatment, subgroup and visit, between each fixed effect and visit, and between the covariate and visit are also included. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject.

Source: ISE, Appendix 6.4, Figure 41

## 6.1.5 Trial 3853 – T2DM

Please refer to Dr. Alex Cambon for his statistical analysis of the primary endpoint for all trials. The results discussed here are the applicant's analyses provided in CSR for trial 3853.

### 6.1.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment, with the objective of demonstrating non-inferiority of (b) (4) compared to NovoLog.

Table 30 provides an overall summary of change in HbA1c from baseline to Week 26. The change from baseline in HbA1c after 26 weeks of treatment was -1.38% with (b) (4) compared to -1.36% with NovoLog, and the treatment difference was -0.02% with the upper bound of the two-sided 95% CI less than 0.4% (95% CI: -0.15; 0.10).

**Table 30: Trial 3853 – Summary of Change in HbA1c (%) From Baseline to Week 26 (FAS)**

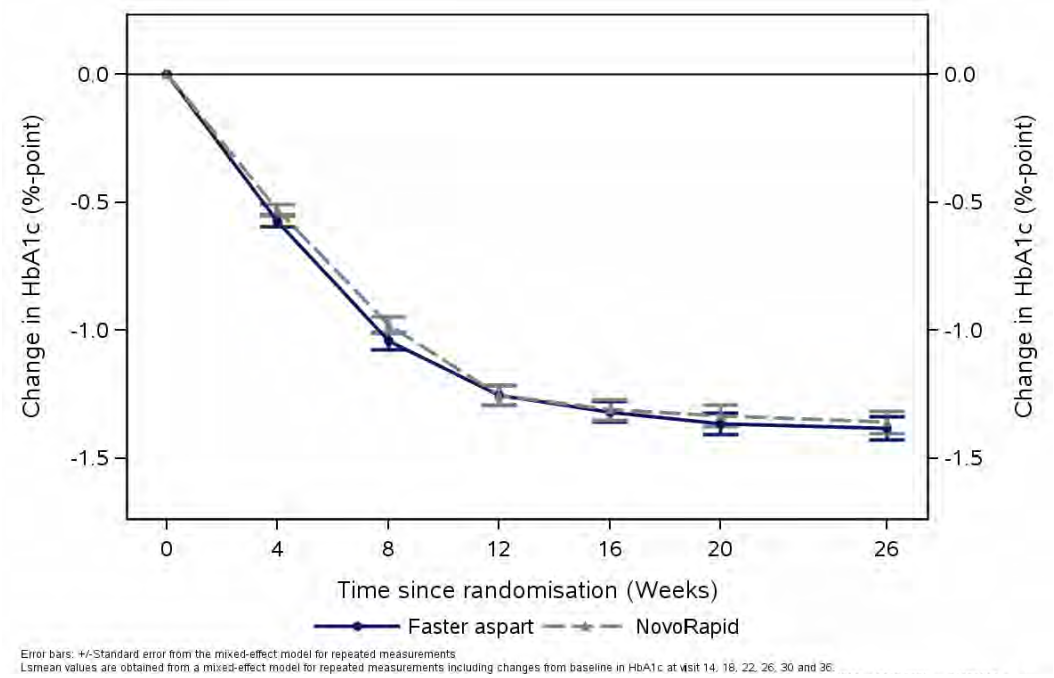
| Treatment | (b) (4) (N=345) | NovoLog (N=344) |
|---|---|---|
| Baseline mean (Week 0) | **7.96** | 7.89 |
| Week 26 mean | 6.63 | 6.59 |
| Adjusted change from baseline | -1.38 | -1.36 |
| Diff vs NovoLog (95% CI) | -0.02 (-0.15; 0.10) | |

Note: Analyzed using a mixed-effect model for repeated measures; model included treatment, region, and CGM strata as fixed effects, subjects as random effect, baseline HbA1c as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 3853, Table 11-2

The sensitivity analyses of the primary endpoint to evaluate the impact of missing data supported the results of the primary analysis (not shown). See Statistical Review for further discussion of sensitivity analyses.

The estimated adjusted mean changes in HbA1c from baseline by treatment week over 26 weeks between treatment arms are depicted in Figure 25. In both treatment arms, the HbA1c decline appeared to have reached a plateau at around 12-16 weeks.

**Figure 25: Trial 3853 – LS Mean Change from Baseline in HbA1c (%) by Treatment Week (FAS)**




Source: CSR 3853, Figure 14.2.33

**HbA1c responders**

The proportion of subjects achieving HbA1c targets of <7% and ≤6.5% is summarized in Table 31. At baseline, slightly more subjects had HbA1c <7% and ≤6.5% in the NovoLog group. After 26 weeks of treatment, 74.8% and 75.9% of subjects achieved HbA1c of <7%, and 54.5% and 56.4% of subjects achieved HbA1c of <6.5% in the (b) (4) and NovoLog group respectively. No statistically significant treatment difference was observed in the proportion of subjects achieving HbA1c <7% and ≤6.5% after 26 weeks of treatment.

**Table 31: Trial 3853 – HbA1c Responders After 26 Weeks (FAS)**

| Treatment | (b) (4) (N=381) | NovoLog (N=344) |
|---|---|---|
| **HbA1c <7%** | | |
| Baseline | 4.9% | 7.3% |
| Week 26 | 74.8% | 75.9% |
| Diff (Week 26 – Baseline) | 69.9% | 68.6% |
| Odds Ratio versus NovoLog (95% CI) | 1.01 (0.70; 1.44) | |
| **HbA1c <7% without severe hypoglycemia** | | |
| Week 26 | 71.9% | 72.7% |
| Odds Ratio versus NovoLog (95% CI) | 1.02 (0.73; 1.44) | |
| **HbA1c <7% without severe hypoglycemia and with minimal weight gain*** | | |
| Week 26 | 35.4% | 37.8% |
| Odds Ratio versus NovoLog (95% CI) | 0.98 (0.71; 1.36) | |
| **HbA1c ≤6.5%** | | |
| Baseline | 0% | 0.9% |
| Week 26 | 54.5% | 56.4% |
| Diff (Week 26 – Baseline) | 54.5% | 55.5% |
| Odds Ratio versus NovoLog (95% CI) | 0.99 (0.73; 1.35) | |
| **HbA1c ≤6.5% without severe hypoglycemia** | | |
| Week 26 | 52.5% | 53.5% |
| Odds Ratio versus NovoLog (95% CI) | 1.02 (0.75; 1.38) | |
| **HbA1c ≤6.5% without severe hypoglycemia and with minimal weight gain*** | | |
| Week 26 | 25.8% | 26.5% |
| Odds Ratio versus NovoLog (95% CI) | 1.08 (0.75; 1.54) | |

*Minimal weight gain was defined as weight gain of <3%.
Analysis based on a logistic regression model including treatment, region and strata as factors and baseline as covariate. For responder endpoints with minimal weight gain baseline body weight is also included as covariate.
Source: CSR 3853, Table 14.2.39, 14.2.40

### 6.1.5.2 Secondary Efficacy Endpoints

The following were confirmatory secondary endpoints in trial 3853 and were part of hierarchical testing for hypothesis testing to evaluate for superiority of (b) (4) compared to NovoLog:

- Step 2: The change from baseline in 2-hour PPG increment (meal test) after 26;

- Step 3: The number of treatment-emergent severe or BG confirmed hypoglycemic events from baseline until Week 26;
- Step 4: The change from baseline in body weight after 26 weeks of randomized treatment.

The superiority of (b) (4) compared to NovoLog in the change from baseline in 2-hour PPG increment could not be confirmed, and the hierarchical testing procedure was stopped in Step 2. Hypoglycemic events are discussed in safety section 7.3.4. This section will summarize the change in PPG increment, body weight, and insulin dose.

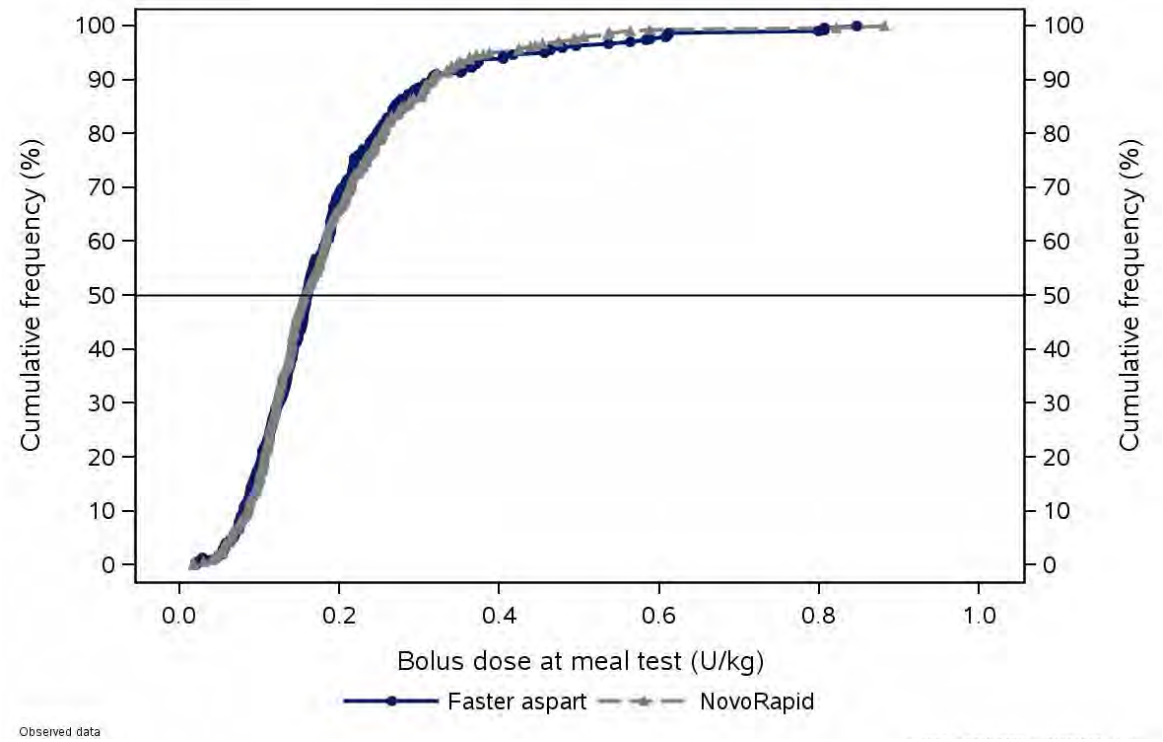
**Postprandial Glucose in Standardized Meal Test**

The changes from baseline in PPG and PPG increment after 26 week of treatment measured as part of a standardized meal test are described here.

At baseline and after 26 weeks of treatment, the PPG was measured 60 minutes (1-hour), 120 minutes (2-hour), 180 minutes (3-hour) and 240 minutes (4-hours) after starting the standardized liquid meal. The 1, 2, 3 and 4-hour PPG increments were derived separately by subtracting each PPG measurement from the plasma glucose measured before the meal test (-2 minutes).

For the meal test at Week 26, the bolus insulin dose for each subject was calculated by the investigator based on the carbohydrate content of the meal and the previous total daily doses of both basal and bolus insulin. The distribution of bolus doses administered at Week 26 during the meal test was similar for both treatment groups, as shown in Figure 26.

**Figure 26: Trial 3853 – Distribution of Bolus Dose During Meal Test in U/kg (FAS)**

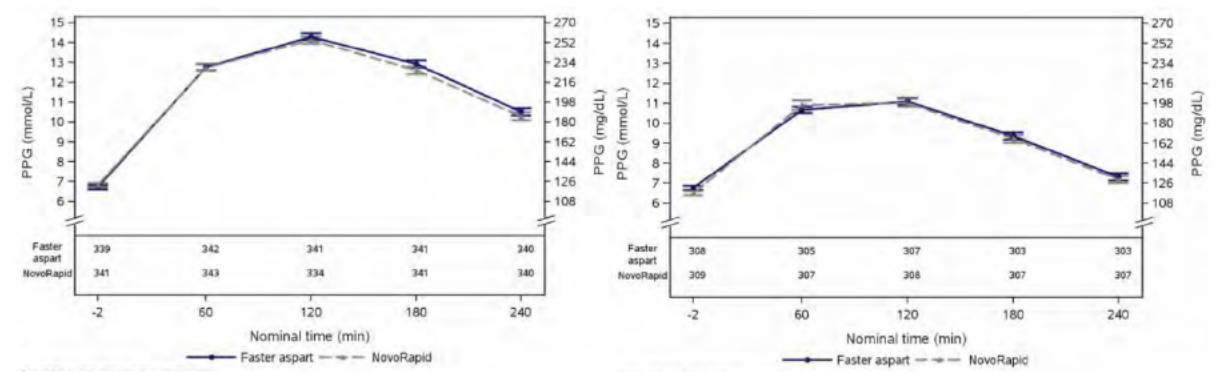



Source: CSR 3853, 14.2.202

Postprandial Glucose (PPG):

The mean plasma glucose (central laboratory-measured) levels measured at baseline and at Week 26 are shown in Figure 27. The mean plasma glucose level peaked at 120 minutes after meal consumption and decreased in both treatment groups. After 26 weeks of treatment, the mean PPG levels declined during 4 hours after meal consumption in both (b) (4) and NovoLog treatment groups.

**Figure 27: Trial 3853 – Mean Postprandial Glucose (Meal Test) at Baseline (left) and at Week 26 (right)**




Full analysis set. PPG: postprandial glucose. Error bars:± standard error (mean). Observed data, except for the cases where glucose or glucagon is administered, in which case the last measurement before rescue intervention will be carried forward. The conversion factor between mmol/L and mg/dL is 0.0555. Numbers under graph are number of subjects per treatment group.

Source: CSR 3853, Figure 11-4

The estimated change from baseline after 26 weeks of treatment in postprandial glucose with meal test at 60, 120, 180, and 240 minutes are summarized in Table 32. The observed PPG reduction at each of this time point was similar between treatment groups without any statistically significant treatment difference.

**Table 32: Trial 3853 Meal Test – Change from Baseline in Postprandial Glucose (mg/dL) After 26 Weeks of Treatment (FAS)**

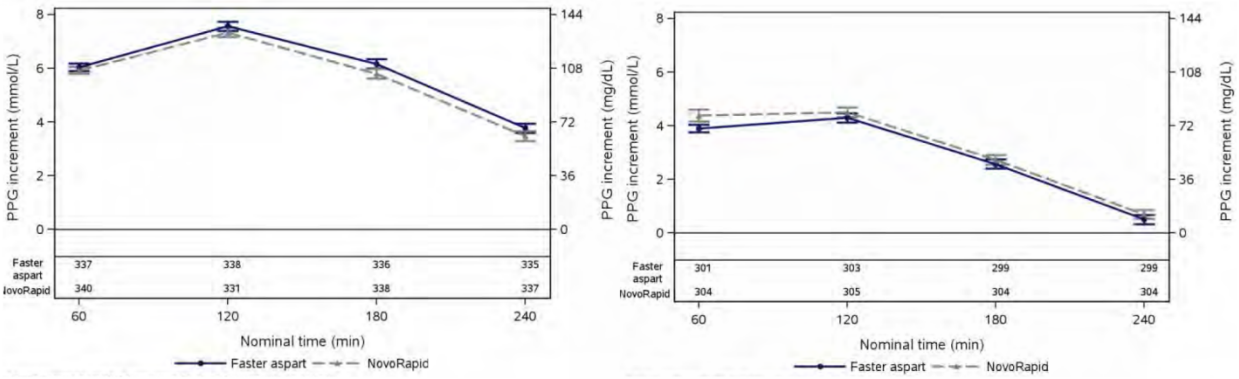
| | (b) (4) (N=345) | NovoLog (N=344) |
|---|---|---|
| PPG at 60 min, N | 304 | 306 |
| Change from baseline at Wk 26, mg/dL | -38.03 | -33.28 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -4.75 (-14.56; 5.06) | |
| PPG at 120 min, N | 305 | 300 |
| Change from baseline at Wk 26, mg/dL | -57.89 | -57.25 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -0.64 (-9.54; 8.26) | |
| PPG at 180 min, N | 300 | 304 |
| Change from baseline at Wk 26, mg/dL | -62.17 | -62.61 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | 0.44 (-8.30; 9.19) | |
| PPG at 240 min, N | 300 | 303 |
| Change from baseline at Wk 26, mg/dL | -55.78 | -56.80 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | 1.03 (-7.37; 9.42) | |

Change from baseline in postprandial glucose (meal test) is analyzed using an ANOVA model with treatment, region and strata as factors and baseline postprandial glucose (meal test) as covariate.
Source: CSR 3853, Table 14.2.44

Postprandial Glucose (PPG) Increment:

The mean increments in plasma glucose during the meal test at baseline and at Week 26 are displayed in Figure 28. The mean PPG increments declined after randomized treatment for both (b) (4) and NovoLog treatment groups.

**Figure 28: Trial 3853 – Postprandial Glucose Increment (Meal Test) at Baseline (left) and at Week 26 (rigt)**




Full analysis set. PPG: postprandial glucose. Error bars:± standard error (mean). Observed data, except for the cases where glucose or glucagon is administered, in which case the last measurement before rescue intervention will be carried forward. The conversion factor between mmol/L and mg/dL is 0.0555. Numbers under graph are number of subjects per treatment group.
Source: CSR 3852, Figure 11-5

The change from baseline in 2-hour PPG increment after 26 weeks of treatment was a confirmatory secondary endpoint (Step 2; Table 33). After 26 weeks of treatment, the mean change from baseline in 2-hour PPG increment was -58.34 mg/dL in the (b) (4) group and -51.77 mg/dL in the NovoLog group, and treatment difference did not reaching statistical difference (-6.57 mg/dL [95% CI: -14.54, 1.41]). Therefore, the superiority in 2-hour PPG increment with (b) (4) compared to NovoLog could not be confirmed.

The estimated treatment difference in change from baseline in 1-hour PPG increment after 26 weeks reached statistical significance favoring (b) (4) group, with treatment difference between (b) (4) versus NovoLog of -10.63 mg/dL (95% CI: -19.56, -1.69). There was no statistically significant differences between treatment for change from baseline in 3 hour and 4 hour PPG increments. See Table 33 for summary of PPG increment change after 26 weeks of treatment.

**Reviewer's comment: Although the 1-hour PPG increment reached statistically significant treatment difference, this was not a pre-specified confirmatory endpoint and the result is considered exploratory.**

**Table 33: Trial 3853 Meal Test – Change from Baseline in Postprandial Glucose Increment (mg/dL) after 26 Weeks of Treatment (FAS)**

| | (b) (4) (N=345) | NovoLog (N=344) |
|---|---|---|
| PPG increment at 60 min, N | 297 | 300 |
| Change from baseline at Wk 26, mg/dL | -38.54 | -27.92 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -10.63 (-19.56; -1.69) | |
| PPG increment at 120 min, N | 299 | 294 |
| Change from baseline at Wk 26, mg/dL | -58.34 | -51.77 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -6.57 (-14.54; 1.41) | |
| PPG increment at 180 min, N | 293 | 298 |
| Change from baseline at Wk 26, mg/dL | -63.12 | -57.22 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -5.91 (-13.82; 2.01) | |
| PPG increment at 240 min, N | 293 | 298 |
| Change from baseline at Wk 26, mg/dL | -56.84 | -51.76 |
| Treatment difference (mg/dL) at Wk 26 versus NovoLog (95% CI) | -5.08 (-12.56; 2.41) | |

Change from baseline in PPG increment (meal test) is analyzed using an ANOVA model with treatment, region and strata as factors and baseline PPG (meal test) as covariate.
Source: CSR 3853, Table 11-5

## Change from Baseline in Body Weight

The mean changes from baseline in body weight after 26 weeks of treatment are as shown in Table 34. Both treatment groups had similar weight gain of about 2.7 kg over 26 weeks of treatment without any treatment difference.

**Table 34: Trial 3853 – Mean Change in Body Weight (kg) After 26 Weeks (FAS)**

| | (b) (4) (N=345) | NovoLog (N=344) |
|---|---|---|
| Baseline | 89.0 | 88.3 |
| Week 26 | 92.1 | 90.8 |
| Adjusted change from baseline* | 2.68 | 2.67 |
| Treatment difference versus NovoLog (95% CI)* | 0 (-0.60; 0.61) | |

*Change from baseline in body weight is analyzed using MMRM including Week 12 and Week 26 visits; model includes treatment, region, strata as fixed effects, subject as random effect, baseline body weight as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 3852, 14.2.96, Table 11.6

## Mean daily insulin dosage (basal, bolus, total)

Table 35 summarize daily basal, bolus, and total insulin dose subjects received at baseline (Week 0 for basal and Week 1 for bolus) and at the end of trial.

## Table 35: Trial 3853 – Daily Basal, Bolus, and Total Insulin Dose in Units/kg and Units

| Visit (Week) | Treatment | Safety analysis set | Descriptive statistics N | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|---|---|
| Daily basal insulin dose (all meals) in U/kg | | | | | | | | |
| Visit 10 (Week 0) | Faster aspart | 341 | 339 | 0.59 | 0.25 | 0.56 | 0.15 | 2.08 |
| | NovoRapid | 341 | 338 | 0.57 | 0.26 | 0.51 | 0.14 | 1.96 |
| Visit 11 (Week 1) | Faster aspart | 341 | 341 | 0.59 | 0.25 | 0.56 | 0.05 | 2.13 |
| | NovoRapid | 341 | 340 | 0.58 | 0.26 | 0.52 | 0.13 | 1.93 |
| End of trial | Faster aspart | 341 | 341 | 0.55 | 0.28 | 0.53 | 0.07 | 2.38 |
| | NovoRapid | 341 | 341 | 0.54 | 0.27 | 0.48 | 0.09 | 1.86 |
| Daily bolus insulin dose (all meals) in U/kg | | | | | | | | |
| Visit 11 (Week 1) | Faster aspart | 341 | 336 | 0.22 | 0.08 | 0.21 | 0.02 | 0.52 |
| | NovoRapid | 341 | 338 | 0.22 | 0.07 | 0.21 | 0.06 | 0.48 |
| End of trial | Faster aspart | 341 | 339 | 0.68 | 0.63 | 0.49 | 0.08 | 4.90 |
| | NovoRapid | 341 | 340 | 0.65 | 0.55 | 0.51 | 0.08 | 4.75 |
| Daily total insulin dose (all meals) in U/kg | | | | | | | | |
| Visit 11 (Week 1) | Faster aspart | 341 | 336 | 0.81 | 0.27 | 0.78 | 0.07 | 2.40 |
| | NovoRapid | 341 | 337 | 0.80 | 0.28 | 0.76 | 0.31 | 2.16 |
| End of trial | Faster aspart | 341 | 339 | 1.24 | 0.78 | 1.02 | 0.32 | 5.11 |
| | NovoRapid | 341 | 340 | 1.18 | 0.69 | 1.02 | 0.24 | 5.18 |
| Daily basal insulin dose (all meals) in U | | | | | | | | |
| Visit 10 (Week 0) | Faster aspart | 341 | 339 | 52.8 | 24.5 | 50.0 | 9 | 224 |
| | NovoRapid | 341 | 338 | 51.1 | 27.7 | 46.0 | 12 | 243 |
| Visit 11 (Week 1) | Faster aspart | 341 | 341 | 52.5 | 25.2 | 50.0 | 6 | 230 |
| | NovoRapid | 341 | 340 | 51.6 | 27.7 | 46.0 | 12 | 231 |
| End of trial | Faster aspart | 341 | 341 | 51.5 | 30.5 | 48.0 | 4 | 268 |
| | NovoRapid | 341 | 341 | 49.6 | 29.4 | 42.0 | 10 | 207 |
| Daily bolus insulin dose (all meals) in U | | | | | | | | |
| Visit 11 (Week 1) | Faster aspart | 341 | 336 | 19.1 | 5.9 | 18.7 | 3 | 48 |
| | NovoRapid | 341 | 338 | 18.8 | 6.2 | 18.3 | 6 | 63 |
| End of trial | Faster aspart | 341 | 339 | 62.9 | 56.9 | 43.0 | 6 | 409 |
| | NovoRapid | 341 | 340 | 59.1 | 51.9 | 45.5 | 9 | 377 |
| Daily total insulin dose (all meals) in U | | | | | | | | |
| Visit 11 (Week 1) | Faster aspart | 341 | 336 | 72.0 | 27.2 | 68.7 | 9 | 259 |
| | NovoRapid | 341 | 337 | 70.4 | 29.5 | 64.7 | 25 | 251 |
| End of trial | Faster aspart | 341 | 339 | 114.5 | 77.3 | 95.0 | 19 | 560 |
| | NovoRapid | 341 | 340 | 108.6 | 71.4 | 91.5 | 22 | 584 |

N: Number of subjects, SD: Standard deviation

Source: CSR 3853, Table 11-15

*Basal Insulin:* The basal insulin dose was titrated weekly using a treat-to-target approach during the run-in period. The mean daily basal insulin dose increased during the run-in period from 0.41 U/kg to 0.59 U/kg in those that were subsequently randomized to (b) (4) versus 0.40 U/kg to 0.57 U/kg in those who were later randomized to NovoLog. After randomization, the basal insulin dose was to remain stable, unless Investigator determined adjustment is needed. After 26 weeks of treatment period, the mean daily basal insulin dose was 0.55 U/kg (0.04 U/kg decrease since baseline) in the (b) (4) group and 0.54 U/kg (0.03 U/kg decrease since baseline) in the NovoLog group.

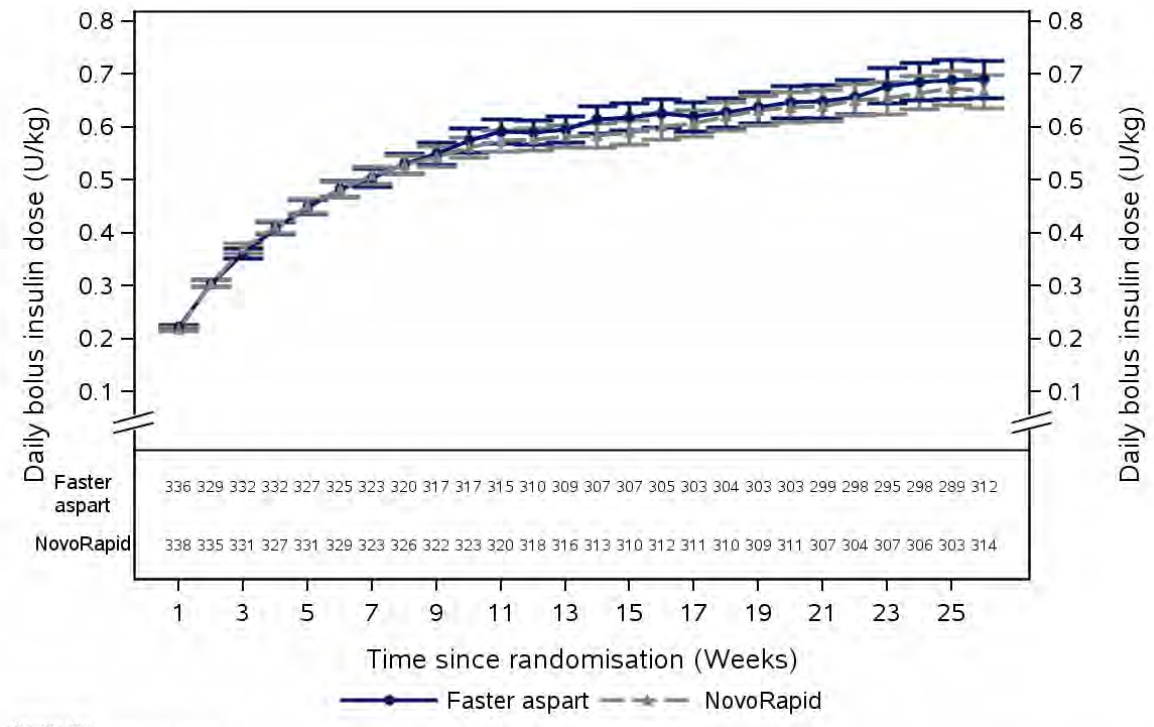
**Reviewer's comment: The basal insulin dose appeared to have increased slightly during treatment period, at a similar dose level in both treatment groups.**

*Bolus Insulin:* After randomization, subjects were randomized to begin treatment with either (b) (4) or NovoLog as mealtime insulin at each main meal in addition to their basal insulin and metformin. Both treatment arms were to initiate mealtime insulin at 4 U before each main meal, and dose adjusted daily based on pre-meal and bedtime SMPGs on the previous day according to pre-specified titration algorithm.

All subjects received a mean of 0.22 U/kg of daily bolus insulin dose by Week 1, which increased to a mean daily bolus dose of 0.68 U/kg in subjects receiving (b) (4) and 0.65 U/kg in subjects receiving NovoLog; however the median daily bolus dose was similar between (b) (4) group (0.49 U/kg; 0.08 to 4.90) compared to NovoLog group (0.51 U/kg; range 0.08 to 4.75 U/kg).

Figure 29 depicts the mean daily bolus insulin dose for each treatment arm over time. The bolus insulin dose increased during the first 8-12 weeks of treatment period, after which it stabilized. Overall, the mean bolus insulin dose seemed to have increased at a similar level in both treatment arms during 26 weeks of treatment period.

**Figure 29: Trial 3853 – Mean Daily Bolus Insulin Dose in Units/kg by Treatment Week (Safety Analysis Set)**




Observed data; error bars are ±standard error (mean)
Source: CSR 3853, Figure 11-16

**Reviewer's comment: All subjects initiated 4 U/kg of mealtime insulin before each main meal after randomization. After 26 weeks of treatment period, the median daily bolus dose was similar (about 0.5 U/kg daily) in both (b) (4) and NovoLog treatment groups.**

*Extra Insulin:* Very few extra bolus insulin doses were administered in this study. In 14.2.11 of CSR where daily bolus insulin dose in units by treatment week are summarized, extra doses of bolus insulin ('Other') were administered between mean bolus extra dose of 0 to 0.1 U for each treatment week during the trial; subjects in (b) (4) treatment group received mean of 0.1 U of bolus insulin dose 4 times during the study period (Weeks 5, 11, 14, and 18) and subjects in NovoLog treatment group received mean of 0.1 U of bolus insulin dose 3 times (Weeks 6, 26, and End of Trial).

**Reviewer's comment: In the applicant's response to our Information Request related to additional/extra bolus insulin doses on June 23, 2016, the applicant summarized that about 11.1% of subjects (38/341) in both (b) (4) and NovoLog group received extra bolus insulin during the trial 3852, and the extra bolus doses corresponded to 0.2% of total number of all bolus dose injections in both**

**treatment group, which corresponded to 292 injections and 260 injections in (b) (4) and NovoLog treatment groups.**

*Total Insulin:* The mean total insulin dose was 0.81 U/kg in subjects receiving (b) (4) and 0.80 U/kg in subjects receiving NovoLog at baseline. After 26 weeks of treatment, the mean total insulin dose increased to 1.24 U/kg (0.43 U/kg increase since baseline) in subjects receiving (b) (4) and 1.18 U/kg (0.38 U/kg increase since baseline) in subjects receiving NovoLog. The median total insulin dose was similar in both treatment groups at the end of study period (1.02 U/kg).

**Reviewer's comment: The increase in total insulin dose in each treatment group appear to correlate well with corresponding increase in bolus insulin dose and slight decrease in basal insulin dose during the treatment period. As discussed above, the amount of extra bolus insulin dose appears to be balanced between treatment groups.**

For both treatment groups, by the end of study treatment period, 56% of total daily insulin dose was being given by bolus insulin dose (Table 36).

**Table 36: Trial 3853 – Basal/Bolus Split of Total Daily Insulin Dose (U/kg)**

| | Faster aspart Basal / Bolus | NovoRapid Basal / Bolus |
|---|---|---|
| Visit 11 (Week 1) | 72 / 27 | 73 / 27 |
| Visit 36 (Week 26) | 44 / 56 | 44 / 56 |

Safety analysis set. Basal: Percentage basal insulin, Bolus: Percentage bolus insulin. For subjects without a measurement at week 26 the predicted value from a mixed-effect model for repeated measurements for daily insulin dose after 26 weeks of treatment is used. Consequently, the percentages do not necessarily match a total of 100%.
Source: CSR 3853, Table 11-17

### 6.1.5.3 Other Endpoints

The change from baseline in FPG is presented below, as this efficacy endpoint have the most clinical relevance.

**Change from Baseline in FPG**

After 26 weeks of treatment, the estimated change from baseline in FPG was 0.36 mg/dL and -4.31 mg/dL in the (b) (4) and NovoLog treatment groups respectively, and there was no statistically significant treatment difference between treatment groups. See Table 37 for summary of FPG data.

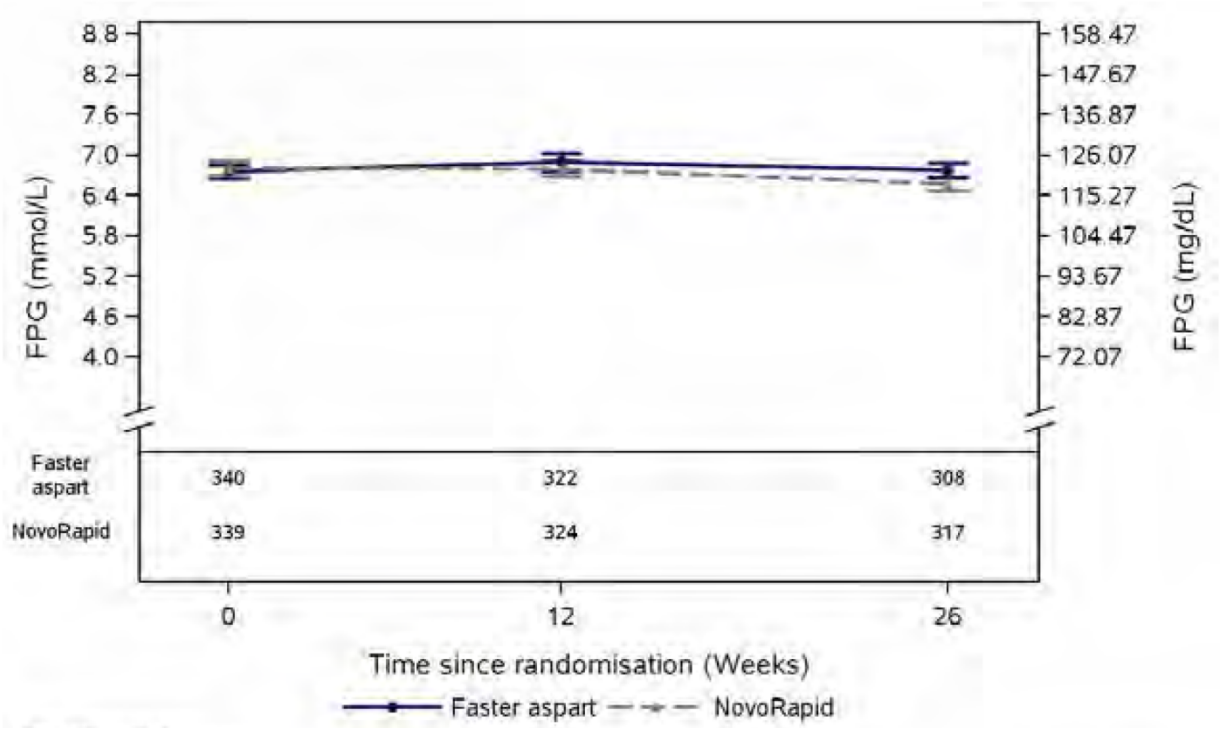
**Table 37: Trial 3853 – Mean Change in Fasting Plasma Glucose (mg/dL) After 26 Weeks (FAS)**

| | (b) (4) | NovoLog |
|---|---|---|
| Baseline Mean | 121.73 | 122.72 |
| Week 26 Mean | 122.04 | 118.41 |
| Adjusted change from baseline* | 0.36 | -4.31 |
| Treatment difference versus NovoLog (95% CI)* | 4.67 (-0.49; 9.85) | |

*Change from baseline is analyzed using MMRM including Week 12, 24, and 26 visit measures; model includes treatment, region, strata as fixed effects, subject as random effect, baseline body weight as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 3853, 14.2.84, 14.2.85

The mean FPG by treatment week is depicted in Figure 30, which remained fairly flat without much change during the study period.

**Figure 30: Trial 3853 – Fasting Plasma Glucose by Treatment Week (FAS)**




Error bars ± standard error (mean); Observed data; Conversion factor between mmol/L and mg/dL 0.0555. Numbers under graph are number of subjects per treatment group.
Source: CSR 3853, Figure 11-14

### 6.1.5.4 Subpopulations

The subgroup analyses on primary efficacy endpoint (i.e., change in HbA1c from baseline to Week 26) by demographics, disease factors, and regions in (b) (4)

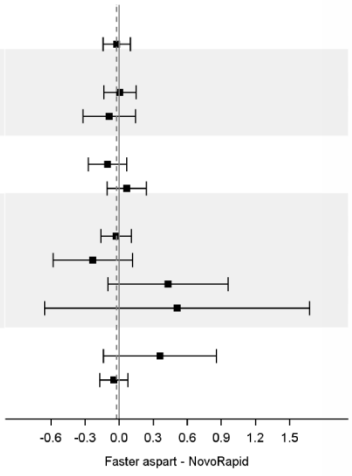
compared to mealtime NovoLog are shown in Figure 31, Figure 32, and Figure 33 respectively.

Overall, the applicant's analysis of treatment effect (mean change in HbA1c from baseline to Week 26) of (b) (4) versus NovoLog was consistent across different subgroups in trial 3853. The only notable subgroup finding was in regions, where the HbA1c reduction with (b) (4) appeared to be larger than NovoLog in subjects from Europe and Asia, whereas the HbA1c reduction was larger with NovoLog in North America (Figure 33).

**Reviewer's comments: The clinical significance of this finding is unclear, but this may be due to chance given the multiple comparisons being made in subgroup analyses. This finding was not observed in subgroup analysis of trial 3852. In addition, the primary analysis model included region as fixed effects to account for any treatment difference that may occur due to this factor.**

**Figure 31: Forest Plot of Estimated Treatment Difference for Change From Baseline in HbA1c (%) by Demographic Factors for Subjects in Trial 3853 - (b) (4) versus NovoLog (FAS)**

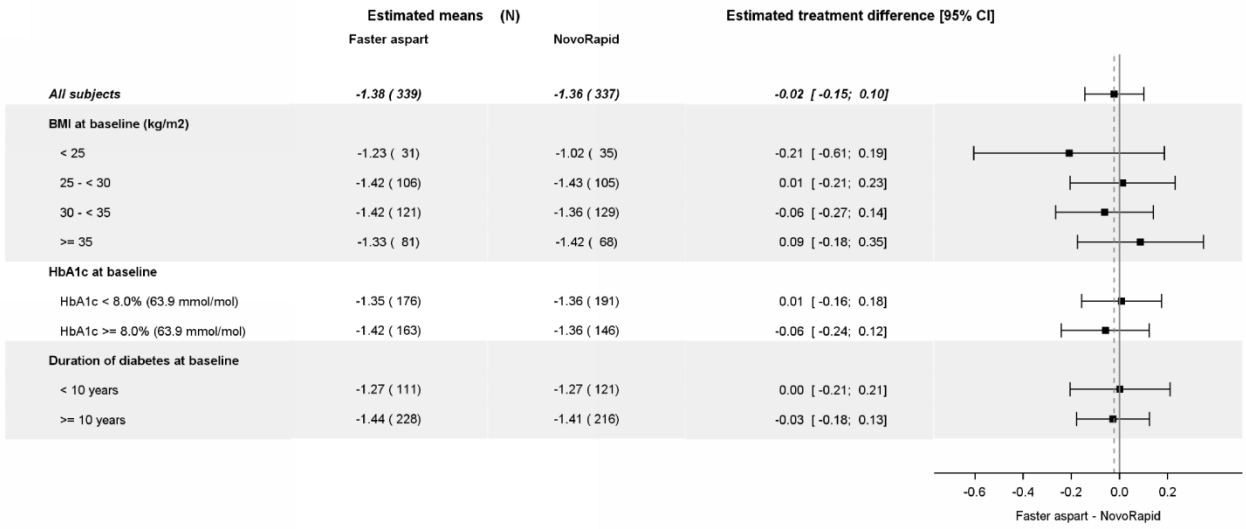
| | Estimated means (N) | | Estimated treatment difference [95% CI] |
|---|---|---|---|
| | Faster aspart | NovoRapid | |
| *All subjects* | *-1.38 ( 339)* | *-1.36 ( 337)* | *-0.02 [ -0.15; 0.10]* |
| Age at baseline | | | |
| 18-64 years | -1.34 ( 237) | -1.35 ( 244) | 0.01 [ -0.14; 0.15] |
| >= 65 years | -1.48 ( 102) | -1.39 ( 93) | -0.09 [ -0.32; 0.15] |
| Sex | | | |
| Female | -1.47 ( 179) | -1.37 ( 169) | -0.10 [ -0.27; 0.07] |
| Male | -1.28 ( 160) | -1.35 ( 168) | 0.07 [ -0.11; 0.24] |
| Race | | | |
| White | -1.45 ( 273) | -1.42 ( 275) | -0.03 [ -0.16; 0.11] |
| Asian | -1.25 ( 40) | -1.01 ( 41) | -0.23 [ -0.58; 0.12] |
| Black or African American | -0.83 ( 21) | -1.27 ( 18) | 0.43 [ -0.10; 0.96] |
| Other | -1.01 ( 5) | -1.52 ( 3) | 0.51 [ -0.66; 1.68] |
| Ethnicity | | | |
| Hispanic or Latino | -1.20 ( 25) | -1.56 ( 18) | 0.36 [ -0.14; 0.86] |
| Not Hispanic or Latino | -1.39 ( 314) | -1.35 ( 319) | -0.05 [ -0.17; 0.08] |




Change from baseline in HbA1c is analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30 and 36. The model includes treatment, subgroup, region and strata (CGM subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate. The interaction between treatment, subgroup and visit, between each fixed effect and visit, and between the covariate and visit are also included. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject.
NovoRapid is known as NovoLog in the U.S.

Source: ISE, Appendix 6.4, Figure 49

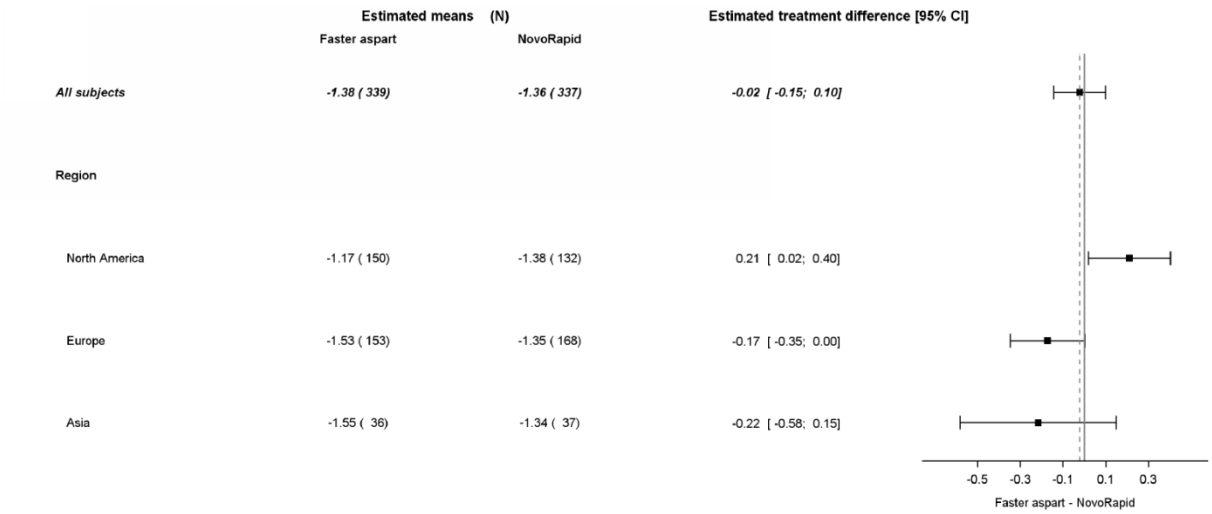
**Figure 32: Forest Plot of Estimated Treatment Difference for Change From Baseline in HbA1c (%) by Disease Factors for Subjects in Trial 3853 - (b) (4) versus NovoLog (FAS)**




Change from baseline in HbA1c is analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30 and 36. The model includes treatment, subgroup, region and strata (CGM subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate. The interaction between treatment, subgroup and visit, between each fixed effect and visit, and between the covariate and visit are also included. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject.
NovoRapid is known as NovoLog in the U.S.

Source: ISE, Appendix 6.4, Figure 51

**Figure 33: Forest Plot of Estimated Treatment Difference for Change From Baseline in HbA1c (%) By Region for Subjects in Trial 3853 - (b) (4) versus NovoLog (FAS)**




Change from baseline in HbA1c is analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30 and 36. The model includes treatment, subgroup, region and strata (CGM subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate. The interaction between treatment, subgroup and visit, between each fixed effect and visit, and between the covariate and visit are also included. An unstructured covariance matrix will be used to describe the variability for the repeated measurements for a subject.
NovoRapid is known as NovoLog in the U.S.

Source: ISE, Appendix 6.4, Figure 55

## 6.1.6 Trial 4049 – T2DM

### 6.1.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in HbA1c after 18 weeks of treatment. Table 38 provides an overall summary of change in HbA1c from baseline to Week 18. After 18 weeks of treatment, the estimated change from baseline in HbA1c was -1.16% in the basal-bolus group and -0.22% in the basal only group, with treatment difference of 0.94% statistically significant (95% CI: -0.17, -0.72).

**Table 38: Trial 4049 – Summary of Change in HbA1c (%) From Baseline to Week 18 (FAS)**

| Treatment | (b) (4) basal (N=116) | Basal (N=120) |
|---|---|---|
| Baseline mean (Week 0) | 7.93 | 7.92 |
| Week 18 mean | 6.78 | 7.70 |
| Adjusted change from baseline | -1.16 | -0.22 |
| Treatment Difference (95% CI) | -0.94 (-0.17; -0.72) | |

Note: Analyzed using a mixed-effect model for repeated measures; model included treatment, region, and strata as fixed effects, subjects as random effect, baseline HbA1c as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 4049, Table 14.2.26, 14.2.27

Sensitivity analyses of the primary endpoint to evaluate the impact of missing data supported the results of the primary analysis (not shown). See the Statistical Review for further discussion of sensitivity analyses.

**HbA1c responders**

The proportion of subjects achieving HbA1c targets of <7% and <6.5% after 18 weeks of treatment in trial 4049 is summarized in Table 39. As would be expected, statistically significant proportion of subjects in basal-bolus treatment group compared to basal only treatment group achieved HbA1c goals.

**Table 39: Trial 4049 – HbA1c Responders After 18 Weeks (FAS)**

| Treatment | (b) (4) +Basal (N=116) | Basal (N=120) |
|---|---|---|
| **HbA1c <7%** | | |
| Baseline | 6.9% | 6.7% |
| Week 18 | 60.3% | 18.3% |
| Odds Ratio (95% CI) | 9.31 (4.71, 18.33) | |
| **HbA1c <7% without severe hypoglycemia** | | |
| Week 18 | 58.6% | 17.5% |
| Odds Ratio (95% CI) | 9.19 (4.64, 18.20) | |
| **HbA1c <7% without severe hypoglycemia and with minimal weight gain*** | | |
| Week 18 | 30.2% | 13.3% |
| Odds Ratio (95% CI) | 2.94 (1.48, 18.20) | |
| **HbA1c ≤6.5%** | | |
| Baseline | 0.9% | 0.8% |
| Week 18 | 44.8% | 6.7% |
| Odds Ratio (95% CI) | 14.67 (6.19, 34.73) | |
| **HbA1c ≤6.5% without severe hypoglycemia** | | |
| Week 18 | 43.1% | 6.7% |
| Odds Ratio (95% CI) | 13.83 (5.81, 32.93) | |
| **HbA1c ≤6.5% without severe hypoglycemia and with minimal weight gain*** | | |
| Week 18 | 20.7% | 5.8% |
| Odds Ratio (95% CI) | 4.56 (1.83, 11.34) | |

*Minimal weight gain was defined as weight gain of <3%.
Analysis based on a logistic regression model including treatment, region and strata as factors and baseline as covariate. For responder endpoints with minimal weight gain baseline body weight is also included as covariate.
Source: CSR 3853, Table 11-3, 11-4

### 6.1.6.2 Secondary Efficacy Endpoints

There was no confirmatory secondary efficacy endpoint in this trial. However, the following secondary supportive endpoints that may have the most clinical relevance are presented below: FPG, body weight, and insulin dose.

**Change from Baseline in FPG**

After 18 weeks of treatment, the estimated change from baseline in FPG was similar in both treatment groups without statistically significant treatment difference, as summarized in Table 37.

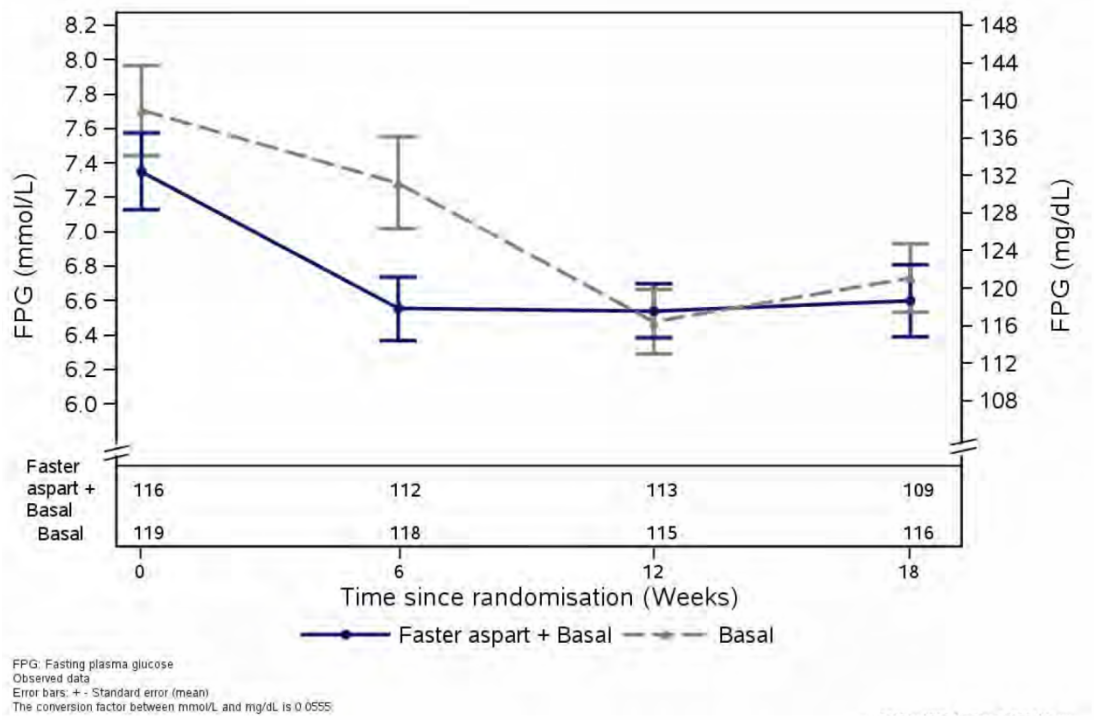
**Table 40: Trial 4049 – Mean Change in Fasting Plasma Glucose (mg/dL) After 18 Weeks (FAS)**

| | (b) (4) +basal (N=116) | Basal (N=120) |
|---|---|---|
| Baseline Mean | 132.49 | 138.91 |
| Week 18 Mean | 118.97 | 121.36 |
| Adjusted change from baseline* | -16.03 | -13.84 |
| Treatment difference (95% CI)* | -2.19 (-11.88; 7.51) | |

*Change from baseline is analyzed using MMRM including changes from baseline in FPG at visit 16, 22, and 28; model includes treatment, region, strata as fixed effects, subject as random effect, baseline FPG as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 4049, Table 14.2.39, 14.2.40

Although the mean FPG declined further at Week 6 in the basal-bolus group compared to basal group, the mean FPG was very similar after 18 weeks of treatment as shown in Figure 34.

**Figure 34: Trial 4049 – Mean Plot of Fasting Plasma Glucose By Treatment Week (FAS)**




Source: CSR 4049, Figure 11-7

## Change from Baseline in Body Weight

The mean changes from baseline in body weight after 18 weeks of treatment are as shown in Table 41. The estimated mean body weight increased 1.83 kg in the basal-

bolus treatment group compared to 0.17 kg in the basal group, and this treatment difference was statistically significant (1.66 [95% CI: 0.89, 2.43]).

**Table 41: Trial 4049 – Mean Change in Body Weight (kg) After 18 Weeks (FAS)**

| | (b) (4) +basal (N=116) | Basal (N=120) |
|---|---|---|
| Baseline | 82.2 | 85.1 |
| Week 18 | 84.1 | 85.5 |
| Adjusted change from baseline* | 1.83 | 0.17 |
| Treatment difference (95% CI)* | 1.66 (0.89, 2.43) | |

*Change from baseline in body weight is analyzed using MMRM including change from baseline in body weight at visit 16, 22, and 28; model includes treatment, region, strata as fixed effects, subject as random effect, baseline body weight as covariate and interaction between all fixed effects and visit, and between the covariate and visit.
Source: CSR 3852, Table 14.2.51, Table 11-4

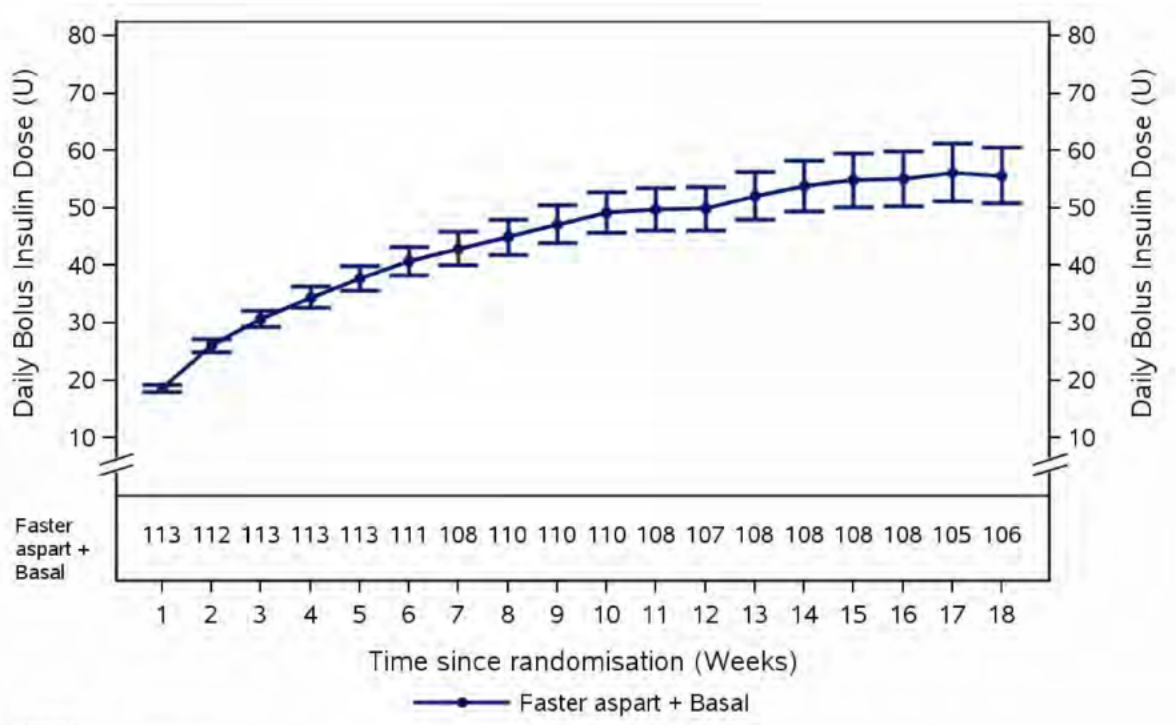
**Reviewer's comment: The greater increase in body weight in the basal-bolus treatment group compared to basal only treatment group is expected since the basal-bolus treatment group is receiving additional basal insulin regimen and insulin treatment is associated with weight gain.**

**Insulin Dose**

The mean daily basal insulin dose at baseline/randomization (Week 0) was 0.6 U/kg in both treatment groups, and was 0.5 U/kg and 0.6 U/kg after 26 weeks of treatment period in (b) (4) plus basal group and basal group respectively.

At randomization, subjects in the (b) (4) plus basal group started 4 U of (b) (4) at each main meal in addition to their basal insulin and metformin treatment, and the mean daily bolus dose increased to 55.6 U (0.66 U/kg) after 18 weeks of treatment period. Figure 35 depicts the mean daily bolus insulin dose for each treatment arm over time. The bolus insulin dose increased during the first 8-12 weeks of treatment period, after which it seemed to have stabilized.

**Figure 35: Mean Daily Bolus Insuln Dose in Units by Treatment Week in Trial 4049 (SAS)**




Source: CSR 4049, Figure 11-9

The mean total daily insulin dose increased from 66.5 U (0.8 U/kg) at Week 1 (1 week after randomization) to 101.8 U (1.2 U/kg) at the end of the trial in the (b) (4) plus basal group due to adding (b) (4) as mealtime insulin. In the basal group, the mean total daily insulin dose was 52.0 U (0.6 U/kg) at Week 1 and 55.9 U (0.6 U/kg) at the end of trial. After 18 weeks of treatment, the mean total insulin dose ratio ( (b) (4) plus basal versus basal) was 1.83 when measured as U.

(b) (4)

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(b) (4)

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing issues are discussed throughout the review.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There was no evidence of loss of effect over time in Phase 3 trials in subjects with T1DM or T2DM during 26 weeks of treatment period.

### 6.1.10 Additional Efficacy Issues/Analyses

None.

# 7 Review of Safety

## ***Safety Summary***

No imbalance in the incidence of deaths was observed between (b) (4) and NovoLog, and none of the deaths were likely to have been caused by the study drug.

In both pivotal T1DM and T2DM trials (3852 and 3853 respectively), the most common serious adverse events and adverse events leading to study withdrawal were related to hypoglycemia. One case of hypersensitivity (signs included facial edema and rash) with positive rechallenge that led to study discontinuation was reported in the (b) (4) plus basal group in trial 4049; the event had positive temporal relationship to (b) (4) administration.

In T1DM trial (3852), the event rate of severe and severe or BG confirmed hypoglycemia was similar between mealtime (b) (4) and NovoLog; the event rate of severe or BG confirmed hypoglycemia was slightly lower with postmeal (b) (4) compared to NovoLog (54.4 PYE versus 58.6 PYE). The majority of severe or BG confirmed hypoglycemia occurred during daytime.

In T2DM trial (3853), the event rate of severe hypoglycemia was slightly higher with mealtime (b) (4) compared to NovoLog, although not statistically significant (16.9 versus 10.9 events per 100 PYE). A slight imbalance in the event rate of severe or BG hypoglycemia was also seen with (b) (4) compared to NovoLog (17.9 versus 16.6 events per 100 PYE). The majority of severe or BG confirmed hypoglycemia occurred during daytime.

Differences were observed in severe or BG confirmed hypoglycemia related to meals between treatment groups. In T1DM trial (3852), a statistically higher rate of severe or BG confirmed hypoglycemic episodes during the *first hour* after a meal was observed for mealtime (b) (4) compared to NovoLog (147.6 and 96.4 per 100 PYE with estimated treatment ratio of 1.48 [95% CI: 1.11, 1.96]). In comparison, lower rate of severe or BG confirmed hypoglycemic episodes occurred with postmeal (b) (4) compared to NovoLog during the first hour after a meal (22.5% or 0.7 PYE versus 28.4% or 1.0 PYE). In T2DM trial (3853), a statistically higher rate of severe or BG confirmed hypoglycemic episodes *within 2 hours* after a meal was observed with (b) (4) compared to NovoLog (226.5 and 148.5 per 100 PYE with estimated treatment ratio of 1.60 [95% CI: 1.13, 2.27]).

In trial 4049, hypoglycemic episodes were more frequent in the (b) (4) plus basal group compared to basal group, which was anticipated given intensification with bolus insulin in the (b) (4) group.

In the 6-week CSII trial (3931), severe or BG confirmed hypoglycemic episodes were reported slightly higher in the (b) (4) group compared to NovoLog (76% or 50 PYE versus 67% or 23 PYE). A trend for higher rates of BG confirmed hypoglycemic episodes related to meals was also observed in (b) (4) treatment group compared to NovoLog, particularly during 1 and 2 hours after a meal, although none reached statistical significance.

Other notable difference in adverse events included injection site reaction that occurred more in T1DM trial 3852, with numerical imbalance not favoring (b) (4) compared to NovoLog: 9 AEs in 7 subjects (1.8%) in the mealtime (b) (4) group, 10 AEs in 9 subjects (2.4%) in the postmeal (b) (4) group, and 3 AEs in 3 subjects (0.8%) in the NovoLog group.

In the diabetes pooled dataset, the only adverse event that occurred at >5% incidence and did not favor (b) (4) compared to NovoLog was nasopharyngitis (13.4% versus 12.8%), but the treatment difference is very small (<1%).

No immunogenicity concerns were identified with (b) (4) However, the conclusion that immunogenicity is not a concern with this product cannot be made at this time because OBP has determined that the assay validation for insulin antibody testing is not adequate (see OBP review and CDTL memo for details).

## 7.1 Methods

**Safety analysis set** was used for the evaluation of safety, which is defined as all subjects who received at least one dose of the investigational product or comparators. Subjects in the safety analysis set contributed 'as treated'.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation primarily focused on the data from the two pivotal Phase 3 trials of basal-bolus insulin regimen in T1DM (trial 3852) and T2DM (trial 3853), as these trials studied the intended patient population, represented the majority of the overall exposure with (b) (4) and allowed comparison of randomized, double-blind safety data with another comparator group (NovoLog). The safety data from the remaining three trials (4049, 3931, (b) (4)) provide supportive safety information. Trials (b) (4) (b) (4) 3931 evaluated the use of (b) (4) in CSII with external pumps.

The safety data will be mainly presented by trial. Also, safety data from the clinical pharmacology trials will be presented briefly by trial if relevant.

The cut-off date for the application for evaluation of safety was March 10, 2015. All trials were completed except for trial 3852, where the additional 26 weeks of treatment were still ongoing at the cut-off date, and only blinded safety data (deaths, SAEs and pregnancies) from this additional treatment period were submitted and reviewed.

### 7.1.2 Categorization of Adverse Events

Adverse events (AEs) were coded using version 17.0 of MedDRA in trials 3852, 3853, 4049, and 3931. (b) (4) All AEs were presented by System Organ Class (SOC) and Preferred Term (PT).

A treatment-emergent AE (TEAE) were defined as an AE that had 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.

AEs included:

- A clinically significant worsening of a concomitant illness;
- A clinically laboratory AE: A clinically laboratory abnormality which is clinically significant, an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management.

An AE is either a serious AE (SAE) or non-serious AE.

SAEs are those that result in death, life-threatening experience, in patient hospitalization or prolongation of hospitalization, persistent or significant disability or capacity, a congenital anomaly or birth defect, or important medical events based on medical judgement.

An external independent Endpoint Adjudication Committee (EAC) was established to adjudicate cardiovascular events after randomization in a blinded and independent manner. Major adverse cardiovascular events (MACE) were defined as a composite endpoint consisting of positively adjudicated non-fatal myocardial infarction (ST segment elevation myocardial infarction [STEMI] or non-STEMI), non-fatal stroke and CV death.

See section 7.3.4 for categorization of hypoglycemia, and 7.3.5.2 for categorization of CV events.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As discussed in section 7.1.1, safety data will mainly be presented by each trial. However, to explore safety events that may be occur at low rate, some safety evaluations were also done for a 'diabetes pool' including trials 3852, 3853, 4049, and 3931. (b) (4) In this diabetes pool, NovoLog and basal insulin comparators are combined as a single comparator treatment group, and all (b) (4) groups (mealtime, postmeal and CSII) are combined and compared to the pooled comparator treatment group in the diabetes pool.

The AE rates and proportion of subjects with AEs were adjusted using the Cochran-Mantel-Haenszel (CMH) method to take study differences in exposure into account.

Diabetes pool was mainly used to look at the incidence of the overall AEs.

The results from a pre-specified meta-analysis of major adverse cardiovascular events (MACEs) are discussed using diabetes pool in section 7.3.5.2 rather than by individual trials.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In five clinical trials (3852, 3853, 4049, 3931, (b) (4)), a total of 1287 subjects were exposed to (b) (4) for a total of 572.2 patient year of exposure (PYE), 775 subjects (354.1 PYE) to NovoLog, and 120 subjects (40.8 PYE) to basal insulin only. See summary of overall exposure by treatment group and by trial in Table 50.

**Table 50: Summary of Exposure by Treatment Group and Trial**

| | Faster aspart (mealtime) N (PYE) | Faster aspart (postmeal) N (PYE) | Faster aspart (total) N (PYE) | NovoRapid N (PYE) | Basal N (PYE) | Comparator N (PYE) | Total N (PYE) |
|---|---|---|---|---|---|---|---|
| Diabetes pool | 386 (186.4) | 377 (183.0) | 1244 (570.5) | 733 (352.5) | 120 ( 40.8) | 853 (393.3) | 2097 (963.8) |
| T1DM | | | | | | | |
| 3852 | 386 (186.4) | 377 (183.0) | 763 (369.4) | 380 (188.9) | | 380 (188.9) | 1143 (558.2) |
| T2DM | | | | | | | |
| 3853 | | | 341 (159.8) | 341 (162.3) | | 341 (162.3) | 682 (322.1) |
| 4049 | | | 115 ( 38.4) | | 120 ( 40.8) | 120 ( 40.8) | 235 ( 79.2) |
| CSII trials | | | | | | | |
| 3931 | | | 25 ( 2.9) | 12 ( 1.4) | | 12 ( 1.4) | 37 ( 4.3) |
| (b) (4) | | | | | | | |

N: Number of subjects, PYE: Patient years of exposure. One patient year of exposure = 365.25 days. Exposure during run-in is excluded. The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931. NovoRapid is known as NovoLog in the U.S. 'Comparator' consists of NovoRapid plus basal insulin.

Source: SCS, Table 1-7

In the diabetes pool, 1244 subjects were exposed to (b) (4) for a total of 570.5 patient year of exposure (PYE), 733 subjects (352.5 PYE) were exposed to NovoLog, and 120 subjects (40.8 PYE) were exposed to only basal insulin therapy. Trials 3852 and 3852 accounted for the majority of exposure to (b) (4) (93%). In the diabetes pool, the majority of subjects had exposure to (b) (4) or NovoLog for at least 6 months (78% [967/1244] versus 88% [646/733]).

As shown in Table 51, the majority of subjects were 18-64 years of age (73%), White (87%), and not Hispanic (90%). The majority of subjects were enrolled from North America or Europe regions. The exposure to (b) (4) was slightly higher for male than for female (308.3 PYE versus 262.1 PYE), but we would not expect this small difference to affect the safety evaluation. In addition, more Hispanic/Latino subjects were exposed to (b) (4) compared NovoLog in the diabetes pool, and this was due to larger Hispanic/Latino subject participation in trial 4049 where there was no comparator NovoLog treatment arm.

**Table 51: Summary of Exposure by Demographic and Baseline Characteristics in the Diabetes Pool**

| | Faster aspart N (PYE) | Comparator N (PYE) | Total N (PYE) |
|---|---|---|---|
| Diabetes pool | | | |
| Age group | | | |
| 18-64 Years | 1048 (486.3) | 703 (325.6) | 1751 (812.0) |
| 65 - < 75 Years | 172 ( 73.0) | 128 ( 57.3) | 300 (130.3) |
| >= 65 Years | 196 ( 84.2) | 150 ( 67.7) | 346 (151.8) |
| >= 75 Years | 24 ( 11.2) | 22 ( 10.4) | 46 ( 21.5) |
| Sex | | | |
| Female | 582 (262.1) | 377 (172.7) | 959 (434.8) |
| Male | 662 (308.3) | 476 (220.6) | 1138 (529.0) |
| Race | | | |
| White | 1096 (507.3) | 724 (335.8) | 1820 (843.2) |
| Asian | 78 ( 32.4) | 79 ( 34.1) | 157 ( 66.4) |
| Black or African American | 44 ( 18.0) | 31 ( 13.8) | 75 ( 31.9) |
| Native Hawaiian or Other Pacific Islander | 3 ( 1.5) | 2 ( 1.0) | 5 ( 2.5) |
| American Indian or Alaska Native | 4 ( 1.6) | | 4 ( 1.6) |
| Other | 3 ( 1.5) | 6 ( 3.1) | 9 ( 4.6) |
| Not Applicable | 16 ( 8.1) | 11 ( 5.5) | 27 ( 13.6) |
| Ethnicity | | | |
| Hispanic or Latino | 128 ( 53.5) | 82 ( 33.3) | 210 ( 86.9) |
| Not Hispanic or Latino | 1116 (516.9) | 771 (360.0) | 1887 (876.9) |
| Region | | | |
| Asia | 67 ( 27.9) | 67 ( 28.8) | 134 ( 56.7) |
| Europe | 522 (241.6) | 360 (169.6) | 882 (411.2) |
| North America | 639 (295.9) | 398 (185.2) | 1037 (481.1) |
| South America | 16 ( 5.1) | 28 ( 9.6) | 44 ( 14.8) |

N: Number of subjects, PYE: Patient years of exposure. One patient year of exposure = 365.25 days. Exposure during run-in is excluded. The 'Diabetes pool' consists of trials 3852, 3853, 4049 and 3931. 'Comparator' consists of NovoRapid plus basal insulin. NovoRapid is known as NovoLog in the U.S. Subjects from Belgium did not provide information about race and are categorised under not applicable.

Source: SCS, Table 1-10

Insulin dose was considered an efficacy endpoint in these trials and was discussed in section 6 for each trial.

### 7.2.2 Explorations for Dose Response

Both (b) (4) and NovoLog were titrated to glycemic goals, and thus exploration for dose response is not applicable.

### 7.2.3 Special Animal and/or In Vitro Testing

None.

### 7.2.4 Routine Clinical Testing

Routine clinical testing included safety assessments as discussed in section 5 of this review. Each clinical trial had routine testing at specified intervals (see Table 87). Routine clinical testing was appropriate for safety evaluation of (b) (4)

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See section 4.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hypoglycemia is a major adverse event associated with insulin. Hypoglycemia episodes are discussed in section 7.3.4.

Immune reactions are also potential adverse events associated with insulin use. Immunogenicity was assessed by antibody measurements and is discussed in section 7.4.6.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths in 4049, CSII trials (3931, (b) (4)), or clinical pharmacology trials after randomization.

A total of 5 deaths occurred in the remaining two clinical trials (3852, 3853), 2 with (b) (4) treatment (one each from 3852 and 3853) and 2 with NovoLog treatment (from 3853), and one additional death from ongoing part of trial 3852 (study treatment remains blinded). One death occurred with NovoLog during 30 days of follow-up in trial 3853. These cases are briefly summarized below.

**Trial 3852 – T1DM**

One death was reported during 26 weeks of treatment period, which occurred in the postmeal (b) (4) treatment group:

- **Subject (b) (6) (cardiac arrhythmia; postmeal (b) (4)** A 39 year old man died on Day 96 of the trial, found lifeless in bed. His medical history included benign hypertension (since (b) (6) diabetic neuropathy (since (b) (6) anxiety and depression (since (b) (6) and chronic back pain (since (b) (6) He was obese with BMI of 32 kg/m$^2$ and had been a smoker (20 cigarettes per day for more than 20 years). The fatal event was reported as 'cardiac arrhythmia' with duration of one day. During the week before the event, the clinical status of the event was reported to be 'uncontrolled diabetes', and the latest SMPGs reported about 2 weeks before the event was 438 mg/dL. The autopsy attributed death due to coronary atherosclerotic disease and cardiac arrhythmia, and this death was later adjudicated and classified as a cardiovascular death (see section 7.3.5.2).

One additional death was reported from the extension period of trial 3852 as of March 10, 2015:

- **Subject (b) (6) (myocardial infarction, blinded treatment):** A 57-year old man with a medical history of stroke, stenosis and macroangiopathy experienced a fatal myocardial infarction after about 6 months of receiving the study drug. No documented acute myocardial infarction or stroke occurred during 30 days before death.

**Trial 3853 – T2DM**

Two treatment-emergent deaths occurred in trial 3853: one death in (b) (4) group (pulmonary embolism) and one death in NovoLog group (acute myocardial infarction). One non-treatment-emergent death was reported in NovoLog group (cardiac arrest) during the 30-day follow-up. All three deaths were classified as cardiovascular deaths after adjudication.

Narratives for these three subjects who died are briefly summarized:

- **Subject (b) (6) (pulmonary embolism; (b) (4)** A 64-year old man had past medical history of arterial hypertension, angina pectoris class 2, atherosclerotic cardiosclerosis, postinfarction cardiosclerosis, chronic heart failure in stage 1, obesity 2 level, coronary artery bypass surgery, myocardial infarction, hepatosteatosis, ischemic heart diease, and diabetic nephropathy. After 204 days of starting study drug ((b) (4) and basal insulin), a myxoma was found in the subject's left ventricle causing thrombosis of the aorta and lower extremities and pulmonary embolism that led to hospitalization. The study drug was permanently discontinued on that day and subject withdrawn from the study. The next day subject underwent thrombectomy and was in intensive care unit after cardiac surgery; the next day myxoma was removed and he was considered to have recovered. Two days after cardiac surgery, he had a pneumothorax and was put on hemodialysis. After 10 days of study drug withdrawal, he developed multi-organ failure and acute renal failure and died. The death certificate reported acute heart failure as cause of death. The death was adjudicated as a cardiovascular death by the EAC.
- **Subject (b) (6) (acute myocardial infarction; NovoLog):** A 52-year old man with past history significant for hypertension, diabetic neuropathy & retinopathy with BMI >30 had an acute myocardial infarction leading to hospitalization after 20 days of receiving the study drug (NovoLog and basal insulin) and died on the same day. The death certificate reported acute myocardial infarction as the cause of death. The event was adjudicated and confirmed as cardiovascular death by EAC.
- **Subject (b) (6) (cardiac arrest, NovoLog):** A 67-year old man with past history significant for percutaneous coronary intervention with bare metal stent in mid right coronary artery, heart catherization, vertebrobasilar transient ischemic attack, carotid artery stenosis 60-70% left 50% right, coronary heart disease, hypercholesterolemia, essential hypertension, macroaniography and smoking experienced cardiac arrest

during the night 21 days after last dose administration of study drug (NovoLog and basal insulin) and died. The death certificate reported cardiac arrest as the cause of death. The event was adjudicated and confirmed as cardiovascular death by EAC.

**Reviewer's comments: These deaths related to CV event occurred in subjects with significant past medical history. CV safety was assessed by the applicant by adjudicating all potential MACE events and conducting a meta-analysis, and is discussed in section 7.3.5.2.**

### 7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal SAEs in either of CSII trials in T1DM (b) (4) or 3931).

**Trial 3852 – T1DM**

Sixty-nine subjects (6%) reported 85 SAEs during the trial. Overall, more SAEs were reported in postmeal (b) (4) group (7.4% [28 subjects] or 19.7 per 100 PYE) compared to mealtime (b) (4) (4.9% [19 subjects] or 13.4 per 100 PYE) or NovoLog groups (5.8% [22 subjects] or 12.7 per 100 PYE). All SAEs are summarized by SOC and PT in Table 52.

There were 26 SAEs of 'hypoglycemia' reported in 24 subjects (10, 11, and 5 SAEs in mealtime (b) (4) postmeal (b) (4) and NovoLog groups respectively). In addition, 10 SAEs of 'hypoglycemic unconsciousness' were reported in 9 subjects (5, 3, and 2 SAEs in mealtime (b) (4) postmeal (b) (4) and NovoLog groups respectively). Hypoglycemia are discussed in section 7.3.4 Significant Adverse Events.

Aside from hypoglycemia, there were no SAE that occurred at ≥1% and occurred more frequently in the mealtime (b) (4) compared or postmeal (b) (4) compared to NovoLog as most other events occurred in one subject.

SAEs leading to dropouts are discussed in section 7.3.3 (Table 55).

## Table 52: Trial 3852 – Serious Adverse Events by SOC and PT (SAS)

| | Faster aspart (meal) N | (%) | E | R | Faster aspart (post) N | (%) | E | R | NovoRapid (meal) N | (%) | E | R | Total N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of subjects | 386 | | | | 377 | | | | 380 | | | | 1143 | | | |
| Total exposure (yrs) | 186.36 | | | | 183.00 | | | | 188.88 | | | | 558.23 | | | |
| Events | 19 | ( 4.9) | 25 | 13.4 | 28 | ( 7.4) | 36 | 19.7 | 22 | ( 5.8) | 24 | 12.7 | 69 | ( 6.0) | 85 | 15.2 |
| Metabolism and nutrition disorders | 9 | ( 2.3) | 11 | 5.9 | 11 | ( 2.9) | 12 | 6.6 | 7 | ( 1.8) | 7 | 3.7 | 27 | ( 2.4) | 30 | 5.4 |
| Hypoglycaemia | 8 | ( 2.1) | 10 | 5.4 | 11 | ( 2.9) | 11 | 6.0 | 5 | ( 1.3) | 5 | 2.6 | 24 | ( 2.1) | 26 | 4.7 |
| Diabetic ketoacidosis | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 2 | ( 0.5) | 2 | 1.1 | 3 | ( 0.3) | 3 | 0.5 |
| Lactic acidosis | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Nervous system disorders | 5 | ( 1.3) | 6 | 3.2 | 5 | ( 1.3) | 5 | 2.7 | 3 | ( 0.8) | 3 | 1.6 | 13 | ( 1.1) | 14 | 2.5 |
| Hypoglycaemic unconsciousness | 4 | ( 1.0) | 5 | 2.7 | 3 | ( 0.8) | 3 | 1.6 | 2 | ( 0.5) | 2 | 1.1 | 9 | ( 0.8) | 10 | 1.8 |
| Carotid artery stenosis | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Hypoglycaemic seizure | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Ischaemic stroke | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Transient ischaemic attack | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Infections and infestations | 2 | ( 0.5) | 2 | 1.1 | 4 | ( 1.1) | 4 | 2.2 | 4 | ( 1.1) | 4 | 2.1 | 10 | ( 0.9) | 10 | 1.8 |
| Bronchitis | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Cellulitis | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Gastroenteritis | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Osteomyelitis | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Pharyngitis | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Pilonidal cyst | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Pneumonia staphylococcal | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Pyelonephritis | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Vestibular neuronitis | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Viral infection | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Gastrointestinal disorders | 1 | ( 0.3) | 1 | 0.5 | 3 | ( 0.8) | 4 | 2.2 | 4 | ( 1.1) | 4 | 2.1 | 8 | ( 0.7) | 9 | 1.6 |
| Pancreatitis | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 2 | ( 0.2) | 2 | 0.4 |
| Abdominal pain | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Anal fistula | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Colitis microscopic | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Diarrhoea | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Nausea | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Peritoneal fibrosis | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Vomiting | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Injury, poisoning and procedural complications | 3 | ( 0.8) | 3 | 1.6 | 5 | ( 1.3) | 5 | 2.7 | 1 | ( 0.3) | 1 | 0.5 | 9 | ( 0.8) | 9 | 1.6 |
| Wrong drug administered | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 2 | ( 0.2) | 2 | 0.4 |
| Ankle fracture | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Fall | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Lower limb fracture | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Lumbar vertebral fracture | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Overdose | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Radius fracture | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Road traffic accident | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Cardiac disorders | 1 | ( 0.3) | 1 | 0.5 | 3 | ( 0.8) | 4 | 2.2 | 0 | | | | 4 | ( 0.3) | 5 | 0.9 |
| Coronary artery disease | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 2 | ( 0.2) | 2 | 0.4 |
| Angina pectoris | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |

Continued on next page

| | Faster aspart (meal) N | (%) | E | R | Faster aspart (post) N | (%) | E | R | NovoRapid (meal) N | (%) | E | R | Total N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arrhythmia | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Arteriosclerosis coronary artery | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Investigations | 0 | | | | 0 | | | | 2 | ( 0.5) | 3 | 1.6 | 2 | ( 0.2) | 3 | 0.5 |
| Blood glucose decreased | 0 | | | | 0 | | | | 1 | ( 0.3) | 2 | 1.1 | 1 | ( 0.1) | 2 | 0.4 |
| Cardiovascular evaluation | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.3) | 1 | 0.5 | 2 | ( 0.2) | 2 | 0.4 |
| Adenocarcinoma of colon | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Papillary thyroid cancer | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Surgical and medical procedures | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 2 | ( 0.2) | 2 | 0.4 |
| Coronary arterial stent insertion | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Coronary revascularisation | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Musculoskeletal and connective tissue disorders | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Musculoskeletal pain | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0

Source: CSR 3852, Table 14.3.1.12

## Trial 3853 – T2DM

Fifty-one SAEs were reported in this trial, with more events reported in the NovoLog group: 20 SAEs in 15 subjects (4.4%; 12.5 events per 100 exposure years) in the (b) (4) group and 31 in 24 subjects (7.0%; 19.1 events per 100 exposure years) the NovoLog group. Of note, four SAEs also led to withdrawal of 4 subjects from the trial: one in the (b) (4) group and 3 subjects in NovoLog group, which are discussed in section 7.3.3.

Table 53 provides an overall summary of SAEs by SOC and PTs. The most frequently reported PT in both groups was hypoglycemia, which are discussed in more detail in section 7.3.4. Reported PTs in SAEs that occurred more than once in the (b) (4) group included 'transitional cell carcinoma' (2 subjects in (b) (4) group) and pneumonia-related PT (one event each of 'lobar pneumonia' and 'pneumonia', both in (b) (4) group).

**Table 53: Trial 3853 – Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Terms – Safety Analysis Set**

| | Faster aspart N (%) | E | R | NovoRapid N (%) | E | R |
|---|---|---|---|---|---|---|
| Number of subjects | 341 | | | 341 | | |
| Total exposure (yrs) | 159.81 | | | 162.26 | | |
| Events | 15 ( 4.4) | 20 | 12.5 | 24 ( 7.0) | 31 | 19.1 |
| Metabolism and nutrition disorders | 2 ( 0.6) | 4 | 2.5 | 3 ( 0.9) | 5 | 3.1 |
| Hypoglycaemia | 2 ( 0.6) | 4 | 2.5 | 3 ( 0.9) | 5 | 3.1 |
| Infections and infestations | 5 ( 1.5) | 5 | 3.1 | 2 ( 0.6) | 2 | 1.2 |
| Bacteraemia | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Cellulitis | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Cholecystitis infective | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Lobar pneumonia | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Osteomyelitis | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Otitis externa | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Pneumonia | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Nervous system disorders | 1 ( 0.3) | 1 | 0.6 | 5 ( 1.5) | 6 | 3.7 |
| Carotid artery stenosis | 0 | | | 2 ( 0.6) | 2 | 1.2 |
| Transient ischaemic attack | 0 | | | 2 ( 0.6) | 2 | 1.2 |
| Carotid artery occlusion | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Ischaemic stroke | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| VIIth nerve paralysis | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Cardiac disorders | 3 ( 0.9) | 3 | 1.9 | 3 ( 0.9) | 3 | 1.8 |
| Acute myocardial infarction | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.3) | 1 | 0.6 |
| Angina unstable | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Cardiomyopathy | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Coronary artery occlusion | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Myocardial ischaemia | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 3 ( 0.9) | 3 | 1.9 | 2 ( 0.6) | 2 | 1.2 |
| Transitional cell carcinoma | 2 ( 0.6) | 2 | 1.3 | 0 | | |
| Cardiac myxoma | 1 ( 0.3) | 1 | 0.6 | 0 | | |
| Refractory anaemia with an excess of blasts | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Renal cancer stage II | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Gastrointestinal disorders | 0 | | | 3 ( 0.9) | 3 | 1.8 |
| Colitis ischaemic | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Gastric polyps | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Inguinal hernia | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Injury, poisoning and procedural complications | 0 | | | 3 ( 0.9) | 3 | 1.8 |
| Fall | 0 | | | 2 ( 0.6) | 2 | 1.2 |
| Wrong drug administered | 0 | | | 1 ( 0.3) | 1 | 0.6 |
| Respiratory, thoracic and mediastinal disorders | 1 ( 0.3) | 1 | 0.6 | 2 ( 0.6) | 2 | 1.2 |
| Pulmonary embolism | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.3) | 1 | 0.6 |
| Chronic obstructive pulmonary disease | 0 | | | 1 ( 0.3) | 1 | 0.6 |

Continued on next page

| | Faster aspart N | (%) | E | R | NovoRapid N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | 0 | | | | 2 | ( 0.6) | 2 | 1.2 |
| Diabetic foot | 0 | | | | 1 | ( 0.3) | 1 | 0.6 |
| Stasis dermatitis | 0 | | | | 1 | ( 0.3) | 1 | 0.6 |
| Surgical and medical procedures | 1 | ( 0.3) | 1 | 0.6 | 1 | ( 0.3) | 1 | 0.6 |
| Cholecystectomy | 1 | ( 0.3) | 1 | 0.6 | 0 | | | |
| Coronary artery bypass | 0 | | | | 1 | ( 0.3) | 1 | 0.6 |
| Ear and labyrinth disorders | 1 | ( 0.3) | 1 | 0.6 | 0 | | | |
| Aural polyp | 1 | ( 0.3) | 1 | 0.6 | 0 | | | |
| Investigations | 0 | | | | 1 | ( 0.3) | 1 | 0.6 |
| Arteriogram coronary | 0 | | | | 1 | ( 0.3) | 1 | 0.6 |
| Renal and urinary disorders | 0 | | | | 1 | ( 0.3) | 1 | 0.6 |
| Renal failure acute | 0 | | | | 1 | ( 0.3) | 1 | 0.6 |
| Vascular disorders | 1 | ( 0.3) | 1 | 0.6 | 0 | | | |
| Hypertension | 1 | ( 0.3) | 1 | 0.6 | 0 | | | |

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 patient years of exposure, yrs: Years.
Treatment-emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. MedDRA version 17.0.
Source: CSR 3853, Table 12-8

**Reviewer's comment: In T1DM population (trial 3852), although the rate of SAE was highest in the postmeal (b) (4) treatment group, aside from hypoglycemia events there is no apparent pattern of SAE differences between treatment groups.**

**In T2DM population (trial 3853), there was a higher rate of SAE in the NovoLog group compared to (b) (4) treatment group, without any apparent SAE pattern for (b) (4) that would be of concern.**

**Trial 4049 – T2DM**

Fifteen SAEs were reported in trial 4049, 8 SAEs in 6 subjects (5.2% or 20.8 per 100 PYE) in the (b) (4) plus basal group compared to 7 SAEs in 5 subjects (4.2% or 17.2 per 100 PYE) in the basal group.

The most frequently reported SAE was 'fall' reported in 2 subjects with (b) (4) plus basal group compared to one subject with basal group. One subject from (b) (4) plus basal group reported "wrong drug administered" which is discussed in section 7.3.5.1.

One SAE of 'peripheral arterial occlusive disease' who received (b) (4) plus basal (subject (b) (6) led to discontinuation from trial (this event is further discussed in section 7.3.3).

**Table 54: Trial 4049 – Summary of Serious Adverse Events by System Organ Class and Preferred Terms (SAS)**

| | Faster aspart + Basal | | | | Basal | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 115 | | | | 120 | | | |
| Total exposure (yrs) | 38.40 | | | | 40.75 | | | |
| Events | 6 | ( 5.2) | 8 | 20.8 | 5 | ( 4.2) | 7 | 17.2 |
| Injury, poisoning and procedural complications | 3 | ( 2.6) | 3 | 7.8 | 2 | ( 1.7) | 2 | 4.9 |
| Fall | 2 | ( 1.7) | 2 | 5.2 | 1 | ( 0.8) | 1 | 2.5 |
| Carbon monoxide poisoning | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Wrong drug administered | 1 | ( 0.9) | 1 | 2.6 | 0 | | | |
| Metabolism and nutrition disorders | 2 | ( 1.7) | 2 | 5.2 | 0 | | | |
| Hypoglycaemia | 2 | ( 1.7) | 2 | 5.2 | 0 | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 | | | | 2 | ( 1.7) | 2 | 4.9 |
| Breast cancer | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Malignant respiratory tract neoplasm | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Cardiac disorders | 1 | ( 0.9) | 1 | 2.6 | 0 | | | |
| Cardiovascular disorder | 1 | ( 0.9) | 1 | 2.6 | 0 | | | |
| Hepatobiliary disorders | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Cholelithiasis | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Infections and infestations | 1 | ( 0.9) | 1 | 2.6 | 0 | | | |
| Respiratory tract infection | 1 | ( 0.9) | 1 | 2.6 | 0 | | | |
| Nervous system disorders | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Hypoglycaemic unconsciousness | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Respiratory, thoracic and mediastinal disorders | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Lung infiltration | 0 | | | | 1 | ( 0.8) | 1 | 2.5 |
| Vascular disorders | 1 | ( 0.9) | 1 | 2.6 | 0 | | | |
| Peripheral arterial occlusive disease | 1 | ( 0.9) | 1 | 2.6 | 0 | | | |

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 exposure years, yrs: Years
Treatment emergent events occur after trial product administration after randomisation and no later than 7 days after last trial product administration.
MedDRA version 17.0
Source: CSR 4049, Table 12-7

## Clinical Pharmacology Trials

Among 9 clinical pharmacology trials, one SAE was reported in trial 3889 where 'pupil unequal' was reported by a subject two days after receiving a single dose of (b) (4) The subject continued in the trial.

**Reviewer's comments: Overall, review of reported serious adverse events did not raise any new safety concerns with (b) (4) compared to NovoLog.**

### 7.3.3 Dropouts and/or Discontinuations

There were no AEs leading to withdrawal in trial (b) (4).

**Trial 3852 – T1DM**

Eleven subjects withdrew from the trial due to AE, 5 subjects (1.3%) in the mealtime (b) (4) group, 4 subjects (1.1%) in the postmeal (b) (4) group, and 2 subjects (0.5%) in the NovoLog group. One subject from postmeal (b) (4) group (subject (b) (6) had a fatal outcome and described in section 7.3.1.

The most common AE leading to dropouts was related hypoglycemia, most frequently in the postmeal (b) (4) group (4 subjects with either hypoglycemia or hypoglycemic unconsciousness) compared to NovoLog group (3 subjects with hypoglycemia or hypoglycemia unconsciousness) and least frequently in the mealtime (b) (4) group (one subject with hypoglycemia and another subject with neuroglycopenia [this subject had 6 episodes of hypoglycemia before neuroglycopenia]). Hypoglycemia is discussed in section 7.3.4.

Five subjects dropped out due to withdrawal criterion #4 (hypoglycemia posing a safety problem): 3 subjects in the postmeal (b) (4) group and 2 subjects in the NovoLog group (Table 55).

In addition, 2 subjects who were in the 'withdrawal by subject' category noted in the CRF that they were dropping out of trial for other safety-related reasons: 1 subject in the mealtime (b) (4) reported "increased hypoglycemia since being on Levemir" and 1 subject in the postmeal (b) (4) reported "lows and highs all the time".

**Table 55: Trial 3852 – Adverse Events Leading to Dropouts and Other Safety-Related Dropouts**

| Subject ID | Preferred term or withdrawal criterion | Duration of treatment[a] (weeks) | Serious (Y/N) | Causality (bolus/basal insulin) | Outcome |
|---|---|---|---|---|---|
| **Faster aspart (meal)** | | | | | |
| (b) (6) | Neuroglycopenia | 1.0 | N | Probable/Unlikely | Recovered |
| | Hypoglycaemia | 4.7 | Y | Possible/Possible | Recovered |
| | Herpes zoster | 10.3 | N | Unlikely/Unlikely | Not recovered |
| | Fall | 4.3 | Y | Unlikely/Unlikely | Recovered |
| | Blood triglycerides increased | 1.6 | N | Unlikely/Unlikely | Recovered |
| | Safety-related WD by subject | 6.1 | NA | NA | NA |
| **Faster aspart (post)** | | | | | |
| (b) (6) | Hypoglycaemic unconsciousness | 8.1 | Y | Probable/Probable | Recovered |
| | Hypoglycaemia | 1.6 | Y | Possible/Unlikely | Recovered |
| | Lactic acidosis | | Y | Unlikely/Unlikely | Recovered |
| | Pneumonia staphylococcal | | Y | Unlikely/Unlikely | Recovered |
| | Overdose | | Y | Unlikely/Unlikely | Recovered |
| | Road traffic accident | 12.3 | Y | Unlikely/Unlikely | Recovered |
| | Arrhythmia | 13.7 | Y | Unlikely/Unlikely | Fatal |
| | WD criterion #4 (hypoglycaemia) | 6.6 | NA | NA | NA |
| | WD criterion #4 (hypoglycaemia) | 4.1 | NA | NA | NA |
| | WD criterion #4 (hypoglycaemia) | 2.6 | NA | NA | NA |
| | Safety-related WD by subject | 13.7 | NA | NA | NA |
| **NovoRapid® (meal)** | | | | | |
| (b) (6) | Hypoglycaemic unconsciousness | 15.0 | Y | Possible/Possible | Recovered |
| | Injection-related reaction | 15.1 | N | Unlikely/Possible | Recovered |
| | WD criterion #4 (hypoglycaemia) | 22.1 | NA | NA | NA |
| | WD criterion #4 (hypoglycaemia) | 21.3 | NA | NA | NA |

[a] at time of withdrawal; Relationship (causality) with trial products (bolus and basal insulins) is based on assessment by the investigator, Y/N: yes/no, WD: withdrawal.

Source: SCS, Table 2-16

**Reviewer's comment: Postmeal (b) (4) treatment group had the most study discontinuations due to hypoglycemia-related events compared to mealtime (b) (4) or NovoLog in trial 3852.**

**Trial 3853 – T2DM**

Five subjects withdrew from the trial due to adverse events, 2 in subjects receiving (b) (4) and 3 in subjects receiving NovoLog. Four events were SAEs (2 of which had fatal outcome and discussed in section 7.3.1; subjects (b) (6)) and one was non-serious AE of 'post infarction angina' (Table 56).

In addition, one subject ((b) (6) from (b) (4) group dropped out due to withdrawal criterion #5 (hypoglycemia posing a safety problem). He did not report any other TEAEs, but did report four hypoglycemic episodes during the month before withdrawn, three asymptomatic and one documented symptomatic episode with plasma glucose of 50 mg/dL. Subject reported self-treat for all these episodes. Two episodes of hypoglycemic episodes with plasma glucose of 50 mg/dL occurred during the week before discontinuation.

Four subjects in the 'withdrawal by subject' category had notes in CRF indicating withdrawal due to other safety-related reasons: 1 in the (b) (4) group reported "withdrawal due to frequent hypoglycemia" and 3 subjects in the NovoLog group reported "mainly hypoglycemic episodes", "subject believes dizziness and vomiting are due to trial product", or "frequent hypoglycemia".

One subject that is not shown in Table 56 from (b) (4) group (subject (b) (6) who withdrew due to 'other' reason discontinued the study due to weight gain and an increasing number of hypoglycemic events after 10 weeks of treatment. He reported one TEAE (diarrhea), and 12 episodes of documented symptomatic and 3 asymptomatic hypoglycemic episodes with the range of plasma glucose of 46-68 mg/dL. Subject reported self-treatment for all these episodes.

**Table 56: Trial 3853 – Adverse Events Leading to Dropouts and Other Safety-Related Dropouts**

| Subject ID | Preferred term or withdrawal criterion | Duration of treatment[a] (weeks) | Serious (Y/N) | Causality (bolus/basal insulin) | Outcome |
|---|---|---|---|---|---|
| **Faster aspart** | | | | | |
| (b) (6) | *Pulmonary embolism* | 29.1 | Y | Possible/Possible | Fatal |
| | *Post infarction angina* | 1.6 | N | Unlikely/Unlikely | Recovered/Resolved |
| | WD criterion #5 (hypoglycaemia) | 8.0 | NA | NA | NA |
| | Safety-related WD by subject | 2.9 | NA | NA | NA |
| **NovoRapid®** | | | | | |
| (b) (6) | *Acute myocardial infarction* | 2.9 | Y | Unlikely/Unlikely | Fatal |
| | *Ischaemic stroke* | 22.7 | Y | Unlikely/Unlikely | Recovered/Resolved |
| | *Renal cancer stage II* | 17.6 | Y | Unlikely/Unlikely | Not recovered/Not resolved |
| | Safety-related WD by subject | 14.1 | NA | NA | NA |
| | Safety-related WD by subject | 13.6 | NA | NA | NA |
| | Safety-related WD by subject | 5.3 | NA | NA | NA |

[a] at time of withdrawal, Relationship (causality) with trial products (bolus and basal insulins) is based on assessment by the investigator, Y/N: yes/no, WD, withdrawal

So

urce: SCS, Table 2-18

**Reviewer's comment: No apparent imbalance was seen between treatment groups for number of patients who discontinued due to adverse events in trial 3853.**

**Trial 4049 – T2DM**

Three AEs led to dropouts, two in the (b) (4) plus basal group (one of which was a SAE) and one in the basal group (due to hematuria). One event of peripheral arterial occlusive disease (also an SAE) occurred in an elderly male with extensive medical history and the event do not appear to be related to the treatment (subject (b) (6)

One hypersensitivity event in the (b) (4) plus basal group led to study discontinuation:

> Subject (b) (6) (hypersensitivity): A 58-year old woman treated with (b) (4) plus basal (insulin detemir) experienced two events of hypersensitivity 7 and 81 days after initiation of treatment. During the first event, she experienced perspiration and **facial edema** 2 hours after an 08:00 bolus dose, and a **rash** in both arms and on the chest around 3 hours after the bolus dose. (b) (4) was

interrupted and reintroduced after 2 days, and again she experienced same symptoms. She had no history of allergy. She was withdrawn from the study when the event recurred.

**Reviewer's comment: This hypersensitivity reaction was temporally related to (b) (4) and recurred when the patient was rechallenged. Hypersensitivity with insulin is a known safety concern and have also been reported with NovoLog as well.**

There were no subjects who withdrew due to hypglycemia or hyperglycemia events. One subject in the 'withdrawal by subject' category had a note in their CRF indicating withdrawal due to other safety-related parameters, as this subject was in the basal group and reported "lack of blood sugar control".

**Trial 3931 – CSII in T1DM**

One non-serious AE that led to withdrawal was reported in a subject who received (b) (4) and experienced worsening of rheumatoid arthritis after 17 days of treatment (subject (b) (6) the subject had a history of rheumatoid arthritis and had been taking diclofenac. After study withdrawal and treatment with methotrexate and prednisolone, the rheumatoid arthritis was considered "recovered/resolved" after 26 days.

(b) (4)

### 7.3.4 Significant Adverse Events - Hypoglycemia

Hypoglycemia is one of major safety endpoints to consider in the benefit-risk profile for a new diabetes product, particularly with an insulin product in type 1 diabetes since people with T1DM are at an increased risk for hypoglycemia.

Hypoglycemic episodes were recorded on a specific hypoglycemia episode form and were generally not reported as AEs. If a hypoglycemic episode met the SAE criteria, then AE and SAE forms were also filled out.

During trials, plasma glucose was to be measured and recorded when hypoglycemia is suspected. Plasma glucose was also measured for 7-point and 4-point SMPG profiles during trials. All plasma glucose values ≤70 mg/dL or >70 mg/dL with hypoglycemic symptoms were to be recorded by the subject in their diary and transferred by the investigator to a hypoglycemic episode form at the next site visit.

The applicant's definition of '**severe hypoglycemia**' was same as ADA definition (i.e., an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions). In addition to ADA classification of hypoglycemia, the applicant also used the following additional categories using the plasma glucose cut-off level of 56 mg/dL rather than ADA criteria of 70 mg/dL:

- **Severe or BG confirmed symptomatic hypoglycemia**: An episode severe according to ADA classification or BG confirmed by a plasma glucose value <56 mg/dL with symptoms consistent with hypoglycemia;
- **BG confirmed hypoglycemia:** An episode that is BG confirmed by plasma glucose value <56 mg/dL with or without symptoms consistent with hypoglycemia;
- **Severe or BG confirmed hypoglycemia:** An episode severe according to ADA classification or BG confirmed by a plasma glucose value <56 mg/dL with or without symptoms consistent with hypoglycemia;

All hypoglycemia were also classified as to whether they were:

- nocturnal (00:01-05:59 inclusive) or daytime;
- related to or unrelated to meals (relation to time since start of meal as occurring during first 1, 2, 4 and 6 hours after a meal).

All hypoglycemic episodes were defined as treatment-emergent if the onset of the episode occurred at the first day of exposure to randomized treatment and no later than one day after the last day of randomized treatment.

Descriptive statistics used the safety analysis set ("as treated"). Statistical analyses of hypoglycemia were done using the full analysis set ("as planned") and not safety analysis set.

The occurrence of severe or BG confirmed hypoglycemia for subjects following carbohydrate counting or bolus dosing algorithm was analyzed using a negative binomial regression model with a log-link function and the logarithm of the time in which the hypoglycemic episode was considered treatment emergent as offset. The model included treatment, region and strata as factors. Analyses of trial 3852 data were stratified per administration of (b) (4) (mealtime and postmeal).

Few hypoglycemic episodes were reported in the clinical pharmacology trials, but will not be discussed in this section as these were reported during the glucose clamp situations, and were small, single-dose trials that may not be relevant for clinical setting.

**Reviewer's comment: This section focuses on severe hypoglycemia and severe or BG confirmed hypoglycemia because these have more clinical precedence and has precedence for labeling.**

**Of note, these trials excluded patients who had recurrent severe hypoglycemia or hypoglycemic unawareness, or hospitalization for diabetic ketoacidosis during past 6 months before screening. Therefore, these trials excluded patients with known predisposition to frequent severe hypoglycemia.**

**Trial 3852: T1DM**

A summary of overall hypoglycemic episodes by classification in trial 3852 is provided in Table 57.

**Table 57: Hypoglycemic Episodes by Classification in Trial 3852**

| | Faster aspart (meal) | | | | Faster aspart (post) | | | | NovoRapid (meal) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 386 | | | | 377 | | | | 380 | | | |
| Total events | 376 | (97.4) | 24091 | 12927 | 368 | (97.6) | 22517 | 12305 | 378 | (99.5) | 23607 | 12499 |
| BG confirmed | 357 | (92.5) | 10947 | 5874 | 358 | (95.0) | 9914 | 5418 | 368 | (96.8) | 11027 | 5838 |
| Severe or BG confirmed symptomatic | 349 | (90.4) | 8830 | 4738 | 347 | (92.0) | 8372 | 4575 | 357 | (93.9) | 9321 | 4935 |
| Severe or BG confirmed | 358 | (92.7) | 10993 | 5899 | 358 | (95.0) | 9961 | 5443 | 370 | (97.4) | 11078 | 5865 |
| NN unclassifiable | 374 | (96.9) | 13098 | 7028 | 366 | (97.1) | 12556 | 6861 | 375 | (98.7) | 12529 | 6633 |
| ADA | | | | | | | | | | | | |
| Severe | 26 | ( 6.7) | 46 | 25 | 30 | ( 8.0) | 47 | 26 | 32 | ( 8.4) | 51 | 27 |
| Documented symptomatic | 362 | (93.8) | 17026 | 9136 | 351 | (93.1) | 16393 | 8958 | 361 | (95.0) | 17599 | 9318 |
| Asymptomatic | 323 | (83.7) | 6583 | 3532 | 328 | (87.0) | 5739 | 3136 | 319 | (83.9) | 5561 | 2944 |
| Probable symptomatic | 79 | (20.5) | 304 | 163 | 64 | (17.0) | 244 | 133 | 72 | (18.9) | 257 | 136 |
| Pseudo-hypoglycaemia | 36 | ( 9.3) | 119 | 64 | 31 | ( 8.2) | 72 | 39 | 42 | (11.1) | 134 | 71 |
| ADA unclassifiable | 12 | ( 3.1) | 13 | 7 | 9 | ( 2.4) | 22 | 12 | 5 | ( 1.3) | 5 | 3 |

Safety analysis set. N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 exposure years, BG: Blood glucose
Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL.
NN unclassifiable: includes events that are non-severe and not BG confirmed and events that cannot be classified due to missing data.
All events are treatment-emergent. Treatment-emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Source: CSR 3852, Table 12-11

***Severe Hypoglycemia:***

Slightly higher proportion of subjects reported severe hypoglycemia in the NovoLog group (8.4%) compared to mealtime (b) (4) (6.7%) or postmeal (b) (4) (8.0%) groups, but the event rate was similar across the treatment groups (Table 57).

The majority of subjects experienced one episode of severe hypoglycemia event (14, 20, and 21 in mealtime (b) (4) postmeal (b) (4) and NovoLog groups respectively), with the rest reporting 2 or more episodes. The highest number of severe hypoglycemic episodes per subject was 7 episodes reported in one subject receiving

postmeal (b) (4) treatment. Her episode was reported to be related to either diet or physical activity, and she had HbA1c of 6.6% after 26 weeks of treatment period:

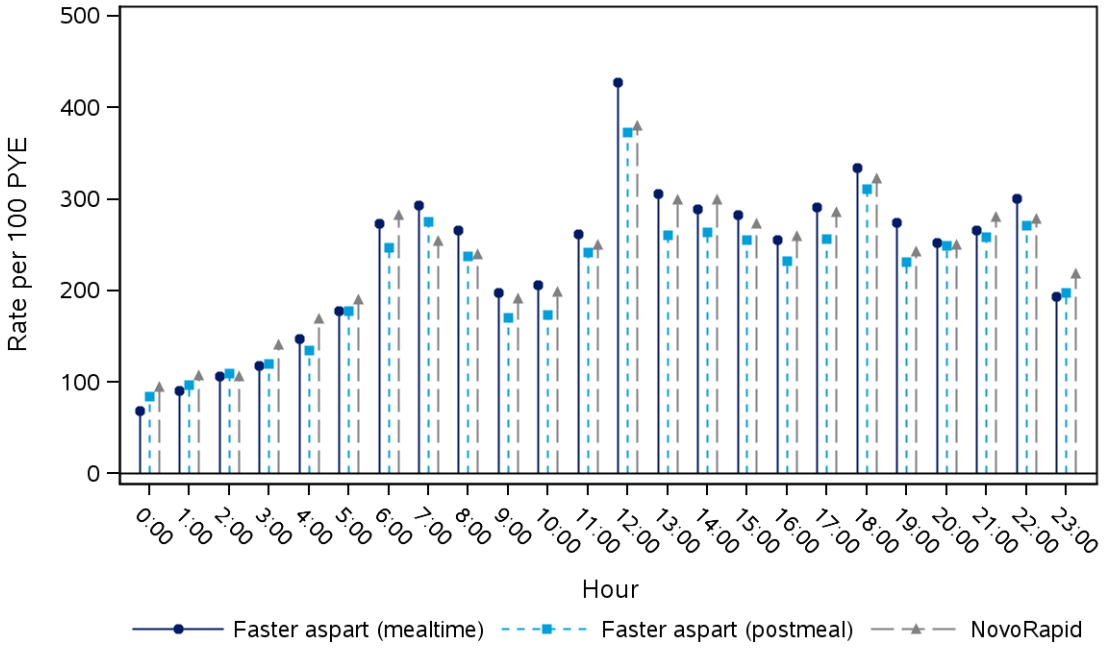
> Subject (b) (6) A 37-year old female subject received postmeal (b) (4) and basal insulin detemir for T1DM. On Day 9 of the trial, she experienced daytime episodes of severe hypoglycemia (PG 37 mg/dL) with symptoms of weakness. The symptoms disappeared after administration of oral carbohydrate by another person. She reported diet change as the reason for the episode. On Day 17, she again experiences daytime severe hypoglycemia (PG 49 mg/dL) with weakness, again alleviated after administration of oral carbohydrate by another person. She reported increased physical activity as reason for the episode. On Day 59, she experienced another daytime severe hypoglycemia (PG 25 mg/dL) with weakness, alleviated with administration of oral carbohydrate by another person; she reported diet change as reason for the episode. On Day 84, she experienced severe hypoglycemia in the morning (PG 26 mg/dL) and evening (PG 36 mg/dL) with weakness, both resolved after treatment with oral carbohydrate by another person. She reported diet change as the reason for the morning episode. On Day 107, she experienced daytime episode of severe hypoglycemia (PG 20 mg/dL) with weakness, resolving after treatment with an intake of oral carbohydrate by another person; she reported increased physical activity as the reason for the episode. On Day 124, she experienced daytime episode of severe hypoglycemia (PG 60 mg/dL) with loss of consciousness. Her condition resolved after treatment with an IV glucose by another person; she reported increased physical activity as the reason for the episode. This episode was the only one reported as SAE.

***Severe or BG Confirmed Hypoglycemia:***

Slightly higher number of proportion of subjects reported severe or BG confirmed hypoglycemia during 26 weeks of treatment in the NovoLog group (97.4%) compared to mealtime (b) (4) (92.7%) or postmeal (b) (4) (95%) treatment groups, and the observed event rate per 100 PYE was similar between NovoLog (5865) and mealtime (b) (4) (5899) and slightly lower in postmeal (b) (4) (5443) (Table 57).

The majority of sever or BG confirmed hypoglycemia occurred during daytime, with 88%, 87%, and 86% of episodes in the mealtime (b) (4) postmeal (b) (4) and NovoLog groups. Figure 37 shows that the episodes were clustered around mealtimes, which would be expected as (b) (4) and NovoLog are mealtime insulins. The highest frequency of severe or BG confirmed hypoglycemic episodes occurred around 12:00 pm.

**Figure 37: Distribution of Severe or BG Confirmed Hypoglycemic Episodes During the Day in Trial 3852**




Treatment emergent episodes occur after trial product administration after randomisation and no later than 1 day after last trial product administration.
Episodes with missing time stamps are excluded. Hour x: [x:00, x:59], PYE: Patient years of exposure
NovoRapid is known as NovoLog in the U.S.

Source: SCS, Figure 2-24

***Severe or BG Confirmed Hypoglycemia Related to A Meal:***

Severe BG confirmed hypoglycemic episodes related to a meal, using 1, 2, 4, and 6 hour points are summarized in Table 58.

**Table 58: Severe or BG Confirmed Hypoglycemia Related to A Meal in Trial 3852**

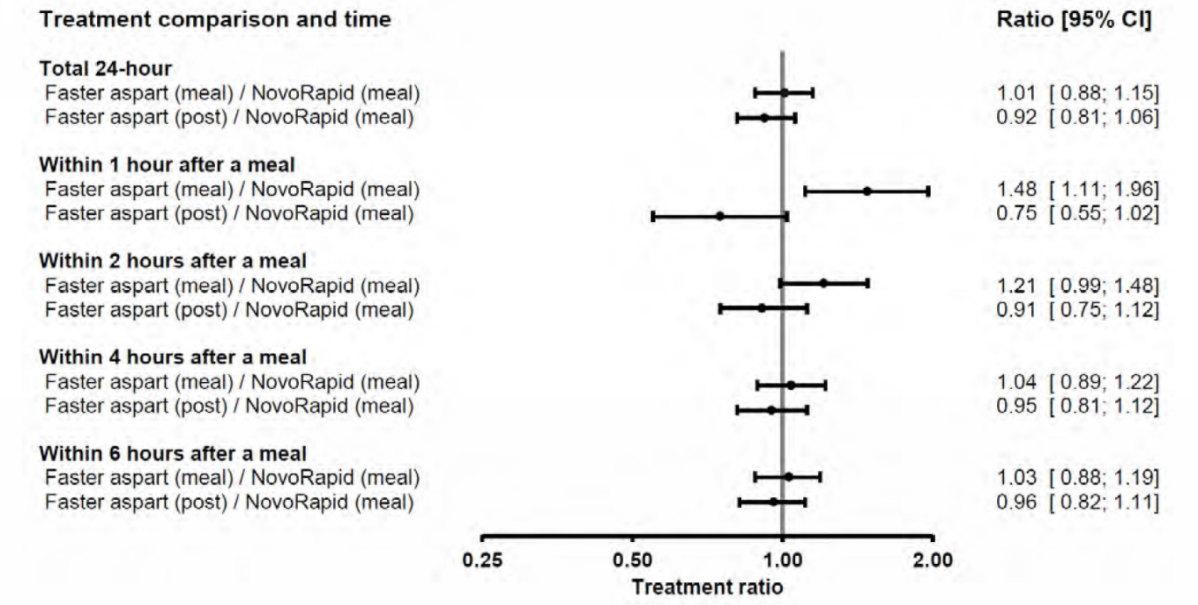
| | Faster aspart (meal) | | | | Faster aspart (post) | | | | NovoRapid (meal) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 386 | | | | 377 | | | | 380 | | | |
| Severe or BG confirmed | | | | | | | | | | | | |
| Within 1 h after a meal | 131 | (33.9) | 275 | 147.6 | 85 | (22.5) | 131 | 71.6 | 108 | (28.4) | 182 | 96.4 |
| Within 2 h after a meal | 258 | (66.8) | 1391 | 746.4 | 231 | (61.3) | 969 | 529.5 | 251 | (66.1) | 1108 | 586.6 |
| Within 4 h after a meal | 338 | (87.6) | 4624 | 2481 | 325 | (86.2) | 4026 | 2200 | 332 | (87.4) | 4395 | 2327 |
| Within 6 h after a meal | 347 | (89.9) | 6903 | 3704 | 338 | (89.7) | 6195 | 3385 | 350 | (92.1) | 6713 | 3554 |
| Total | 358 | (92.7) | 10993 | 5899 | 358 | (95.0) | 9961 | 5443 | 370 | (97.4) | 11078 | 5865 |
| Severe or BG confirmed symptomatic | | | | | | | | | | | | |
| Within 1 h after a meal | 120 | (31.1) | 235 | 126.1 | 77 | (20.4) | 117 | 63.9 | 100 | (26.3) | 166 | 87.9 |
| Within 2 h after a meal | 238 | (61.7) | 1234 | 662.2 | 210 | (55.7) | 847 | 462.8 | 236 | (62.1) | 1023 | 541.6 |
| Within 4 h after a meal | 324 | (83.9) | 4002 | 2147 | 310 | (82.2) | 3532 | 1930 | 322 | (84.7) | 3997 | 2116 |
| Within 6 h after a meal | 335 | (86.8) | 5842 | 3135 | 329 | (87.3) | 5394 | 2948 | 341 | (89.7) | 5964 | 3158 |
| Total | 349 | (90.4) | 8830 | 4738 | 347 | (92.0) | 8372 | 4575 | 357 | (93.9) | 9321 | 4935 |

Safety analysis set. N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 exposure years, BG: Blood glucose
Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL).
'After a meal': after start of a main meal.
Episodes with missing time stamps or with missing main meal time are not included.
All events are treatment-emergent. Treatment-emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Source: CSR 3852, Table 12-13

A higher rate of severe or BG confirmed hypoglycemia was seen for mealtime [redacted] within the first 1 hour after meal compared to NovoLog (Figure 38; estimated rate ratio 1.48 [95% CI: 1.11, 1.96]), with observed event rate of 148, 72, and 96 episodes per 100 PYE in the mealtime [redacted] postmeal [redacted] and NovoLog treatment groups respectively (Table 58). A higher rate in the mealtime [redacted] group compared to NovoLog group was also observed within 2 hours after a meal, but this difference was not statistically significant.

**Reviewer's comments: This increased hypoglycemia rate within 1 and 2 hours after a meal in the mealtime [redacted] group compared to NovoLog should be interpreted in light of the PD profile of [redacted] where lower 1- and 2-hour PPG was seen with mealtime [redacted] compared to NovoLog. The lower hypoglycemia rate within 1 and 2 hours after a meal in the postmeal [redacted] group compared to NovoLog, although not statistically significant, is also in keeping with the PD profile of [redacted] where a higher 1- and 2-hour PPG was seen with postmeal [redacted] compared to NovoLog.**

**Figure 38: Meal-Related and Total Estimated Treatment Ratios Based on Estimated Rates per 100 PYE for Severe or BG Confirmed Hypoglycemic Episodes in Trial 3852**



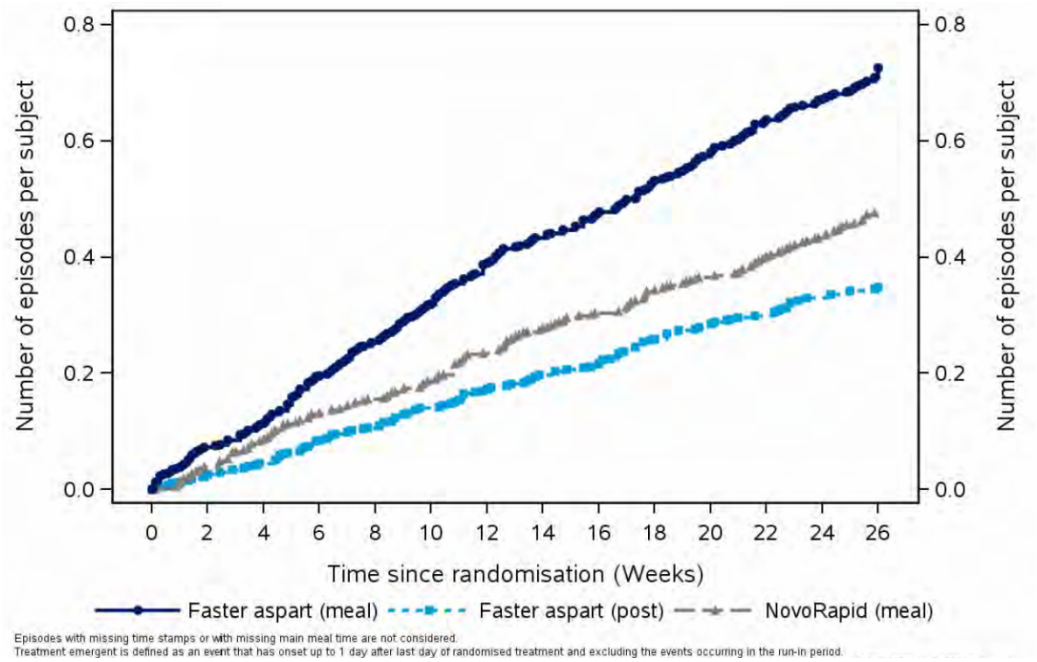

Cross-reference: Based on EOT Tables 14.3.1.39 and 14.3.1.42

CI: Confidence interval. 'After a meal': after start of a main meal. For analyses 1, 2, 4 or 6 hours after a meal: episodes with missing time stamps or with missing main meal time are not included.

Source: CSR 3852, Figure 12-3

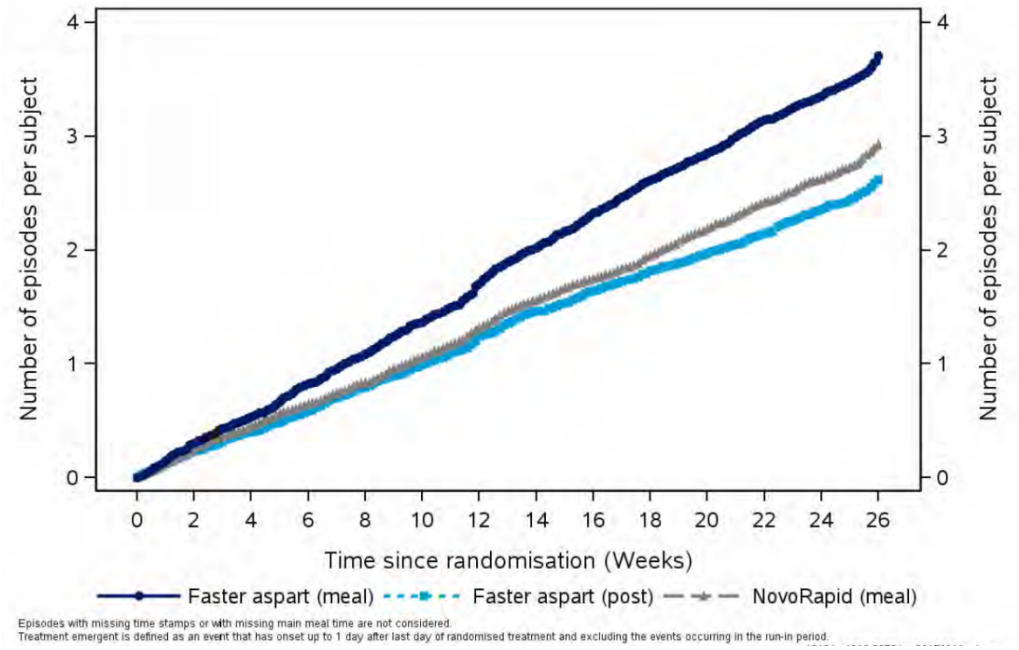
The mean cumulative function of severe or BG confirmed hypoglycemic episodes within 1 hour after a meal is shown in Figure 39 and 2 hours after a meal is shown in Figure 40.

**Figure 39: Mean Cumulative Function: Severe or BG Confirmed Hypoglycemic Episodes 1 Hour After Main Meal in Trial 3852 (SAS)**




Source: CSR 3852, 14.3.1.71

**Figure 40: Mean Cumulative Function: Severe or BG Confirmed Hypoglycemic Episodes 2 Hours After Main Meal in Trial 3852 (SAS)**




Source: CSR 3852, 14.3.1.72

***Hypoglycemia According to Carbohydrate Counting or Bolus Titration Algorithm:***

The applicant conducted *post hoc* analyses to determine whether the type of bolus dosing titration affected the occurrence of severe or BG confirmed hypoglycemia, since in trial 3852 bolus insulin doses were titrated towards preprandial glycemic targets with either carbohydrate counting or a simple dosing algorithm. The number of subjects following each dosing approach for each treatment group is summarized in Table 59.

**Table 59: Subjects by Bolus Insulin Dosing Approach in Trial 3852**

| | **Mealtime faster aspart** | | **Postmeal faster aspart** | | **NovoRapid®/NovoLog®** | |
|---|---|---|---|---|---|---|
| | Carbohydrate counting | Bolus titration algorithm | Carbohydrate counting | Bolus titration algorithm | Carbohydrate counting | Bolus titration algorithm |
| Number of subjects (N) | 224 | 162 | 221 | 156 | 224 | 156 |

Source: SCS, Table 2-40

Table 60 presents the overall and meal-related severe or BG confirmed hypoglycemia in subjects for each dosing approach by treatment group. The rate of severe or BG confirmed hypoglycemia was statistically higher within 1 hour after a meal in subjects adjusting bolus dosing according to the algorithm (estimated rate ratio of 1.91 [95% CI: 1.23, 2.99]). This likely reflect the difference in the bolus dose that subjects received as median bolus doses increased more during 26 weeks of treatment in subjects using the titration algorithm compared to those using carbohydrate counting, as discussed in section 6.1.4.1.

**Table 60: Severe or BG Confirmed Hypoglycemia Related to a Meal in Subjects Following Either Carbohydrate Counting or Bolus Dosing Algorithm in Trial 3852**

| Bolus dosing approach | Time period | Mealtime faster aspart/NovoRapid® | | Postmeal faster aspart/NovoRapid® | |
|---|---|---|---|---|---|
| | | Estimates | Ratio [95% CI] | Estimates | Ratio [95% CI] |
| Carbohydrate counting | **Overall** | | 1.01 [0.85;1.18] | | 0.98 [0.83;1.15] |
| | Within 1 hour after a meal | 96.56/83.98 | 1.15 [0.80; 1.65] | 59.94/83.98 | 0.71 [ 0.48; 1.05] |
| | Within 2 hours after a meal | 545.41/471.31 | 1.16 [0.89; 1.50] | 484.92/471.31 | 1.03 [0.79;1.34] |
| | Within 4 hours after a meal | 2010.06/1982.42 | 1.01 [0.83; 1.24] | 2079.33/1982.42 | 1.05 [0.86;1.28] |
| | Within 6 hours after a meal | 3113.66/3084.03 | 1.01 [0.84; 1.22] | 3192.56/3084.03 | 1.04 [0.86; 1.25] |
| Bolus dosing algorithm | **Overall** | | 1.00 [0.80; 1.25] | | 0.84 [0.68; 1.06] |
| | Within 1 hour after a meal | 206.49/107.87 | 1.91 [1.23; 2.99] | 85.59/107.87 | 0.79 [0.49; 1.29] |
| | Within 2 hours after a meal | 941.17/739.29 | 1.27 [0.93; 1.75] | 573.55/739.29 | 0.78 [0.56; 1.07] |
| | Within 4 hours after a meal | 2961.30/2787.41 | 1.06 [0.81; 1.39] | 2313.42/2787.41 | 0.83 [0.64; 1.08] |
| | Within 6 hours after a meal | 4307.72/4173.32 | 1.03 [0.80; 1.33] | 3556.58/4173.32 | 0.85 [0.66; 1.10] |

N: Number of subjects, CI: Confidence interval, BG: Blood glucose, PYE: Patient years of exposure
CGM: Continuous glucose monitoring
For analysis related to meals, episodes with missing time stamps or with missing main meal time are not included.
Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL)
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Number of hypoglycaemic episodes is analysed using a negative binomial regression model with a log-link function and the logarithm of the time in which the hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, region and strata (combination of basal treatment regimen and CGM and frequently sampled meal test sub-group) as factors.
NovoRapid is known as NovoLog in the U.S.
Source: SCS, Table 2-41

## Trial 3853 – T2DM

A summary of overall hypoglycemic episodes by classification in trial 3853 is provided in Table 61.

**Table 61: Trial 3853 – Classification of Treatment Emergent Hypoglycemic Episodes**

| | Faster aspart | | | | NovoRapid | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 341 | | | | 341 | | | |
| Total events | 322 | ( 94.4) | 10381 | 6496.0 | 321 | ( 94.1) | 9749 | 6008.3 |
| BG confirmed | 262 | ( 76.8) | 2830 | 1770.9 | 250 | ( 73.3) | 2675 | 1648.6 |
| Severe or BG confirmed symptomatic | 245 | ( 71.8) | 2257 | 1412.3 | 223 | ( 65.4) | 2140 | 1318.9 |
| Severe or BG confirmed | 262 | ( 76.8) | 2857 | 1787.8 | 250 | ( 73.3) | 2692 | 1659.1 |
| NN Unclassifiable | 317 | ( 93.0) | 7524 | 4708.2 | 319 | ( 93.5) | 7057 | 4349.2 |
| ADA | | | | | | | | |
| Severe hypoglycaemia | 11 | ( 3.2) | 27 | 16.9 | 13 | ( 3.8) | 17 | 10.5 |
| Asymptomatic hypoglycaemia | 272 | ( 79.8) | 4215 | 2637.6 | 256 | ( 75.1) | 3599 | 2218.1 |
| Documented symptomatic hypoglycaemia | 286 | ( 83.9) | 6038 | 3778.3 | 282 | ( 82.7) | 6044 | 3724.9 |
| Probable symptomatic hypoglycaemia | 22 | ( 6.5) | 56 | 35.0 | 22 | ( 6.5) | 33 | 20.3 |
| Pseudo-hypoglycaemia | 13 | ( 3.8) | 43 | 26.9 | 20 | ( 5.9) | 56 | 34.5 |
| ADA Unclassifiable | 2 | ( 0.6) | 2 | 1.3 | 0 | ( 0.0) | | |

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 patient years of exposure, BG: Blood glucose, NN: Novo Nordisk, ADA: American Diabetes Association. Severe or BG confirmed: subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL). NN unclassifiable: includes events that are non-severe and not BG confirmed and events that cannot be classified due to missing data. Treatment-emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

Source: CSR 3853, Table 12-17

***Severe Hypoglycemia:***

During the treatment period, severe hypoglycemia was reported in 11 subjects (3.2%) and 13 subjects (3.8%) in the (b) (4) and NovoLog treatment groups respectively. Although the proportion of subjects with severe hypoglycemia was slightly higher in the NovoLog group, the number of total events and thus event rate was higher in the (b) (4) treatment group; 27 events (16.9 events per 100 PYE) were reported in the (b) (4) group and 17 events (10.9 events per 100 PYE) were reported in the NovoLog group. The treatment difference in the rate of severe hypoglycemia was 6 events per 100 PYE with the estimated rate ratio of 1.25 ( (b) (4) versus NovoLog) that was not statistically significant (95% CI: 0.44; 3.55).

Of 27 severe hypoglycemic events in the (b) (4) group, 18 episodes were reported in 3 subjects (5 episodes in subject (b) (6) 5 episodes in subject (b) (6) and 8 episodes in subject (b) (6) (Table 62). Two of these subjects ( (b) (6) (b) (6) had HbA1c level of 5.9% and 6.2% respectively after 26 weeks of treatment. Of 17 severe hypoglycemic events in the NovoLog group, 6 episodes were reported in 2 subjects (3 episodes each in subject (b) (6) and (b) (6) with HbA1c level of 6.4% and 5.9% respectively after 26 weeks of randomized treatment.

**Table 62: Frequency of Severe Hypoglycemic Episodes per Subject in Trial 3853**

| Number of episodes of severe hypoglycaemia experienced by subject | Number of subjects | |
|---|---|---|
| | Faster aspart | NovoRapid®/NovoLog® |
| 1 | 7 | 11 |
| 2 | 1 | 0 |
| 3 | 0 | 2 |
| 5 | 2 | 0 |
| 8 | 1 | 0 |

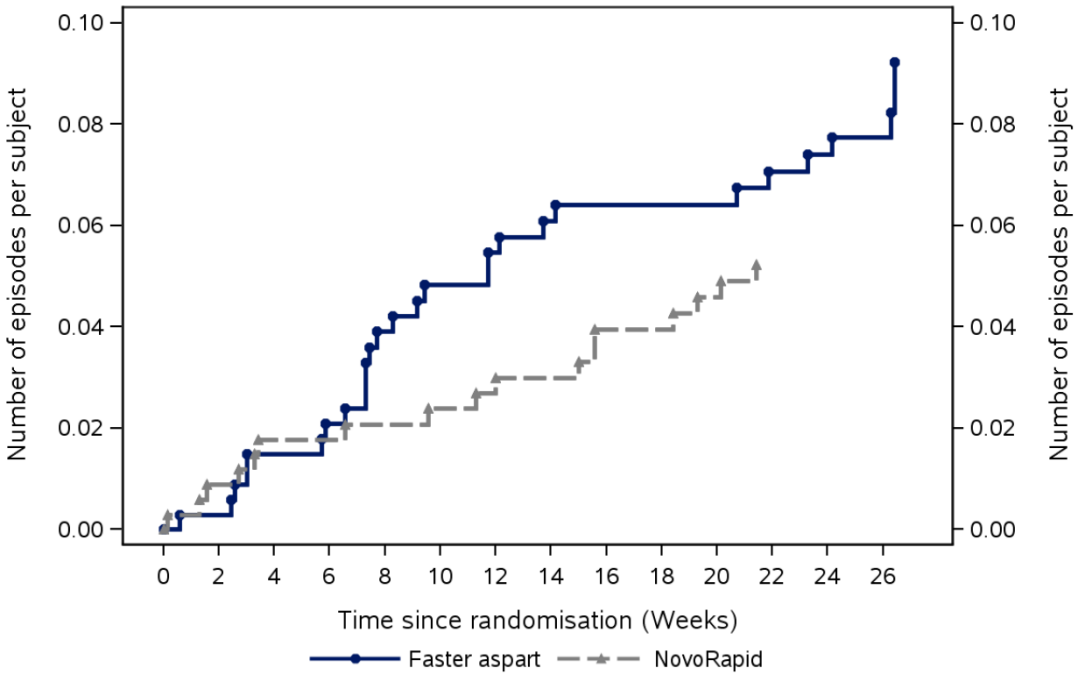
Source: SCS, Table 2-43

A mean cumulative plot of severe hypoglycemic episodes shows that the severe hypoglycemic episodes appear to increase in the (b) (4) group at around Week 7 compared to the NovoLog group (Figure 41). When looking at by treatment weeks (Table 63), there was a higher number of events during Weeks 5-12 in the (b) (4) group compared to NovoLog group.

**Reviewer's comments: The reason for this slight increase in severe hypoglycemia events observed during Weeks 5-12 in the (b) (4) treatment compared to NovoLog is unclear, as daily bolus insulin dose by treatment week appear to suggest comparable daily bolus insulin dose between treatment groups during those weeks (not shown; see CSR 3853, Table 14.2.10).**

**Despite small imbalance between treatment groups, treatment with (b) (4) did not lead to a significantly increased risk of severe hypoglycemia compared to NovoLog.**

**Figure 41: Trial 3853 – Mean Cumulative Plot of Treatment Emergent Severe Hypoglycemic Episodes (Safety Analysis Set)**




Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

Source: CSR 3853, 14.3.1.44

**Table 63: Severe and Severe or BG Confirmed Hypoglycemic Episodes by Classification and Time in Trial 3853 (Safety Analysis Set)**

| | Faster aspart N | (%) | E | R | NovoRapid N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|
| Severe | | | | | | | | |
| 0 - 4 Weeks | 3 | ( 0.9) | 5 | 15.9 | 4 | ( 1.2) | 6 | 19.1 |
| 5 - 8 Weeks | 5 | ( 1.5) | 9 | 37.0 | 1 | ( 0.3) | 1 | 4.1 |
| 9 - 12 Weeks | 4 | ( 1.2) | 5 | 21.2 | 3 | ( 0.9) | 3 | 12.4 |
| 13 - 16 Weeks | 1 | ( 0.3) | 2 | 8.7 | 3 | ( 0.9) | 3 | 12.7 |
| 17 - 20 Weeks | 1 | ( 0.3) | 1 | 4.4 | 3 | ( 1.0) | 3 | 13.0 |
| 21 - 24 Weeks | 3 | ( 1.0) | 3 | 13.5 | 1 | ( 0.3) | 1 | 4.4 |
| >= 25 Weeks | 2 | ( 0.7) | 2 | 24.4 | 0 | | | |
| Severe or BG confirmed | | | | | | | | |
| 0 - 4 Weeks | 162 | ( 47.5) | 527 | 1676.4 | 141 | ( 41.3) | 424 | 1353.1 |
| 5 - 8 Weeks | 155 | ( 46.3) | 545 | 2240.4 | 155 | ( 46.4) | 483 | 1968.0 |
| 9 - 12 Weeks | 157 | ( 48.8) | 542 | 2301.1 | 162 | ( 49.1) | 540 | 2236.7 |
| 13 - 16 Weeks | 133 | ( 42.4) | 400 | 1732.5 | 137 | ( 42.4) | 421 | 1785.1 |
| 17 - 20 Weeks | 134 | ( 43.2) | 383 | 1691.3 | 134 | ( 42.5) | 404 | 1745.3 |
| 21 - 24 Weeks | 107 | ( 35.2) | 304 | 1363.2 | 104 | ( 33.5) | 305 | 1337.2 |
| >= 25 Weeks | 88 | ( 29.3) | 156 | 1899.9 | 64 | ( 21.0) | 115 | 1375.8 |

N: Number of subjects, %: Percentage of subjects at risk, E: Number of events, R: Event rate per 100 patient years of exposure, BG: Blood glucose, NN: Novo Nordisk, ADA: American Diabetes Association
x-y weeks: Greater or equal to x weeks and less than or equal to y weeks plus 6 days
Nocturnal period: The period between 00:01 and 05:59 (both included). Episodes with missing time stamps are excluded
Severe or BG confirmed: subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56mg/dL)
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

Source: CSR 3853, 14.3.1.35

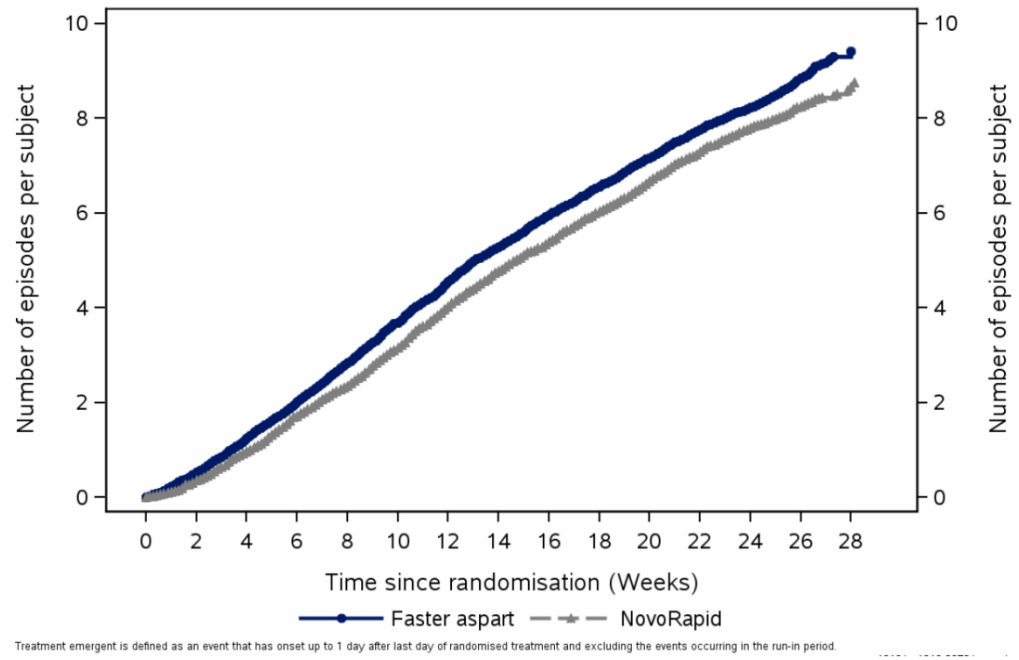
The distribution of severe hypoglycemia was lower during the night and occurred mostly during daytime in both treatment groups (figure not shown; Figure 14.3.1.45 in the CSR).

***Severe or BG Confirmed Hypoglycemia:***

The total number of severe or BG confirmed hypoglycemia was a confirmatory secondary endpoint in this trial (Step 3). A slightly larger proportion of subjects reported severe or BG confirmed hypoglycemic episodes in the (b) (4) group (76.8%) compared to the NovoLog group (73.3%). Four and five of these events in the (b) (4) and NovoLog group respectively were considered SAE.

Similarly, the event rate of severe or BG confirmed hypoglycemia was slightly higher: 1787.8 episodes per 100 PYE in the (b) (4) group and 1659.1 episodes per 100 PYE in the NovoLog group (Table 61). The estimated rate ratio was 1.09 ((b) (4) versus NovoLog) and was not statistically significant (95% CI: 0.88; 1.36). Although not statistically significant, the number of severe or BG confirmed hypoglycemia episodes per subject appear to occur slightly higher with (b) (4) compared to NovoLog during the treatment period, with the curve separation occurring at around Week 4 (Figure 42).

**Figure 42: Trial 3853 – Treatment-Emergent Severe or BG Confirmed Hypoglycemic Episodes (Mean Cumulative Function; Safety Analysis Set)**



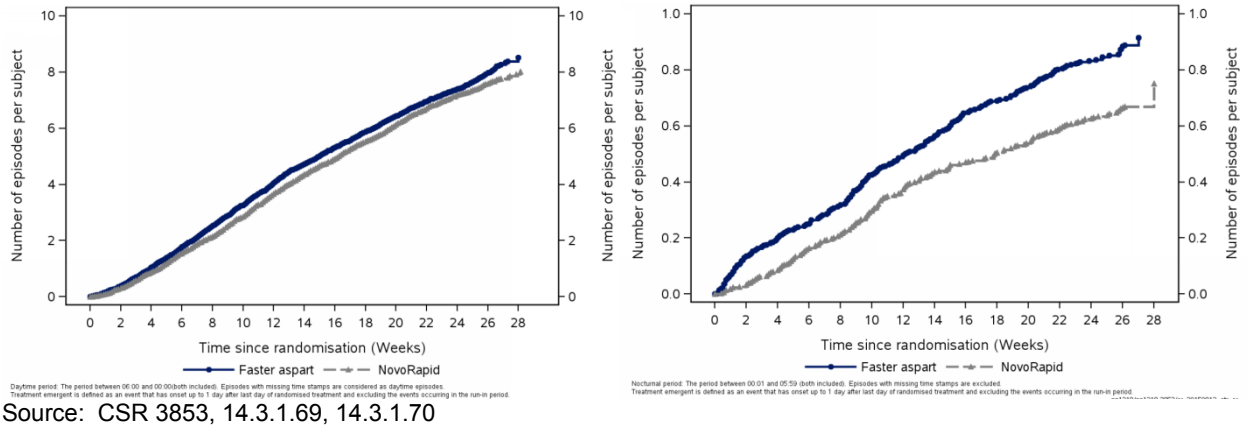

Source: CSR 3853, Figure 12-2

The majority of severe or BG confirmed hypoglycemic episodes were symptomatic. About 71.8% and 65.3% in the (b) (4) and NovoLog group respectively reported severe or BG confirmed symptomatic hypoglycemic episodes (Table 61).

In addition, the majority of severe or BG confirmed hypoglycemic episodes occurred in the daytime, as 75.4% and 71.8% were daytime episodes in the (b) (4) and NovoLog group respectively. The rate of daytime severe or BG confirmed hypoglycemic episodes per subject increased at similar rate in both groups (see left Figure 43).

The nocturnal severe or BG confirmed hypoglycemic episodes occurred slightly more frequently in the (b) (4) group (30.5%; 178.3 episodes per 1000 PYE) compared to NovoLog group (24.6%; 133.7 episodes per 1000 PYE). A plot of nocturnal severe or BG confirmed hypoglycemic episodes show separation of curves with slightly higher rates in the (b) (4) treatment group compared to the NovoLog group starting at/before Week 2 (right of Figure 43). The estimated rate ratio of (b) (4) versus NovoLog for nocturnal severe or BG confirmed hypoglycemia was not statistically significant (estimated rate ratio 1.38 [95% CI: 0.96, 2.00]).

**Figure 43: Trial 3853 – Treatment Emergent Daytime (Left) and Nocturnal (Right) Severe or BG Confirmed Hypoglycemic Episodes (Mean Cumulative Function; Safety Analysis Set)**




Source: CSR 3853, 14.3.1.69, 14.3.1.70

The nocturnal severe or BG confirmed hypoglycemic episodes appeared to have occurred in a higher proportion of subjects and at higher event rate in subjects in the (b) (4) group compared to NovoLog group during the first 4 weeks of treatment, and then again during Weeks 13-16 (Table 64). The reason for this is unclear.

**Table 64: Trial 3853 – Summary of Severe or BG Confirmed Nocturnal Hypoglycemic Episodes by Time (Safety Analysis Set)**

| | Faster aspart N | (%) | E | R | NovoRapid N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|
| Number of subjects | 341 | | | | 341 | | | |
| Total events | 156 | ( 45.7) | 598 | 374.2 | 136 | ( 39.9) | 457 | 281.6 |
| Severe or BG confirmed | | | | | | | | |
| 0 - 4 Weeks | 47 | ( 13.8) | 77 | 244.9 | 31 | ( 9.1) | 40 | 127.7 |
| 5 - 8 Weeks | 33 | ( 9.9) | 46 | 189.1 | 27 | ( 8.1) | 42 | 171.1 |
| 9 - 12 Weeks | 37 | ( 11.5) | 49 | 208.0 | 30 | ( 9.1) | 50 | 207.1 |
| 13 - 16 Weeks | 34 | ( 10.8) | 45 | 194.9 | 14 | ( 4.3) | 25 | 106.0 |
| 17 - 20 Weeks | 22 | ( 7.1) | 32 | 141.3 | 22 | ( 7.0) | 29 | 125.3 |
| 21 - 24 Weeks | 16 | ( 5.3) | 23 | 103.1 | 15 | ( 4.8) | 20 | 87.7 |
| >= 25 Weeks | 13 | ( 4.3) | 13 | 158.3 | 9 | ( 3.0) | 11 | 131.6 |

N: Number of subjects, %: Percentage of subjects at risk, E: Number of events, R: Event rate per 100 patient years of exposure, BG: Blood glucose, NN: Novo Nordisk, ADA: American Diabetes Association
x-y weeks: Greater or equal to x weeks and less than or equal to y weeks plus 6 days
Nocturnal period: The period between 00:01 and 05:59 (both included). Episodes with missing time stamps are excluded
Severe or BG confirmed: subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56mg/dL)
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

Source: CSR 3853, 14.3.1.36

***Severe or BG Confirmed Hypoglycemia Related to A Meal:***

Severe BG confirmed hypoglycemic episodes related to a meal, using 1, 2, 4, and 6 hour points are summarized in Table 65. The event rates of severe or BG confirmed hypoglycemic episodes within 2 hours of a meal were 226.5 and 148.5 per 100 PYE in the [redacted] and NovoLog group respectively (Table 65), with treatment difference between [redacted] and NovoLog of about 78 per 100 PYE. The estimated rate ratio of [redacted] versus NovoLog for severe or BG confirmed hypoglycemic episodes within 2 hours after a meal was statistically significantly higher in subjects in the [redacted] treatment group after 26 weeks (1.16 [95% CI: 1.13, 2.27]). Also see Figure 44.

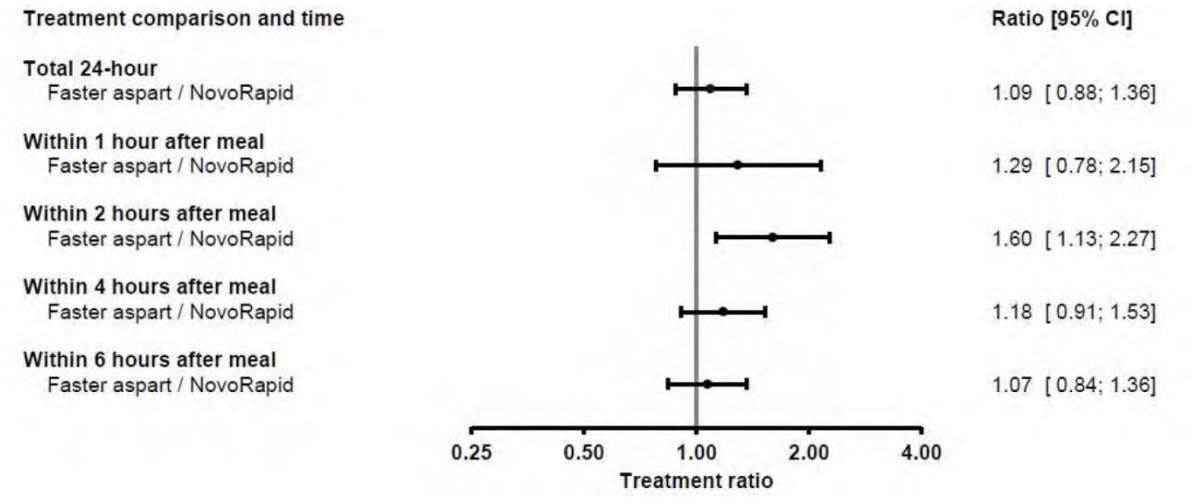
## Table 65: Trial 3853 – Summary of Severe or BG Confirmed Hypoglycemic Episodes Related to a Meal (Safety Analysis Set)

| | Faster aspart | | | | NovoRapid | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 341 | | | | 341 | | | |
| Severe or BG confirmed | | | | | | | | |
| Up to 1 hour after a meal | 45 | ( 13.2) | 78 | 48.8 | 39 | ( 11.4) | 62 | 38.2 |
| Up to 2 hours after a meal | 112 | ( 32.8) | 362 | 226.5 | 96 | ( 28.2) | 241 | 148.5 |
| Up to 4 hours after a meal | 208 | ( 61.0) | 1248 | 780.9 | 179 | ( 52.5) | 1092 | 673.0 |
| Up to 6 hours after a meal | 238 | ( 69.8) | 2036 | 1274.0 | 217 | ( 63.6) | 1987 | 1224.6 |
| Total severe or BG confirmed | 262 | ( 76.8) | 2857 | 1787.8 | 250 | ( 73.3) | 2692 | 1659.1 |
| Severe or BG confirmed symptomatic | | | | | | | | |
| Up to 1 hour after a meal | 44 | ( 12.9) | 75 | 46.9 | 33 | ( 9.7) | 54 | 33.3 |
| Up to 2 hours after a meal | 107 | ( 31.4) | 333 | 208.4 | 86 | ( 25.2) | 215 | 132.5 |
| Up to 4 hours after a meal | 196 | ( 57.5) | 1076 | 673.3 | 164 | ( 48.1) | 933 | 575.0 |
| Up to 6 hours after a meal | 227 | ( 66.6) | 1735 | 1085.7 | 197 | ( 57.8) | 1659 | 1022.4 |
| Total severe or BG confirmed symptomatic | 245 | ( 71.8) | 2257 | 1412.3 | 223 | ( 65.4) | 2140 | 1318.9 |

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 patient years of exposure, BG: Blood glucose, ADA: American Diabetes Association.
Severe or BG confirmed: subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56mg/dL). Episodes with missing time stamps or with missing main meal time are not included. Treatment-emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.

Source: CSR 3853, Table 12-19

## Figure 44: Trial 3853 – Estimated Treatment Ratios Based on Estimated Rates Per 100 PYE for Severe or BG Confirmed Hypoglycemic Episodes in Total and Meal-Related

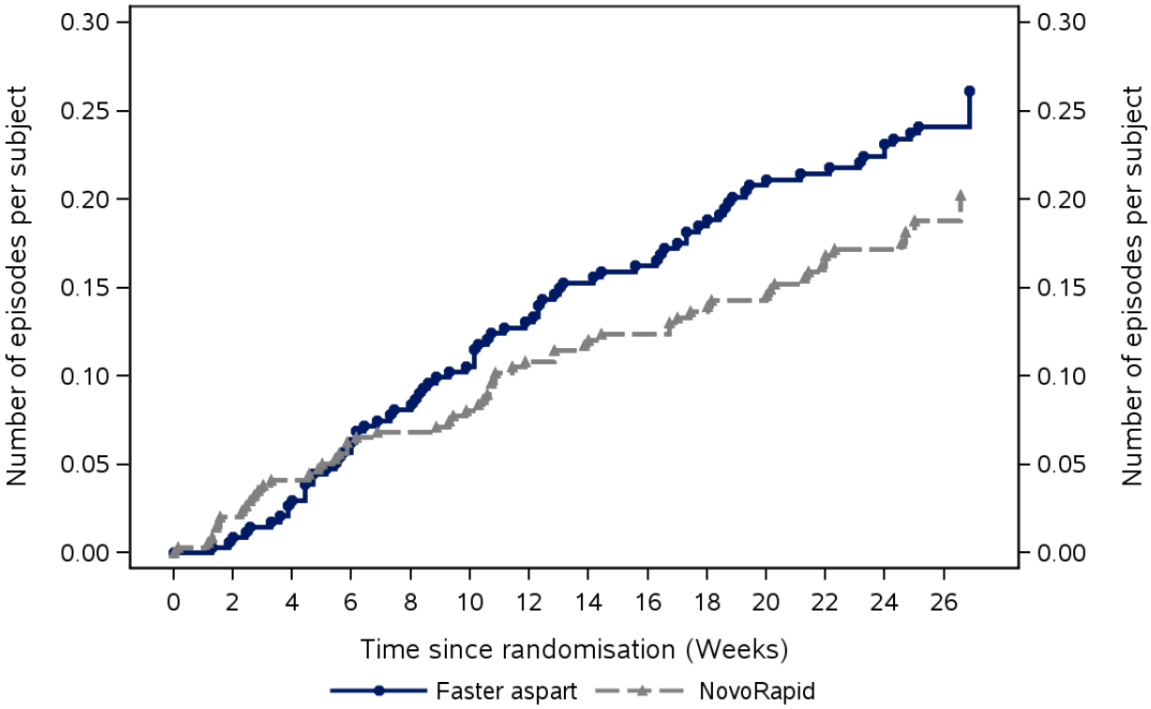



CI: Confidence interval. 'After meal': after start of a main meal. For analyses 1, 2, 4 or 6 hours after a meal: episodes with missing time stamps or with missing main meal time are not included.

Source: CSR 3853, Figure 12-4

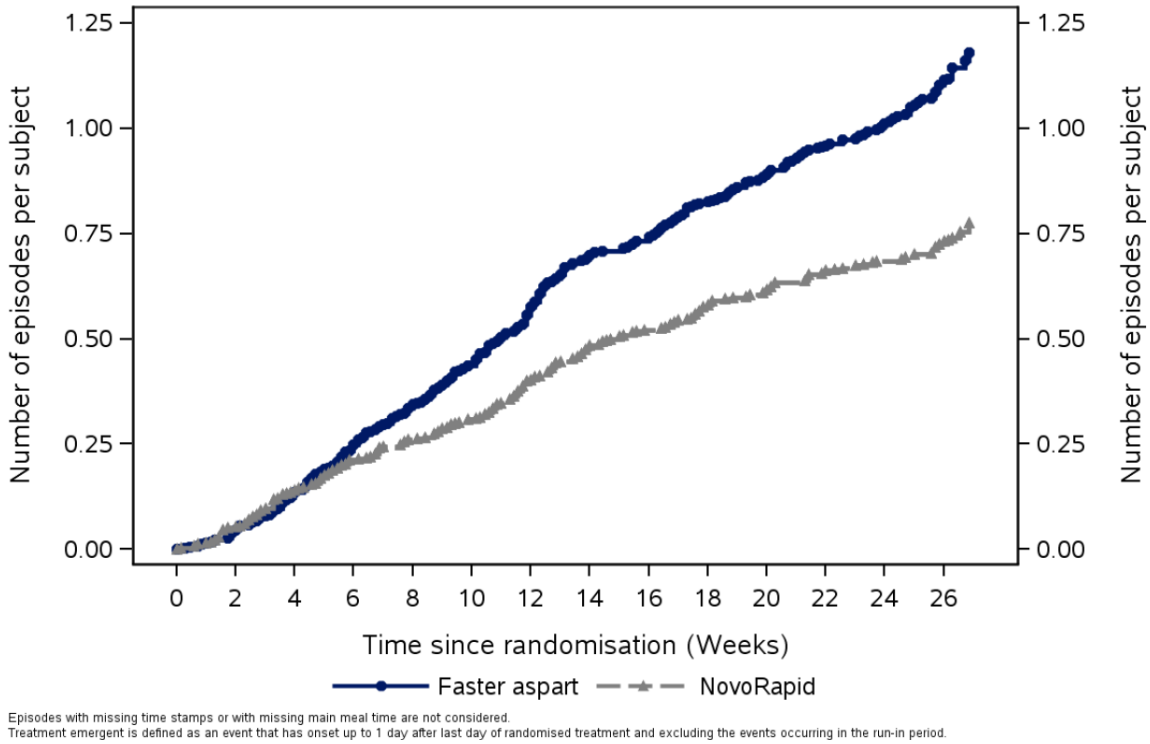
The number of severe or BG confirmed hypoglycemic episodes after the main meal per subject increased at a faster rate in the (b) (4) group compared to NovoLog group during 1 hour after the main meal at around Week 8 (Figure 45) and at around Week 6 during 2 hours after the main meal, and appear to increase at a faster rate up to Week 26 (Figure 46). This was not seen 4 hours or 6 hours after the meal (not shown, see Figure 14.3.1.73 and 14.3.1.74 of CSR).

**Figure 45: Trial 3853 – Treatment Emergent Severe or BG Confirmed Hypoglycemic Episodes 1 Hour After Main Meal (Mean Cumulative Function; Safety Analysis Set)**




Source: CSR 3853, 14.3.1.71

**Figure 46: Trial 3853 – Treatment Emergent Severe or BG Confirmed Hypoglycemic Episodes 2 Hours After Main Meal (Mean Cumulative Function; Safety Analysis Set)**




Source: CSR 3853, 14.3.1.72

**Reviewer's comments: In both T1DM and T2DM, a trend for a higher incidence of severe and BG confirmed hypoglycemic events within 1 and 2 hours after a meal was observed with mealtime (b) (4) compared to NovoLog, although this treatment difference was statistically significant only at one hour after a meal in T1DM and 2 hours after a meal in T2DM population. This observation is in keeping with the PD profile of (b) (4) where lower 1- and 2-hour PPG was seen with mealtime (b) (4) compared to NovoLog.**

**Trial 4049 – T2DM**

A summary of overall hypoglycemic episodes by classification in trial 4049 is provided Table 66.

**Table 66: Hypoglycemic Episodes by Classification in Trial 4049**

| | Faster aspart + Basal N | (%) | E | R | Basal N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|
| Number of subjects | 115 | | | | 120 | | | |
| Total events | 89 | ( 77.4) | 1908 | 4968.1 | 70 | ( 58.3) | 347 | 851.5 |
| BG confirmed | 67 | ( 58.3) | 486 | 1265.5 | 29 | ( 24.2) | 79 | 193.9 |
| Severe or BG confirmed symptomatic | 61 | ( 53.0) | 403 | 1049.3 | 26 | ( 21.7) | 63 | 154.6 |
| Severe or BG confirmed NN unclassifiable | 67 | ( 58.3) | 493 | 1283.7 | 30 | ( 25.0) | 80 | 196.3 |
| | 88 | ( 76.5) | 1415 | 3684.4 | 67 | ( 55.8) | 267 | 655.2 |
| ADA | | | | | | | | |
| Severe | 3 | ( 2.6) | 7 | 18.2 | 1 | ( 0.8) | 1 | 2.5 |
| Documented symptomatic | 79 | ( 68.7) | 1217 | 3168.9 | 46 | ( 38.3) | 189 | 463.8 |
| Asymptomatic | 67 | ( 58.3) | 657 | 1710.7 | 51 | ( 42.5) | 154 | 377.9 |
| Probable symptomatic | 12 | ( 10.4) | 22 | 57.3 | 2 | ( 1.7) | 3 | 7.4 |
| Pseudo-hypoglycaemia | 4 | ( 3.5) | 5 | 13.0 | 0 | | | |
| ADA unclassifiable | 0 | | | | 0 | | | |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 exposure years, BG: Blood glucose
Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL)
Treatment emergent episodes occur after trial product administration after randomisation and no later than 1 day after last trial product administration.

Source: CSR 4049, Table 12-11

***Severe Hypoglycemia:***

There were 8 episodes of severe hypoglycemia, 7 episodes in 3 subjects (2.6%) in the (b) (4) plus basal and one episode in a subject (0.8%) in the basal group.

One subject ( (b) (6) in the (b) (4) plus basal group experienced 5 severe hypoglycemic episodes. He was a 69-year old subject with HbA1c of 6.1% after 18 weeks of treatment.

All but one of 7 severe hypoglycemic episodes in the (b) (4) plus basal group were nocturnal; the severe hypoglycemia in the basal group was during daytime.

***Severe or BG Confirmed Hypoglycemia:***

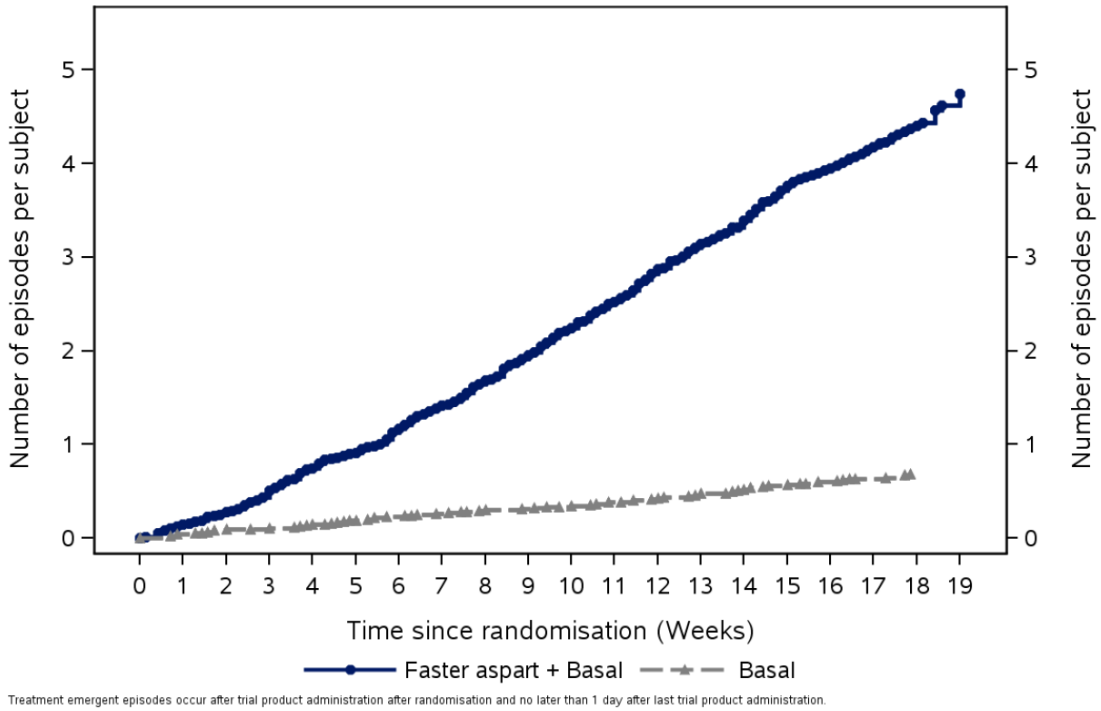
A total of 493 severe or BG confirmed hypoglycemic episodes were reported in the (b) (4) plus basal group in 67 subjects (58.3%; 1283.7 episodes per 100 PYE) and 80 episodes were reported in 30 subjects (25%; 196.3 episodes per 100 PYE) in the basal group. Three episodes in three subjects ( (b) (6) ) were assessed as SAEs. The treatment ratio ( (b) (4) plus basal versus basal) was 8.24 (95% CI: 4.93, 13.76).

The majority of subjects in the basal group reported a single episode per subject, whereas the majority in the (b) (4) plus basal group reported at least 4 episodes per subject during treatment period.

The majority of severe or BG confirmed hyoglycemic episodes were in the daytime, 427 episodes in the (b) (4) plus basal group versus 58 episodes in the basal group. The treatment ratio for the daytime severe or BG confirmed hypoglycemic episodes for the (b) (4) plus basal group compared to basal group was 9.64 (95% CI: 5.57, 16.70). The treatment ratio for rate of nocturnal severe or BG confirmed hypoglycemic episodes for the (b) (4) plus basal group compared to basal group was 4.15 (95 CI: 1.78, 9.67).

A mean cumulative plot of severe hypoglycemic episodes shows that the severe hypoglycemic episodes appear to increase in the (b) (4) plus basal group after Week 2 (Figure 47).

**Figure 47: Mean Cumulative Function – Severe or BG Confirmed Hypoglycemic Episodes in Trial 4049 (SAS)**




Source: CSR 4049, Figure 12-1

***Severe or BG Confirmed Hypoglycemia Related to A Meal:***

Severe BG confirmed hypoglycemic episodes related to a meal, using 1, 2, 4, and 6 hour points are summarized in Table 67.

A total of 98 severe or BG confirmed hypoglycemic episodes were reported within 2 hours after a meal in the (b) (4) plus basal group versus 1 episode in the basal insulin group, with treatement ratio of 103.20 (95% CI: 12.13, 878.25). The treatment ratio within 4 and 6 hours after meal was also statistically increased in the (b) (4) plus basal group compared to basal group (Table 68).

**Table 67: Trial 4049 – Summary of Severe or BG Confirmed Hypoglycemic Episodes Related to a Meal (Safety Analysis Set)**

| | Faster aspart + Basal | | | | Basal | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 115 | | | | 120 | | | |
| Severe or BG confirmed | | | | | | | | |
| Up to 1 hour after a meal | 14 | ( 12.2) | 33 | 85.9 | 0 | | | |
| Up to 2 hours after a meal | 27 | ( 23.5) | 98 | 255.2 | 1 | ( 0.8) | 1 | 2.5 |
| Up to 4 hours after a meal | 51 | ( 44.3) | 240 | 624.9 | 8 | ( 6.7) | 9 | 22.1 |
| Up to 6 hours after a meal | 60 | ( 52.2) | 330 | 859.3 | 12 | ( 10.0) | 15 | 36.8 |
| Total severe or BG confirmed | 67 | ( 58.3) | 493 | 1283.7 | 30 | ( 25.0) | 80 | 196.3 |
| Severe or BG confirmed symptomatic | | | | | | | | |
| Up to 1 hour after a meal | 12 | ( 10.4) | 29 | 75.5 | 0 | | | |
| Up to 2 hours after a meal | 25 | ( 21.7) | 87 | 226.5 | 1 | ( 0.8) | 1 | 2.5 |
| Up to 4 hours after a meal | 47 | ( 40.9) | 206 | 536.4 | 5 | ( 4.2) | 6 | 14.7 |
| Up to 6 hours after a meal | 56 | ( 48.7) | 284 | 739.5 | 8 | ( 6.7) | 9 | 22.1 |
| Total severe or BG confirmed | 61 | ( 53.0) | 403 | 1049.3 | 26 | ( 21.7) | 63 | 154.6 |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 exposure years, BG: Blood glucose
Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL)
Episodes with missing time stamps or with missing main meal time are not included
Treatment emergent episodes occur after trial product administration after randomisation and no later than 1 day after last trial product administration

Source: CSR 4049, Table 12-14

**Table 68: Statistical Analysis of Hypoglycemic Episodes Related to Meals in Trial 4049 (FAS)**

| | Full analysis set | N | Estimate | 95% CI |
|---|---|---|---|---|
| Severe or BG confirmed hypoglycaemia | | | | |
| Hypoglycaemic episodes occurring 2 hours after main meal | | | | |
| LSMeans, events per 100 PYE | | | | |
| Faster aspart + Basal | 116 | 115 | 178.13 | |
| Basal | 120 | 120 | 1.73 | |
| Treatment ratio | | | | |
| Faster aspart + Basal / Basal | | | 103.20 | [ 12.13;878.25] |
| Hypoglycaemic episodes occurring 4 hours after main meal | | | | |
| LSMeans, events per 100 PYE | | | | |
| Faster aspart + Basal | 116 | 115 | 453.58 | |
| Basal | 120 | 120 | 16.26 | |
| Treatment ratio | | | | |
| Faster aspart + Basal / Basal | | | 27.89 | [ 12.33; 63.10] |
| Hypoglycaemic episodes occurring 6 hours after main meal | | | | |
| LSMeans, events per 100 PYE | | | | |
| Faster aspart + Basal | 116 | 115 | 717.03 | |
| Basal | 120 | 120 | 27.30 | |
| Treatment ratio | | | | |
| Faster aspart + Basal / Basal | | | 26.27 | [ 13.08; 52.73] |

N: Number of subjects, CI: Confidence interval, BG: Blood glucose, PYE: Patient years of exposure
Treatment emergent episodes occur after trial product administration after randomisation and no later than 1 day after last trial product administration.
The analysis is based on a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode is considered treatment emergent as offset. The model includes treatment, region and strata as factors.
For the endpoint hypoglycaemic episodes occurring 1 hour after main meal the analysis has been left out as there are no events in the Basal arm.

Source: CSR 4049, Table 14.3.1.43

**Reviewer's comments: The higher rate of hypoglycemia in the (b) (4) plus basal group compared to basal group in trial 4049, particularly in the episodes related to meals, is not surprising since there was an intensification of insulin regimen with mealtime insulin. The event rates of hypoglycemia in trial 4049 (Table 66) were slightly lower or similar to what was observed in trial 3853 (Table 61).**

**Trial 3931 – CSII in T1DM**

There were no severe hypoglycemic episodes reported in this trial.

*Blood Glucose (BG) Confirmed Hypoglycemia:*

During the run-in period, 51 BG confirmed hypoglycemic episodes were reported subjects who were later randomized to (b) (4) and 9 in those who were randomized

to NovoLog; therefore, slightly more BG confirmed hypoglycemic episodes occurred during the run-in period in subjects who were subsequently randomized to (b) (4) during treatment period.

During the treatment period, 144 severe or BG confirmed hypoglycemic episodes (76% [19/25]) were reported in the (b) (4) group compared to 33 (67% [8/12]) in the NovoLog group (Table 69). This corresponded to episode rates of 4953 and 2340 episodes per 100 PYE respectively. The treatment ratio for BG confirmed hypoglycemic episodes ((b) (4) versus NovoLog) was 1.81 and was not statistically significant (95% CI: 0.76, 4.32).

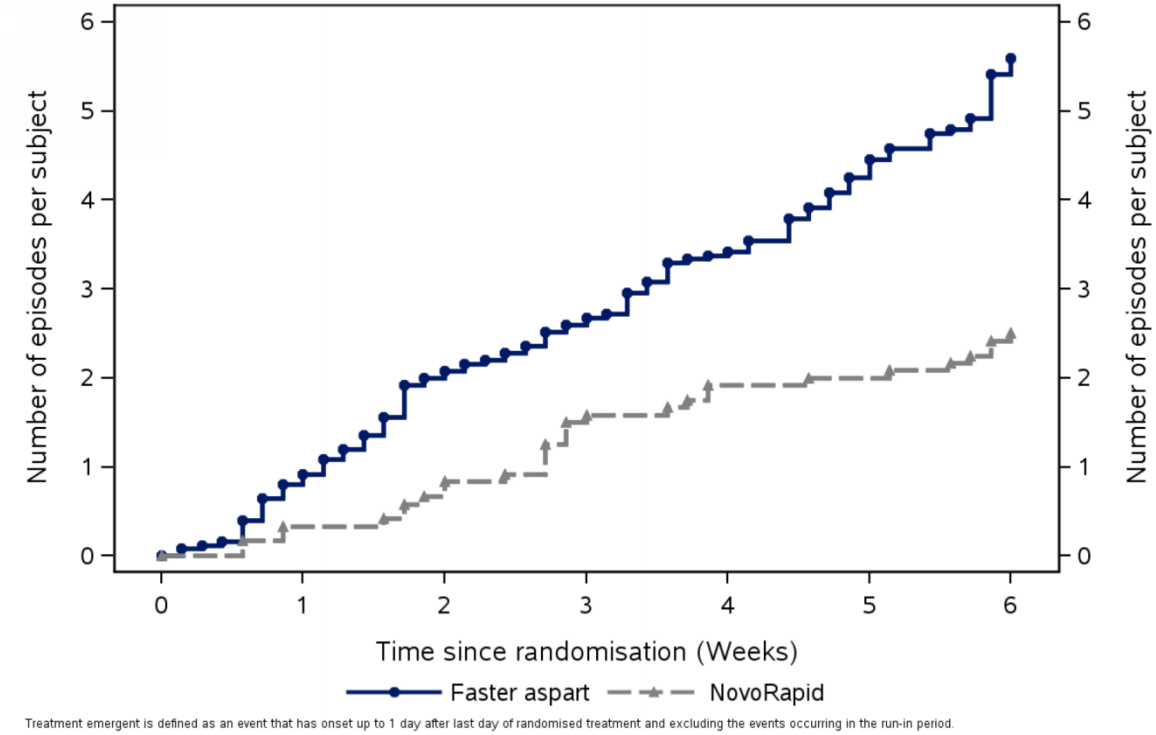
**Table 69: Trial 3931 – Summary of Treatment Emergent Hypoglycemic Episodes by Classification (Safety Analysis Set)**

| | Faster aspart | | | | NovoRapid® | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 25 | | | | 12 | | | |
| Total events | 22 | (88.0) | 351 | 12072 | 9 | (75.0) | 84 | 5957 |
| BG confirmed | 19 | (76.0) | 144 | 4953 | 8 | (66.7) | 33 | 2340 |
| Severe or BG confirmed symptomatic | 19 | (76.0) | 99 | 3405 | 7 | (58.3) | 26 | 1844 |
| Severe or BG confirmed | 19 | (76.0) | 144 | 4953 | 8 | (66.7) | 33 | 2340 |
| NN Unclassifiable | 20 | (80.0) | 207 | 7119 | 9 | (75.0) | 51 | 3617 |
| ADA | | | | | | | | |
| Severe | 0 | | | | 0 | | | |
| Documented symptomatic | 22 | (88.0) | 233 | 8013 | 7 | (58.3) | 58 | 4114 |
| Asymptomatic | 13 | (52.0) | 114 | 3921 | 7 | (58.3) | 26 | 1844 |
| Probable symptomatic | 1 | (4.0) | 2 | 69 | 0 | | | |
| Pseudo-hypoglycaemia | 1 | (4.0) | 1 | 34 | 0 | | | |
| ADA unclassifiable | 1 | (4.0) | 1 | 34 | 0 | | | |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 exposure years, BG: Blood glucose
Severe or BG confirmed: Subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL).
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Source: CSR 3931, Table 12-7

A plot of BG confirmed hypoglycemic episodes per subject shows that the episodes increased at a faster rate in the (b) (4) treatment group compared to NovoLog group (Figure 48).

**Figure 48: Trial 3931 – Mean Cumulative Plot of Treatment Emergent Blood Confirmed Hypoglycemic Episodes (Safety Analysis Set)**




Source: CSR 3931, Figure 12-1

Of subjects reporting BG confirmed hypoglycemic episode, the majority of subjects in the (b) (4) group (11/19) reported 5 or less episodes, whereas the majority of subjects in the NovoLog group (5/8) reported 3 or fewer episodes. Two subjects in the (b) (4) group each reported 24 BG confirmed hypoglycemic episodes while one subject in the NovoLog group reported 13 episodes.

The majority of BG confirmed hypoglycemic episodes were symptomatic (Table 69). Also, the majority of these were daytime episodes (155/177).

BG confirmed hypoglycemia episodes in relation to a meal are summarized in Table 70. Higher rates of BG confirmed hypoglycemic episodes related to meal were observed with (b) (4) compared to NovoLog, particularly within 1 and 2 hours after a meal.

**Table 70: Trial 3931 – Summary of Blood Glucose Confirmed Hypoglycemic Episodes Related to a Meal (Safety Analysis Set)**

| | Faster aspart | | | | NovoRapid® | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 25 | | | | 12 | | | |
| BG confirmed | | | | | | | | |
| Up to 1 hour after meal | 3 | (12.0) | 5 | 172 | 0 | | | |
| Up to 2 hours after meal | 13 | (52.0) | 33 | 1135 | 1 | (8.3) | 1 | 71 |
| Up to 4 hours after meal | 18 | (72.0) | 88 | 3027 | 4 | (33.3) | 6 | 426 |
| Up to 6 hours after meal | 18 | (72.0) | 100 | 3439 | 6 | (50.0) | 8 | 567 |
| Total BG confirmed | 19 | (76.0) | 144 | 4953 | 8 | (66.7) | 33 | 2340 |
| BG confirmed symptomatic | | | | | | | | |
| Up to 1 hour after meal | 2 | (8.0) | 4 | 138 | 0 | | | |
| Up to 2 hours after a meal | 12 | (48.0) | 24 | 825 | 1 | (8.3) | 1 | 71 |
| Up to 4 hours after a meal | 17 | (68.0) | 65 | 2236 | 4 | (33.3) | 6 | 426 |
| Up to 6 hours after a meal | 17 | (68.0) | 73 | 2511 | 6 | (50.0) | 8 | 567 |
| Total BG confirmed symptomatic | 19 | (76.0) | 99 | 3405 | 7 | (58.3) | 26 | 1844 |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 exposure years, BG: Blood glucose
BG confirmed: Subject has a recorded PG < 3.1 mmol/L (56 mg/dL).
Episodes with missing time stamps or with missing main meal time are not included.
Source: CSR 3931, Table 12-10

*Unexplained BG Confirmed Hypoglycemia:*

In this trial, hypoglycemic episodes that could not be explained by an apparent medical, dietary, or insulin dosage reason were defined as "unexplained" (see section 5.3.4). Subjects in the (b) (4) group reported higher episodes of unexplained BG confirmed hypoglycemic episodes compared to NovoLog (94 versus 10 episodes). This corresponded to 52% (13/25) of subjects in the (b) (4) and 25% (3/12) of subjects in the NovoLog group reporting 3233 and 709 episodes per 100 PYE respectively.

**Reviewer's comments: There was an imbalance in severe or BG hypoglycemia rates not favoring the (b) (4) treatment group compared to NovoLog during the treatment period in CSII setting in trial 3931. This imbalance not favoring (b) (4) (b) (4) was also seen in relation to meal where higher rates were seen with compared to NovoLog, although the treatment difference did not reach statistical significance.**

(b) (4)


### 7.3.5 Submission Specific Primary Safety Concerns

The following adverse events were considered to be of particular interest with regard to insulin treatment and were evaluated in trials with (b) (4) as adverse events of special interest.

#### 7.3.5.1 Medication Errors

Medication errors were collected from trials 3852, 3853, 4049, 3931, (b) (4) as events of special interest.

A pre-specified search was done to identify events of medication errors using the following High Level Group Terms (HLGTs) and High Level Term (HLT) search terms of MedDRA:

- Medication errors (primary and secondary terms) HLGT;
- Device issues (primary and secondary terms) HLGT;
- Product quality issue (primary and secondary terms) HLGT; and
- Complications associated with device NEC (primary and secondary terms) HLT.

No medication errors were reported in any of the clinical pharmacology trials or CSII trials (3931, (b) (4)).

**Trial 3852:**

A total of 79 medication errors were identified in 67 subjects based on pre-specified search criteria, with slightly higher incidence in the postmeal (b) (4) treatment group (6.9%) compared to mealtime (b) (4) (4.9%) and NovoLog (5.8%) treatment groups.

The majority of medication errors (65 events in 55 subjects) were 'wrong drug administered', with similar incidence across treatment groups (Table 71). Most of these

events (43 events in 40 subjects) were due to subjects taking bolus insulin instead of basal insulin, and 22 of these events led to a hypoglycemic episode. Nineteen events in 16 subjects were due to subjects taking basal insulin instead of bolus insulin at mealtime, 5 of which led to a hypoglycemic episode. In the remaining 3 events in 3 subjects, 2 led to a hypoglycemic episode. Two of these 'wrong drug administered' were also serious events:

- Subject (b) (6) in the mealtime (b) (4) group took bolus insulin instead of bedtime basal insulin and experienced a serious hypoglycemic episode where she was found unresponsive with BG of 36 mg/dL. Emergency services administered IV glucose and she was hospitalized;
- Subject (b) (6) in the postmeal (b) (4) group took basal insulin instead of bolus insulin at evening meal and had non-serious hypoglycemia [54 mg/dL] and self-treated with glucagon injection.

Nine medication errors were 'accidental overdose', and 5 of these led to a hypoglycemic episode. One event of 'accidental overdose' (subject (b) (6) was due to an overdose of pain medication and not related to the study product and was reported as serious and was withdrawn from the study.

The device failure was a dental filling failure and not related to insulin administration.

**Table 71: Medication Errors by Preferred Term in Trial 3852**

| | Faster aspart (meal) | | | | Faster aspart (post) | | | | NovoRapid® (meal) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 386 | | | | 377 | | | | 380 | | | |
| Total events | 19 | (4.9) | 24 | 12.9 | 26 | (6.9) | 28 | 15.3 | 22 | (5.8) | 27 | 14.3 |
| Wrong drug administered | 17 | (4.4) | 21 | 11.3 | 19 | (5.0) | 21 | 11.5 | 19 | (5.0) | 23 | 12.2 |
| Accidental overdose | 2 | (0.5) | 2 | 1.1 | 5 | (1.3) | 5 | 2.7 | 2 | (0.5) | 2 | 1.1 |
| Extra dose administered | 0 | | | | 1 | (0.3) | 1 | 0.5 | 0 | | | |
| Inappropriate schedule of drug administration | 0 | | | | 0 | | | | 1 | (0.3) | 1 | 0.5 |
| Incorrect dose administered | 0 | | | | 0 | | | | 1 | (0.3) | 1 | 0.5 |
| Device failure | 1 | (0.3) | 1 | 0.5 | 0 | | | | 0 | | | |

Medication errors based on a Novo Nordisk MedDRA query (NNMQ) search. N: number of subjects, %; percentage of subjects, E: number of events, R: event rate per 100 exposure years.
Source: CSR 3852, Table 12-7

**Trial 3853:**

A total of 9 medication errors were identified in 8 subjects; 5 medication errors in 4 subjects in the (b) (4) group and 4 medication errors in 4 subjects in the NovoLog group (Table 72).

The majority (7 events in 6 subjects) of medication errors were 'wrong drug administered', most (5 events in 4 subjects) due to taking bolus insulin instead of basal insulin and the remaining (2 events in 2 subjects) due to taking basal insulin instead of bolus insulin. Two of these events led to hypoglycemia. One event (wrong drug administered in subject (b) (6) was an SAE.

Two 'accidental overdose', one in each treatment group was reported where subjects administered an extra dose of bolus insulin rather than basal insulin; none led to hypoglycemia.

**Table 72: Trial 3853 –Treatment Emergent Medication Error Related AEs**

| Subject ID/ Treatment group | Preferred term | Description of medication error | Associated hypo-glycaemia | Trial product involved/ Causality | Action taken with trial products (bolus and/or basal insulin) |
|---|---|---|---|---|---|
| (b) (6) Faster aspart | *Wrong drug administered* | The subject administered bolus insulin instead of basal insulin due to distraction | Yes | Bolus insulin/ Probable | None |
| (b) (6) Faster aspart | *Wrong drug administered* (2 events) | The subject administered bolus insulin in 2 separate occasions instead of basal insulin due to distraction | No | Bolus insulin/ Unlikely/ (For both events) | None (For both events) |
| (b) (6) Faster aspart | *Wrong drug administered* | The subject administered bolus insulin instead of basal insulin due to distraction | No | Bolus insulin/ Probable | None |
| (b) (6) Faster aspart | *Accidental overdose* | The subject administered an extra dose of bolus insulin instead of basal insulin by mistake | No | Bolus insulin/ Probable | The bolus insulin dose was temporarily stopped |
| (b) (6) NovoRapid | *Accidental overdose* | The subject administered an extra dose of bolus insulin instead of basal insulin due to distraction | No | Bolus insulin/ Probable | Both the bolus and basal insulin doses were reduced |
| (b) (6) NovoRapid | *Wrong drug administered* | The subject administered basal insulin instead of bolus insulin by mistake. | No | Basal insulin/ Unlikely | None |
| (b) (6) NovoRapid | *Wrong drug administered* | The subject decided to administer basal insulin instead of bolus insulin assuming that the bolus insulin was not stored at his house. | No | Basal insulin/ Unlikely | None |
| (b) (6) NovoRapid | *Wrong drug administered* | The subject administered bolus insulin instead of basal insulin due to distraction | Yes | Bolus insulin/ Unlikely | The basal insulin dose was temporarily stopped |

Bolus insulin=faster aspart dose (faster aspart group) and NovoRapid dose (NovoRapid group). Basal insulin=insulin glargine (for both faster aspart and NovoRapid groups). Relationship (causality) with trial products (bolus or basal insulin) is based on investigator(s)'s assessment.
Source: CSR 3853, Table 12-11

**Reviewer's comment: Higher medication errors were reported in trial 3852 compared to trial 3853. Human factor study is being evaluated by DMEPA and they will determine if packaging may lead to increased risk of medication errors due to mix-ups with other insulin products.**

**Trial 4049:**

One treatment emergent medication error, where subject ( (b) (6) administered bolus insulin instead of basal insulin and led to an episode of hypoglycemia.

### 7.3.5.2 Cardiovascular Events

The following types of cardiovascular events, occurring between the first day of exposure to study drug and up to 30 day follow-up visit, were reported using specific AE forms in trials 3852, 3853, 4049 and 3931:

- Acute coronary syndrome
- Cerebrovascular events
- Heart failure requiring hospitalization
- Coronary revascularization procedures
- All deaths (not only deaths suspected as related to cardiovascular events).

An external independent clinical safety event adjudication committee (EAC) adjudicated these CV events in a blinded manner, including all deaths occurring after randomization.

MACEs were defined as a composite endpoint including positively adjudicated non-fatal myocardial infarction (ST segment elevation myocardial infarction [STEMI] or non-STEMI), non-fatal stroke, and cardiovascular death.

A prospectively planned meta-analysis of positively adjudicated MACE was done, where MACEs occurring in trials 3852, 3853, 4049 and 3931 were analyzed with descriptive statistics, on a trial-by-trial basis and as a pool of four trials. An exploratory Cox regression analysis and a CMH analysis of MACE risk difference were also made.

Of note, CV events were not reported in trial 3931.

Diabetes Pool:

A total of 39 events (24 events in 15 subjects from (b) (4) groups and 15 events in 13 subjects from NovoLog groups) were sent to EAC for adjudication: 10 events from trial 3852, 27 events from trial 3853, and 2 events from trial 4049. A total of 19 events were positively adjudicated, 6 events in trial 3852, 12 events in trial 3853, and 1 event in trial 4049. As shown in Table 73, 4 events (0.6 per 100 PYE) in the (b) (4) group and 5 events (1.1 per 100 PYE) in the comparator/NovoLog group were MACE events. All MACE events were reported from trials 3852 and 3853 (none from trials 4049 or 3931).

**Table 73: Adjudicated Cardiovascular Events in the Diabetes Pool (Cochran-Mantel-Haenszel Adjusted)**

| | Faster aspart | | | | Comparator | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 1244 | | | | 853 | | | |
| Events sent for adjudication | 15 | ( 1.3) | 24 | 4.1 | 13 | ( 1.4) | 15 | 3.0 |
| Events positively adjudicated | 8 | ( 0.7) | 11 | 1.8 | 8 | ( 0.8) | 8 | 1.6 |
| MACE | 4 | ( 0.3) | 4 | 0.6 | 5 | ( 0.5) | 5 | 1.1 |
| Cardiovascular death | 2 | ( 0.2) | 2 | 0.3 | 2 | ( 0.2) | 2 | 0.4 |
| NSTEMI | 2 | ( 0.2) | 2 | 0.3 | 1 | ( 0.1) | 1 | 0.2 |
| Stroke | 0 | | | | 2 | ( 0.2) | 2 | 0.5 |
| non-MACE | 4 | ( 0.3) | 7 | 1.2 | 3 | ( 0.3) | 3 | 0.6 |
| Heart failure | 1 | ( 0.1) | 1 | 0.2 | 0 | | | |
| Percutaneous revascularization | 3 | ( 0.2) | 4 | 0.6 | 2 | ( 0.2) | 2 | 0.4 |
| Surgical revascularization | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Unstable angina pectoris | 2 | ( 0.2) | 2 | 0.3 | 0 | | | |

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 patient years of exposure
MACE: Major adverse cardiovascular event, NSTEMI: Non-ST elevation myocardial infarction
MACE is defined as events positively adjudicated to cardiovascular-related death, nonfatal stroke or nonfatal myocardial
infarction. Cardiovascular events were not to be sent for adjudication during the run-in period.
Based on trials 3852, 3853, 4049 and 3931.
MedDRA version 17.0
Source: SCS, Table 2-21

The Cox proportional hazard ratio for time to first MACE for diabetes pool was 0.64 (95% CI: 0.17, 2.43), for trial 3852 was 1.02 (95% CI: 0.09, 11.20), and for trial 3853 was 0.51 (95% CI: 0.09, 2.76). The estimated rate difference for (b) (4) versus NovoLog was -0.41 (95% CI: -1.55, 0.73).

**Reviewer's comment: Overall, the number of MACE events was very low in the (b) (4) clinical development as expected, and no definite conclusion can be drawn but data do not appear to indicate that (b) (4) may increase CV risk compared to NovoLog. This meta-analysis was not conducted to eliminate a pre-specified upper bound of the 95% CI for the hazard ratio of MACE as insulin is exempted from FDA premarketing requirement to demonstrate CV safety with an acceptable hazard ratio.**

### 7.3.5.3 Injection Site Reactions and Lipodystrophy

Injection or infusion site reactions are one of the frequently reported adverse drug reactions with insulin products including NovoLog.

Subjects were instructed to inject bolus insulin subcutaneously in the abdomen and basal insulin in the thigh or deltoid area. For all injection site reactions, investigators were to fill out an AE form and assess relatedness to bolus or basal insulin.

A pre-specified MedDRA search was done among all AEs using the following High Level Terms (HLTs) to identify events of injection or infusion site reactions:

- Administration site reactions NEC (primary and secondary terms);
- Application and installation site reactions (primary and secondary terms);
- Infusion site reactions (primary and secondary terms);
- Injection site reactions (primary and secondary terms).

Lipodystrophy can occur at insulin injection sites, and is a well-known adverse drug reaction for insulins including NovoLog. Erratic absorption of insulin from lipodystrophy can lead to difficulty in achieving glycemic control. A pre-specified MedDRA search was done to identify events of lipodystrophy, using "Lipodystrophies (primary and secondary terms) HLT".

**Trial 3852 – T1DM:**

A total of 22 injection site reactions in 19 subjects were identified based on MedDRA queries: 9 AEs in 7 subjects (1.8%) in the mealtime (b) (4) group, 10 AEs in 9 subjects (2.4%) in the postmeal (b) (4) group, and 3 AEs in 3 subjects (0.8%) in the NovoLog group.

**Table 74: Listing of Adverse Event of Treatment Emergent Injection Site Reactions in Trial 3852**

| | Faster aspart (meal) | | | | Faster aspart (post) | | | | NovoRapid (meal) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 386 | | | | 377 | | | | 380 | | | |
| Total exposure (yrs) | 186.36 | | | | 183.00 | | | | 188.88 | | | |
| Events | 7 | (1.8) | 9 | 4.8 | 9 | (2.4) | 10 | 5.5 | 3 | (0.8) | 3 | 1.6 |
| General disorders and administration site conditions | | | | | | | | | | | | |
| Injection site reaction | 4 | (1.0) | 5 | 2.7 | 5 | (1.3) | 6 | 3.3 | 3 | (0.8) | 3 | 1.6 |
| Injection site bruising | 2 | (0.5) | 2 | 1.1 | 1 | (0.3) | 1 | 0.5 | 0 | | | |
| Injection site hypertrophy | 1 | (0.3) | 1 | 0.5 | 1 | (0.3) | 1 | 0.5 | 0 | | | |
| Injection site erythema | 0 | | | | 1 | (0.3) | 1 | 0.5 | 0 | | | |
| Injection site haematoma | 0 | | | | 1 | (0.3) | 1 | 0.5 | 0 | | | |
| Injection site irritation | 1 | (0.3) | 1 | 0.5 | 0 | | | | 0 | | | |

Injection site reactions based on a NNMQ search.
Safety analysis set. N: Number of subjects, %: Percentage of subjects; E: Number of events; R: Event rate per 100 patient years of exposure; yrs: Years
All adverse events are treatment-emergent. Treatment-emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
Source: CSR 3852, Table 12-9

Investigator reported 26 AEs in 23 subjects as injection site reactions.

There were some discrepancies between MedDRA search and investigator reported injection site reactions. Two AEs in 2 subjects were captured in the MedDRA search but not reported by investigator (injection site hematoma [(b) (6) and injection site hypertrophy [(b) (6) both in the postmeal (b) (4) group). Six AEs (2 in each treatment group) in 6 subjects judged to be injection site reactions by the investigator were not captured in the MedDRA queries as shown in Table 74 and included:

- Mealtime (b) (4) one event each of skin mass ((b) (6) ecchymosis ((b) (6)
- Postmeal (b) (4) one event each of pruritus ((b) (6) rash ((b) (6)
- NovoLog: one event each of rash ((b) (6) injection site reaction ((b) (6)

All injection site reactions, whether captured by MedDRA query or by the investigator, were non-serious. One subject ((b) (6) received NovoLog) withdrew from the trial due to an injection related reaction on study day 69; the event lasted for about 40 days and was thought to be related to basal insulin rather than bolus insulin as the reaction occurred on the thigh 30 minutes after injecting insulin detemir.

Narratives for investigator-identified injections site reactions in 23 subjects were reviewed. Based on my review of these narratives, 9 of 23 subjects had injection site reactions at abdomen, which is likely due to bolus insulin since subjects were instructed

to inject bolus insulin at abdomen; 5 subjects received mealtime (b) (4) 3 subjects received postmeal (b) (4) and one subject received NovoLog.

Three AEs of lipodystrophy were reported in 3 subjects who received postmeal (b) (4) treatment. All were non-serious events, and none led to study withdrawal or dose reduction.

**Trial 3853 – T2DM:**

Seven injection site reactions were reported in 5 subjects (0.7%), 3 events in 3 subjects (0.9%) in the (b) (4) group and 4 events in 2 subjects (0.6%) in the NovoLog group (Table 75). Two events of 'injection site hematoma' were reported in one subject in the NovoLog group. All were non-serious, and none led to study withdrawal. One 'injection site hematoma' led to dose reduction in the NovoLog group.

**Table 75: Listing of Adverse Event of Treatment Emergent Injection Site Reactions in Trial 3853**

| | (b) (6) | | | | | |
|---|---|---|---|---|---|---|
| Faster aspart | | *Injection site reaction* | Non-serious AE | Mild | Unlikely/Unlikely | Recovered/ Resolved |
| Faster aspart | | *Injection site rash* | Non-serious AE | Mild | Unlikely/Unlikely | Recovered/ Resolved |
| Faster aspart | | *Injection site nodule** | Non-serious AE | Mild | Unlikely/Unlikely | Recovered/ Resolved |
| NovoRapid | | *Injection site dermatitis* | Non-serious AE | Mild | Unlikely/Unlikely | Recovered/ Resolved |
| NovoRapid | | *Injection site erythema* | Non-serious AE | Mild | Possible/Unlikely | Recovered/ Resolved |
| | | *Injection site haematoma* (around injection site on abdomen) | Non-serious AE | Mild | Possible/Unlikely | Recovered/ Resolved |
| | | *Injection site haematoma* (around injection site on right upper thigh | Non-serious AE | Mild | Unlikely/Possible | Recovered/ Resolved |

*This AE was caught in the NNMQ search (EOT Table 14.3.1.24) but was not recorded by the investigator as injection site reaction.
Bolus insulin=faster aspart dose (faster aspart group) and NovoRapid dose (NovoRapid group)
Basal insulin=insulin glargine (for both faster aspart and NovoRapid groups). Relationship (causality) with trial products (bolus and basal insulin) is based on investigator(s)'s assessment. MedDRA version 17.0.
Source: CSR 3853, Table 12-14

Lipodystrophy was not reported in this trial.

**Trial 4049 – T2DM:**

A total of 4 injection site reactions were reported in two subjects, one in 1 subject in the (b) (4) plus basal group (injection site hematoma) and 3 events in a subject in the basal group (2 events of injection site erythema and one injection site hematoma). All were non-serious, did not lead to study discontinuation or dose reduction.

**Trial 3931 – CSII:**

Two subjects in the (b) (4) group reported treatment-emergent infusion site reactions:

- Subject (b) (6) reported itching and indurations at the infusion site on Day 40;
- Subject (b) (6) reported redness and soreness at the infusion site (abdomen) on Day 8. This subject also reported a non-serious infusion site reaction (redness at infusion site) during the run-in period. This subject was also discussed in section 6.1.7.1 related to 5 premature changes of infusion sets and also had 3 occurrences of "unexplained hyperglycemia" during treatment period.

Both events were non-serious and both "recovered/resolved"; neither was associated with any local or systemic symptoms.

No lipodystrophy was reported in this trial.

(b) (4)

### 7.3.5.4 Allergic Reactions

Since (b) (4) is a peptide-based drug, potential risk of immunogenicity-related AEs such as allergic reactions is possible and was considered an AE of special interest.

A pre-specified search of all AEs was done in trials to identify allergic reactions based on the following standardized MedDRA queries (SMQs) using both narrow and broad scope terms:

- Anaphylactic reaction
- Angioedema
- Severe cutaneous adverse reactions
- Anaphylactic/anaphylactoid shock conditions
- Anaphylactic/anaphyloid shock conditions
- Hypersensitivity

Allergic reactions are presented by each trial. No allergic reactions were observed in trial (b) (4).

**Trial 3852:**

A total of 123 allergic reactions were reported in 38 subjects (9.8%), 31 subjects (8.2%), and 38 subjects (10%) in the mealtime (b) (4) postmeal (b) (4) and NovoLog group respectively. All AEs were non-serious.

The most frequently reported PT (≥1%) where the event was higher in any (b) (4) treatment group compared to NovoLog was rash, 1.6% with mealtime (b) (4) 0.8% with postmeal (b) (4) and 0.5% with NovoLog (Table 76).

Although the overall number of events are very small (1 to 2 events) and thus inconclusive, 'local swelling', 'edema', 'pruritus', 'urticaria' only occurred in either mealtime or postmeal (b) (4) treatment groups (Table 76).

**Table 76: Summary of Treatment Emergent Allergic Reactions by System Organ Class and Preferred Term in Trial 3852**

| | Faster aspart (meal) | | | Faster aspart (post) | | | NovoRapid (meal) | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N (%) | E | R | N (%) | E | R | N (%) | E | R | N (%) | E | R |
| Number of subjects | 386 | | | 377 | | | 380 | | | 1143 | | |
| Total exposure (yrs) | 186.36 | | | 183.00 | | | 188.88 | | | 558.23 | | |
| Events | 38 ( 9.8) | 42 | 22.5 | 31 ( 8.2) | 36 | 19.7 | 38 (10.0) | 45 | 23.8 | 107 ( 9.4) | 123 | 22.0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | | | | | | | |
| Cough | 10 ( 2.6) | 11 | 5.9 | 12 ( 3.2) | 13 | 7.1 | 12 ( 3.2) | 12 | 6.4 | 34 ( 3.0) | 36 | 6.4 |
| Rhinitis allergic | 2 ( 0.5) | 2 | 1.1 | 1 ( 0.3) | 1 | 0.5 | 2 ( 0.5) | 2 | 1.1 | 5 ( 0.4) | 5 | 0.9 |
| Asthma | 0 | | | 0 | | | 2 ( 0.5) | 2 | 1.1 | 2 ( 0.2) | 2 | 0.4 |
| Allergic pharyngitis | 0 | | | 0 | | | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.1) | 1 | 0.2 |
| Dyspnoea | 0 | | | 1 ( 0.3) | 1 | 0.5 | 0 | | | 1 ( 0.1) | 1 | 0.2 |
| Skin and subcutaneous tissue disorders | | | | | | | | | | | | |
| Rash | 6 ( 1.6) | 6 | 3.2 | 3 ( 0.8) | 3 | 1.6 | 2 ( 0.5) | 2 | 1.1 | 11 ( 1.0) | 11 | 2.0 |
| Eczema | 2 ( 0.5) | 2 | 1.1 | 1 ( 0.3) | 1 | 0.5 | 3 ( 0.8) | 3 | 1.6 | 6 ( 0.5) | 6 | 1.1 |
| Dermatitis | 2 ( 0.5) | 2 | 1.1 | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.3) | 1 | 0.5 | 4 ( 0.3) | 4 | 0.7 |
| Dermatitis contact | 0 | | | 1 ( 0.3) | 1 | 0.5 | 2 ( 0.5) | 2 | 1.1 | 3 ( 0.3) | 3 | 0.5 |
| Blister | 1 ( 0.3) | 1 | 0.5 | 0 | | | 1 ( 0.3) | 1 | 0.5 | 2 ( 0.2) | 2 | 0.4 |
| Pruritus | 0 | | | 2 ( 0.5) | 2 | 1.1 | 0 | | | 2 ( 0.2) | 2 | 0.4 |
| Urticaria | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.3) | 1 | 0.5 | 0 | | | 2 ( 0.2) | 2 | 0.4 |
| Dermatitis allergic | 1 ( 0.3) | 1 | 0.5 | 0 | | | 0 | | | 1 ( 0.1) | 1 | 0.2 |
| Erythema | 1 ( 0.3) | 1 | 0.5 | 0 | | | 0 | | | 1 ( 0.1) | 1 | 0.2 |
| Exfoliative rash | 0 | | | 0 | | | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.1) | 1 | 0.2 |
| Photosensitivity reaction | 0 | | | 0 | | | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.1) | 1 | 0.2 |
| Rash macular | 0 | | | 1 ( 0.3) | 1 | 0.5 | 0 | | | 1 ( 0.1) | 1 | 0.2 |
| Rash pruritic | 1 ( 0.3) | 1 | 0.5 | 0 | | | 0 | | | 1 ( 0.1) | 1 | 0.2 |
| Immune system disorders | | | | | | | | | | | | |
| Seasonal allergy | 5 ( 1.3) | 5 | 2.7 | 3 ( 0.8) | 3 | 1.6 | 6 ( 1.6) | 7 | 3.7 | 14 ( 1.2) | 15 | 2.7 |
| Multiple allergies | 1 ( 0.3) | 1 | 0.5 | 0 | | | 2 ( 0.5) | 2 | 1.1 | 3 ( 0.3) | 3 | 0.5 |
| Drug hypersensitivity | 1 ( 0.3) | 1 | 0.5 | 0 | | | 1 ( 0.3) | 1 | 0.5 | 2 ( 0.2) | 2 | 0.4 |
| Hypersensitivity | 1 ( 0.3) | 1 | 0.5 | 0 | | | 1 ( 0.3) | 1 | 0.5 | 2 ( 0.2) | 2 | 0.4 |
| General disorders and administration site conditions | | | | | | | | | | | | |
| Oedema peripheral | 2 ( 0.5) | 2 | 1.1 | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.3) | 1 | 0.5 | 4 ( 0.3) | 4 | 0.7 |
| Chest discomfort | 0 | | | 2 ( 0.5) | 2 | 1.1 | 1 ( 0.3) | 1 | 0.5 | 3 ( 0.3) | 3 | 0.5 |
| Local swelling | 1 ( 0.3) | 1 | 0.5 | 2 ( 0.5) | 2 | 1.1 | 0 | | | 3 ( 0.3) | 3 | 0.5 |
| Oedema | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.3) | 1 | 0.5 | 0 | | | 2 ( 0.2) | 2 | 0.4 |
| Infections and infestations | | | | | | | | | | | | |
| Conjunctivitis | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.3) | 1 | 0.5 | 3 ( 0.3) | 3 | 0.5 |
| Vascular disorders | | | | | | | | | | | | |
| Hypotension | 1 ( 0.3) | 1 | 0.5 | 0 | | | 1 ( 0.3) | 1 | 0.5 | 2 ( 0.2) | 2 | 0.4 |
| Blood and lymphatic system disorders | | | | | | | | | | | | |
| Eosinophilia | 0 | | | 0 | | | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.1) | 1 | 0.2 |
| Eye disorders | | | | | | | | | | | | |
| Eye swelling | 0 | | | 0 | | | 1 ( 0.3) | 1 | 0.5 | 1 ( 0.1) | 1 | 0.2 |
| Gastrointestinal disorders | | | | | | | | | | | | |
| Eosinophilic oesophagitis | 0 | | | 1 ( 0.3) | 1 | 0.5 | 0 | | | 1 ( 0.1) | 1 | 0.2 |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 patient years of exposure, yrs: Years
Source: CSR 3852, Table 14.3.1.26

## Trial 3853:

Fifty-eight allergic reactions were reported in 51 subjects; 26 AEs in 23 subjects (6.7%) in the (b) (4) group and 32 AEs in 28 subjects (8.2%) in the NovoLog group. Table 77 provides an overall summary of allergic reactions by SOC and PT.

**Table 77: Summary of Treatment Emergent Allergic Reactions by System Organ Class and Preferred Term in Trial 3853**

| | Faster aspart N (%) | E | R | NovoRapid N (%) | E | R | Total N (%) | E | R |
|---|---|---|---|---|---|---|---|---|---|
| Number of subjects | 341 | | | 341 | | | 682 | | |
| Total exposure (yrs) | 159.81 | | | 162.26 | | | 322.06 | | |
| Events | 23 ( 6.7) | 26 | 16.3 | 28 ( 8.2) | 32 | 19.7 | 51 ( 7.5) | 58 | 18.0 |
| General disorders and administration site conditions | 10 ( 2.9) | 10 | 6.3 | 8 ( 2.3) | 9 | 5.5 | 18 ( 2.6) | 19 | 5.9 |
| Oedema peripheral | 4 ( 1.2) | 4 | 2.5 | 5 ( 1.5) | 5 | 3.1 | 9 ( 1.3) | 9 | 2.8 |
| Local swelling | 5 ( 1.5) | 5 | 3.1 | 3 ( 0.9) | 3 | 1.8 | 8 ( 1.2) | 8 | 2.5 |
| Injection site dermatitis | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Injection site rash | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Respiratory, thoracic and mediastinal disorders | 5 ( 1.5) | 6 | 3.8 | 10 ( 2.9) | 12 | 7.4 | 15 ( 2.2) | 18 | 5.6 |
| Cough | 3 ( 0.9) | 4 | 2.5 | 6 ( 1.8) | 8 | 4.9 | 9 ( 1.3) | 12 | 3.7 |
| Asthma | 1 ( 0.3) | 1 | 0.6 | 2 ( 0.6) | 2 | 1.2 | 3 ( 0.4) | 3 | 0.9 |
| Rhinitis allergic | 0 | | | 2 ( 0.6) | 2 | 1.2 | 2 ( 0.3) | 2 | 0.6 |
| Dyspnoea | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Skin and subcutaneous tissue disorders | 3 ( 0.9) | 4 | 2.5 | 6 ( 1.8) | 6 | 3.7 | 9 ( 1.3) | 10 | 3.1 |
| Rash | 2 ( 0.6) | 2 | 1.3 | 2 ( 0.6) | 2 | 1.2 | 4 ( 0.6) | 4 | 1.2 |
| Pruritus | 0 | | | 2 ( 0.6) | 2 | 1.2 | 2 ( 0.3) | 2 | 0.6 |
| Blister | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Eczema | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Eczema nummular | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Rash pruritic | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Immune system disorders | 4 ( 1.2) | 4 | 2.5 | 1 ( 0.3) | 1 | 0.6 | 5 ( 0.7) | 5 | 1.6 |
| Seasonal allergy | 4 ( 1.2) | 4 | 2.5 | 1 ( 0.3) | 1 | 0.6 | 5 ( 0.7) | 5 | 1.6 |
| Renal and urinary disorders | 1 ( 0.3) | 1 | 0.6 | 2 ( 0.6) | 2 | 1.2 | 3 ( 0.4) | 3 | 0.9 |
| Renal failure | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.3) | 1 | 0.6 | 2 ( 0.3) | 2 | 0.6 |
| Renal failure acute | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Blood and lymphatic system disorders | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Eosinophilia | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Investigations | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Eosinophil count abnormal | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Vascular disorders | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Circulatory collapse | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0

Source: CSR 3853, 14.3.1.26

The PTs reported in >1% of subjects and occurred more frequently in the (b) (4) group included local swelling (1.5% [5 subjects] versus 0.9% [3 subjects]), and seasonal allergy (1.2% [4 subjects] versus 0.3% [1 subject]).

**Reviewer's comments: Overall, there does not appear to be an imbalance in allergic reactions with (b) (4) compared to NovoLog treatment. Given the overall small number of reported events, the observed imbalance in certain PTs may be due to chance, particularly with regard to seasonal allergy.**

**Trial 4049**

A total of 17 allergic reactions were reported, 11 in the (b) (4) plus basal group compared to 6 in the basal group. Cough was reported most frequently and in the (b) (4) plus basal group (3.5% [4 subjects]) compared to basal group (0.8% [1 subject]). One 'hypersensitivity' occurred in the (b) (4) plus basal group (subject

(b) (6) which was non-serious event but led to study dropout (described in section 7.3.3).

**Trial 3931 – CSII**

Six allergic reactions were reported, two from the (b) (4) group (cough, allergic rhinitis) and four from NovoLog group (2 episodes of cough and one episode of pruritus and rash). None of these allergic reactions were serious.

### 7.3.5.5 Adverse Events Leading to Dose Reduction

There were no AEs leading to dose reduction in CSII trials (3931, (b) (4)).

**Trial 3852 – T1DM**

During the trial, 14 AEs in 11 subjects (2.8%) in the mealtime (b) (4) group, 12 AEs in 10 subjects (2.7%) in the postmeal (b) (4) group, and 9 AEs in 7 subjects (1.8%) in the NovoLog group led to dose reduction of study drug, and these events are summarized in Table 78.

The most frequent PTs leading to dose reduction were '**hypoglycemia'** and **'hypoglycemic unconsciousness'**, which occurred more frequently in the postmeal (b) (4) group (6 events) compared to mealtime (b) (4) (2 events) or NovoLog groups (none). One 'hypoglycemic seizure' occurred in a subject receiving postmeal (b) (4) treatment.

Excluding hypoglycemia, the most commonly reported AEs leading to dose reduction were 'fall' (3 events in 1 subject in the mealtime (b) (4) group), 'wrong drug administered' (2 events in 2 subjects in the mealtime (b) (4) group), and 'diarrhea' (one event each in mealtime and postmeal (b) (4) groups).

**Table 78: Trial 3852 – Adverse Events Leading to Dose Reduction by SOC and PT**

| | Faster aspart (meal) | | | Faster aspart (post) | | | NovoRapid (meal) | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | N | (%) | E | R | N | (%) | E | R | N | (%) | E | R |
| Number of subjects | 386 | | | | 377 | | | | 380 | | | | 1143 | | | |
| Total exposure (yrs) | 186.36 | | | | 183.00 | | | | 188.88 | | | | 558.23 | | | |
| Events | 11 | ( 2.8) | 14 | 7.5 | 10 | ( 2.7) | 12 | 6.6 | 7 | ( 1.8) | 8 | 4.2 | 28 | ( 2.4) | 34 | 6.1 |
| Gastrointestinal disorders | 3 | ( 0.8) | 3 | 1.6 | 2 | ( 0.5) | 3 | 1.6 | 2 | ( 0.5) | 2 | 1.1 | 7 | ( 0.6) | 8 | 1.4 |
| Diarrhoea | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 2 | ( 0.2) | 2 | 0.4 |
| Dyspepsia | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Food poisoning | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Gastrooesophageal reflux disease | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Inguinal hernia | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Nausea | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Vomiting | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Metabolism and nutrition disorders | 0 | | | | 5 | ( 1.3) | 5 | 2.7 | 2 | ( 0.5) | 3 | 1.6 | 7 | ( 0.6) | 8 | 1.4 |
| Hypoglycaemia | 0 | | | | 5 | ( 1.3) | 5 | 2.7 | 0 | | | | 5 | ( 0.4) | 5 | 0.9 |
| Hypoglycaemia unawareness | 0 | | | | 0 | | | | 1 | ( 0.3) | 2 | 1.1 | 1 | ( 0.1) | 2 | 0.4 |
| Decreased appetite | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Injury, poisoning and procedural complications | 4 | ( 1.0) | 6 | 3.2 | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 5 | ( 0.4) | 7 | 1.3 |
| Fall | 1 | ( 0.3) | 3 | 1.6 | 0 | | | | 0 | | | | 1 | ( 0.1) | 3 | 0.5 |
| Wrong drug administered | 2 | ( 0.5) | 2 | 1.1 | 0 | | | | 0 | | | | 2 | ( 0.2) | 2 | 0.4 |
| Accidental overdose | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Radius fracture | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Nervous system disorders | 3 | ( 0.8) | 4 | 2.1 | 2 | ( 0.5) | 2 | 1.1 | 1 | ( 0.3) | 1 | 0.5 | 6 | ( 0.5) | 7 | 1.3 |
| Hypoglycaemic unconsciousness | 2 | ( 0.5) | 3 | 1.6 | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 3 | ( 0.3) | 4 | 0.7 |
| Headache | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Hypoglycaemic seizure | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Stupor | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Infections and infestations | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 2 | ( 0.2) | 2 | 0.4 |
| Gastroenteritis viral | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Nasopharyngitis | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Blood and lymphatic system disorders | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Lymphadenopathy | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 0 | | | | 1 | ( 0.1) | 1 | 0.2 |
| Musculoskeletal and connective tissue disorders | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |
| Musculoskeletal pain | 0 | | | | 0 | | | | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.1) | 1 | 0.2 |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 patient years of exposure, yrs: Years
Source: CSR 3852, Table 14.3.1.22

Of all the AEs leading to dose reduction, 14 were SAEs: 4 events, 9 events, and one event in the mealtime (b) (4) postmeal (b) (4) and NovoLog groups respectively (Table 79). The most commonly reported SAEs leading to dose reduction were hypoglycemia-related events.

**Table 79: Trial 3852 – SAEs Leading to Dose Reduction**

| Subject ID | Preferred term | Severity | Causality (bolus and/or basal insulin) | Dose reduction |
|---|---|---|---|---|
| **Faster aspart (meal)** | | | | |
| (b) (6) | Hypoglycaemic unconsciousness | Severe | Probable (bolus and basal insulin) | Faster aspart and basal insulin |
| | Hypoglycaemic unconsciousness | Severe | Probable (basal insulin) | Basal insulin |
| | Hypoglycaemic unconsciousness | Severe | Possible (basal insulin) | Basal insulin |
| | Radius fracture | Moderate | Probable (basal insulin) | Basal insulin |
| **Faster aspart (post)** | | | | |
| (b) (6) | Hypoglycaemia | Severe | Probable (bolus insulin) | Faster aspart |
| | Hypoglycaemia | Severe | Probable (bolus insulin) | Faster aspart |
| | Hypoglycaemia | Severe | Probable (bolus and basal insulin) | Faster aspart and basal insulin |
| | Diarrhoea | Severe | Unlikely (bolus insulin) | Faster aspart |
| | Nausea | Severe | Unlikely (bolus insulin) | Faster aspart |
| | Hypoglycaemic seizure | Severe | Unlikely (bolus insulin) | Faster aspart |
| | Hypoglycaemia | Severe | Probable (basal insulin) | Basal insulin |
| | Hypoglycaemic unconsciousness | Severe | Probable (basal insulin) | Basal insulin |
| | Hypoglycaemia | Severe | Probable (basal insulin) | Basal insulin |
| **NovoRapid® (meal)** | | | | |
| (b) (6) | Musculoskeletal pain | Moderate | Unlikely (bolus and basal insulin) | NovoRapid® and basal insulin |

All adverse events are treatment-emergent. Relationship (causality) with trial products (bolus and basal insulins) is based on assessment by the investigator.
Source: CSR 3852, Table 12-6

## Trial 3853 – T2DM

During the trial, 18 AEs in 13 subjects (3.8%) in the (b) (4) group and 10 AEs in 9 subjects (2.6%) in the NovoLog group led to dose reduction of study drug (bolus and/or basal insulin), and these events are summarized in Table 80. These included 4 SAEs in 3 subjects in (b) (4) group (hypoglycemia in 2 subjects and lobar pneumonia in one subject) and 3 SAEs in 2 subjects in NovoLog group (all hypoglycemia), as shown in Table 81. All seven SAEs leading to dose reduction was reported as 'resolved'.

One 'adverse drug reaction' that led to dose reduction in (b) (4) group was reported to be 'pedal edema due to amlodipine' on Day 48 and with relationship determined to be 'unlikely' by the investigator and 'resolved'. The 'accidental overdose' in NovoLog group

was reported as 'accidental overdose of bolus insulin' on Day 12, and the event was reported as recovered/resolved.

**Table 80: Trial 3853 – Adverse Events Leading to Dose Reduction By SOC and PT**

| | Faster aspart N (%) | E | R | NovoRapid N (%) | E | R | Total N (%) | E | R |
|---|---|---|---|---|---|---|---|---|---|
| Number of subjects | 341 | | | 341 | | | 682 | | |
| Total exposure (yrs) | 159.81 | | | 162.26 | | | 322.06 | | |
| Events | 13 ( 3.8) | 18 | 11.3 | 9 ( 2.6) | 10 | 6.2 | 22 ( 3.2) | 28 | 8.7 |
| Infections and infestations | 5 ( 1.5) | 5 | 3.1 | 2 ( 0.6) | 2 | 1.2 | 7 ( 1.0) | 7 | 2.2 |
| Gastroenteritis | 2 ( 0.6) | 2 | 1.3 | 0 | | | 2 ( 0.3) | 2 | 0.6 |
| Enterocolitis infectious | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Lobar pneumonia | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Nasopharyngitis | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Sinusitis | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Upper respiratory tract infection | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Metabolism and nutrition disorders | 2 ( 0.6) | 3 | 1.9 | 2 ( 0.6) | 3 | 1.8 | 4 ( 0.6) | 6 | 1.9 |
| Hypoglycaemia | 2 ( 0.6) | 3 | 1.9 | 2 ( 0.6) | 3 | 1.8 | 4 ( 0.6) | 6 | 1.9 |
| General disorders and administration site conditions | 1 ( 0.3) | 1 | 0.6 | 2 ( 0.6) | 2 | 1.2 | 3 ( 0.4) | 3 | 0.9 |
| Adverse drug reaction | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Asthenia | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Injection site haematoma | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Investigations | 2 ( 0.6) | 2 | 1.3 | 1 ( 0.3) | 1 | 0.6 | 3 ( 0.4) | 3 | 0.9 |
| Weight increased | 2 ( 0.6) | 2 | 1.3 | 1 ( 0.3) | 1 | 0.6 | 3 ( 0.4) | 3 | 0.9 |
| Cardiac disorders | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.3) | 1 | 0.6 | 2 ( 0.3) | 2 | 0.6 |
| Coronary artery stenosis | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.3) | 1 | 0.6 | 2 ( 0.3) | 2 | 0.6 |
| Nervous system disorders | 1 ( 0.3) | 2 | 1.3 | 0 | | | 1 ( 0.1) | 2 | 0.6 |
| Dizziness | 1 ( 0.3) | 2 | 1.3 | 0 | | | 1 ( 0.1) | 2 | 0.6 |
| Ear and labyrinth disorders | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Vertigo positional | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Gastrointestinal disorders | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Vomiting | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Injury, poisoning and procedural complications | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Accidental overdose | 0 | | | 1 ( 0.3) | 1 | 0.6 | 1 ( 0.1) | 1 | 0.3 |
| Psychiatric disorders | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Anxiety | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Vascular disorders | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |
| Hypertension | 1 ( 0.3) | 1 | 0.6 | 0 | | | 1 ( 0.1) | 1 | 0.3 |

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0

Source: CSR 3853, 14.3.1.22

Of all the AEs leading to dose reduction, 7 were SAEs: 4 events in the (b) (4) and 3 events in the NovoLog groups (Table 81). All except one SAE (lobar pneumonia) that led to dose reduction were hypoglycemia, each group reporting 3 events in 2 subjects.

**Table 81: Trial 3853 –SAEs Leading to Dose Reduction**

| Treatment group | Subject ID | Preferred term | Severity | Causality (bolus and/or basal insulin) | Dose reduction |
|---|---|---|---|---|---|
| Faster aspart | (b) (6) | *Hypoglycaemia* | Severe | Probable (basal insulin) | Basal insulin |
| Faster aspart | | *Hypoglycaemia* (first episode) | Moderate | Probable (bolus and basal insulin) | Bolus insulin and basal insulin |
| | | *Hypoglycaemia* (second episode) | Moderate | Probable (basal insulin) | Basal insulin |
| Faster aspart | | *Lobar pneumonia* | Severe | Unlikely (basal insulin) | Basal insulin |
| NovoRapid | | *Hypoglycaemia* | Moderate | Probable (basal insulin) | Basal insulin |
| NovoRapid | | *Hypoglycaemia* (first episode) | Mild | Probable (bolus insulin) | Bolus insulin |
| | | *Hypoglycaemia* (second episode) | Moderate | Possible (bolus insulin) | Bolus insulin |

Bolus insulin=faster aspart dose (faster aspart group) and NovoRapid dose (NovoRapid group). Basal insulin=insulin glargine (for both faster aspart and NovoRapid groups). Relationship (causality) with trial products (bolus and or basal insulin) is based on investigator(s)'s assessment. MedDRA version 17.0.

Source: CSR 3853, Table 12-10

**Reviewer's comment: Most common AE that led to dose reduction was hypoglycemia-related events in both trial 3852 and 3853.**

**Trial 4049 – T2DM**

Five AEs led to dose reduction in this trial all in the (b) (4) plus basal group, three of which were serious (2 events of hypoglycemia and one event of wrong drug administered) and two were non-serious (one event each of insomnia and gastroenteritis).

(b) (4)

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

**Trial 3852:**

AEs by treatment group with frequency of ≥1% and ≥5% are summarized in Table 82 and Table 83 respectively.

The most frequently reported AEs (≥5%) in the treatment groups that occurred more frequently in both (b) (4) treatment group compared to NovoLog group were:

- **Nasopharyngitis:** 20.2% with mealtime (b) (4) 23.9% with postmeal (b) (4) and 19.5% with NovoLog;
- **Nausea:** 4.9% with mealtime (b) (4) 5.0% with postmeal (b) (4) and 4.2% with NovoLog;
- **Back pain:** 5.2% with mealtime (b) (4) 4.0% with postmeal (b) (4) and 3.4% with NovoLog.

The 'injection site reaction' occurred at slightly higher incidence with mealtime (b) (4) (1.0% [4 subjects] or 2.7 per 100 PYE) and postmeal (b) (4) (1.3% [5 subjects] or 3.3

per 100 PYE) groups compared to NovoLog treatment group (0.8% [3 subjects] or 1.6 per 100 PYE). Injection site reactions were also discussed in section 7.3.5.3.

The PT 'hypoglycemic unconsciousness' were also imbalanced not favoring mealtime (b) (4) (1.0% [4 subjects] or 2.7 per 100 PYE) and postmeal (b) (4) (0.8% [3 subjects] or 1.6 per 100 PYE) groups compared to NovoLog treatment group (0.5% [2 subjects] or 1.1 per 100 PYE). Hypoglycemia was also discussed in section 7.3.4.

In addition, there was an imbalance in the incidence of 'diabetic retinopathy' not favoring postmeal (b) (4) treatment group: 0.8% (3 subjects), 2.7% (10 subjects), and 1.1% (4 subjects) in the mealtime (b) (4) postmeal (b) (4) and NovoLog reported diabetic retinopathy (Table 82). None of these were serious, led to study discontinuation, or was associated with insulin dose reduction. Two events of diabetic retinopathy in the postmeal (b) (4) were considered severe by the investigator.

## Table 82: Trial 3852 – Most Frequently Reported (≥1%) Treatment Emergent AEs by System Organ Class and Preferred Term (Safety Analysis Set)

| | Faster aspart (meal) | | | Faster aspart (post) | | | NovoRapid (meal) | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | (%) | E R | N | (%) | E R | N | (%) | E R | N | (%) | E R |
| Number of subjects | 386 | | | 377 | | | 380 | | | 1143 | | |
| Total exposure (yrs) | 186.36 | | | 183.00 | | | 188.88 | | | 558.23 | | |
| Infections and infestations | | | | | | | | | | | | |
| Nasopharyngitis | 78 | (20.2) | 103 55.3 | 90 | (23.9) | 111 60.7 | 74 | (19.5) | 93 49.2 | 242 | (21.2) | 307 55.0 |
| Upper respiratory tract infection | 35 | ( 9.1) | 40 21.5 | 28 | ( 7.4) | 31 16.9 | 29 | ( 7.6) | 38 20.1 | 92 | ( 8.0) | 109 19.5 |
| Influenza | 13 | ( 3.4) | 14 7.5 | 11 | ( 2.9) | 12 6.6 | 25 | ( 6.6) | 28 14.8 | 49 | ( 4.3) | 54 9.7 |
| Urinary tract infection | 8 | ( 2.1) | 9 4.8 | 15 | ( 4.0) | 20 10.9 | 12 | ( 3.2) | 15 7.9 | 35 | ( 3.1) | 44 7.9 |
| Sinusitis | 12 | ( 3.1) | 12 6.4 | 7 | ( 1.9) | 7 3.8 | 17 | ( 4.5) | 20 10.6 | 36 | ( 3.1) | 39 7.0 |
| Gastroenteritis | 15 | ( 3.9) | 16 8.6 | 8 | ( 2.1) | 8 4.4 | 9 | ( 2.4) | 11 5.8 | 32 | ( 2.8) | 35 6.3 |
| Viral infection | 12 | ( 3.1) | 13 7.0 | 3 | ( 0.8) | 4 2.2 | 9 | ( 2.4) | 9 4.8 | 24 | ( 2.1) | 26 4.7 |
| Gastroenteritis viral | 10 | ( 2.6) | 10 5.4 | 5 | ( 1.3) | 6 3.3 | 6 | ( 1.6) | 6 3.2 | 21 | ( 1.8) | 22 3.9 |
| Bronchitis | 6 | ( 1.6) | 6 3.2 | 6 | ( 1.6) | 6 3.3 | 7 | ( 1.8) | 7 3.7 | 19 | ( 1.7) | 19 3.4 |
| Rhinitis | 4 | ( 1.0) | 4 2.1 | 4 | ( 1.1) | 5 2.7 | 2 | ( 0.5) | 3 1.6 | 10 | ( 0.9) | 12 2.1 |
| Cystitis | 4 | ( 1.0) | 5 2.7 | 3 | ( 0.8) | 3 1.6 | 3 | ( 0.8) | 3 1.6 | 10 | ( 0.9) | 11 2.0 |
| Pharyngitis | 5 | ( 1.3) | 5 2.7 | 3 | ( 0.8) | 3 1.6 | 3 | ( 0.8) | 3 1.6 | 11 | ( 1.0) | 11 2.0 |
| Localised infection | 3 | ( 0.8) | 3 1.6 | 1 | ( 0.3) | 1 0.5 | 4 | ( 1.1) | 4 2.1 | 8 | ( 0.7) | 8 1.4 |
| Tooth abscess | 4 | ( 1.0) | 4 2.1 | 2 | ( 0.5) | 3 1.6 | 1 | ( 0.3) | 1 0.5 | 7 | ( 0.6) | 8 1.4 |
| Tonsillitis | 1 | ( 0.3) | 1 0.5 | 1 | ( 0.3) | 1 0.5 | 5 | ( 1.3) | 5 2.6 | 7 | ( 0.6) | 7 1.3 |
| Tooth infection | 4 | ( 1.0) | 4 2.1 | 0 | | | 2 | ( 0.5) | 2 1.1 | 6 | ( 0.5) | 6 1.1 |
| Gastrointestinal disorders | | | | | | | | | | | | |
| Nausea | 19 | ( 4.9) | 22 11.8 | 19 | ( 5.0) | 30 16.4 | 16 | ( 4.2) | 20 10.6 | 54 | ( 4.7) | 72 12.9 |
| Diarrhoea | 21 | ( 5.4) | 25 13.4 | 12 | ( 3.2) | 12 6.6 | 18 | ( 4.7) | 19 10.1 | 51 | ( 4.5) | 56 10.0 |
| Vomiting | 9 | ( 2.3) | 12 6.4 | 16 | ( 4.2) | 17 9.3 | 15 | ( 3.9) | 17 9.0 | 40 | ( 3.5) | 46 8.2 |
| Abdominal pain upper | 13 | ( 3.4) | 14 7.5 | 4 | ( 1.1) | 7 3.8 | 3 | ( 0.8) | 3 1.6 | 20 | ( 1.7) | 24 4.3 |
| Abdominal discomfort | 5 | ( 1.3) | 6 3.2 | 7 | ( 1.9) | 8 4.4 | 9 | ( 2.4) | 9 4.8 | 21 | ( 1.8) | 23 4.1 |
| Toothache | 9 | ( 2.3) | 10 5.4 | 2 | ( 0.5) | 2 1.1 | 7 | ( 1.8) | 8 4.2 | 18 | ( 1.6) | 20 3.6 |
| Abdominal pain | 5 | ( 1.3) | 6 3.2 | 3 | ( 0.8) | 4 2.2 | 4 | ( 1.1) | 4 2.1 | 12 | ( 1.0) | 14 2.5 |
| Dyspepsia | 2 | ( 0.5) | 2 1.1 | 3 | ( 0.8) | 3 1.6 | 5 | ( 1.3) | 6 3.2 | 10 | ( 0.9) | 11 2.0 |
| Constipation | 3 | ( 0.8) | 3 1.6 | 1 | ( 0.3) | 1 0.5 | 5 | ( 1.3) | 5 2.6 | 9 | ( 0.8) | 9 1.6 |
| Food poisoning | 1 | ( 0.3) | 1 0.5 | 2 | ( 0.5) | 2 1.1 | 5 | ( 1.3) | 5 2.6 | 8 | ( 0.7) | 8 1.4 |
| Gastrooesophageal reflux disease | 3 | ( 0.8) | 3 1.6 | 4 | ( 1.1) | 4 2.2 | 1 | ( 0.3) | 1 0.5 | 8 | ( 0.7) | 8 1.4 |
| Nervous system disorders | | | | | | | | | | | | |
| Headache | 29 | ( 7.5) | 45 24.1 | 26 | ( 6.9) | 41 22.4 | 32 | ( 8.4) | 50 26.5 | 87 | ( 7.6) | 136 24.4 |
| Dizziness | 8 | ( 2.1) | 9 4.8 | 8 | ( 2.1) | 9 4.9 | 1 | ( 0.3) | 1 0.5 | 17 | ( 1.5) | 19 3.4 |
| Migraine | 6 | ( 1.6) | 9 4.8 | 7 | ( 1.9) | 7 3.8 | 3 | ( 0.8) | 3 1.6 | 16 | ( 1.4) | 19 3.4 |
| Hypoglycaemic unconsciousness | 4 | ( 1.0) | 5 2.7 | 3 | ( 0.8) | 3 1.6 | 2 | ( 0.5) | 2 1.1 | 9 | ( 0.8) | 10 1.8 |
| Neuropathy peripheral | 4 | ( 1.0) | 4 2.1 | 0 | | | 1 | ( 0.3) | 1 0.5 | 5 | ( 0.4) | 5 0.9 |
| Paraesthesia | 1 | ( 0.3) | 1 0.5 | 0 | | | 4 | ( 1.1) | 4 2.1 | 5 | ( 0.4) | 5 0.9 |
| Injury, poisoning and procedural complications | | | | | | | | | | | | |
| Wrong drug administered | 17 | ( 4.4) | 21 11.3 | 19 | ( 5.0) | 21 11.5 | 19 | ( 5.0) | 23 12.2 | 55 | ( 4.8) | 65 11.6 |
| Fall | 5 | ( 1.3) | 8 4.3 | 4 | ( 1.1) | 5 2.7 | 2 | ( 0.5) | 2 1.1 | 11 | ( 1.0) | 15 2.7 |
| Procedural pain | 5 | ( 1.3) | 10 5.4 | 3 | ( 0.8) | 3 1.6 | 1 | ( 0.3) | 1 0.5 | 9 | ( 0.8) | 14 2.5 |
| Laceration | 3 | ( 0.8) | 3 1.6 | 4 | ( 1.1) | 4 2.2 | 4 | ( 1.1) | 5 2.6 | 11 | ( 1.0) | 12 2.1 |
| Muscle strain | 5 | ( 1.3) | 5 2.7 | 3 | ( 0.8) | 4 2.2 | 3 | ( 0.8) | 3 1.6 | 11 | ( 1.0) | 12 2.1 |
| Ligament sprain | 5 | ( 1.3) | 5 2.7 | 3 | ( 0.8) | 3 1.6 | 2 | ( 0.5) | 2 1.1 | 10 | ( 0.9) | 10 1.8 |
| Accidental overdose | 2 | ( 0.5) | 2 1.1 | 5 | ( 1.3) | 5 2.7 | 2 | ( 0.5) | 2 1.1 | 9 | ( 0.8) | 9 1.6 |
| Musculoskeletal and connective tissue disorders | | | | | | | | | | | | |
| Back pain | 20 | ( 5.2) | 23 12.3 | 15 | ( 4.0) | 17 9.3 | 13 | ( 3.4) | 13 6.9 | 48 | ( 4.2) | 53 9.5 |
| Pain in extremity | 6 | ( 1.6) | 6 3.2 | 9 | ( 2.4) | 11 6.0 | 6 | ( 1.6) | 7 3.7 | 21 | ( 1.8) | 24 4.3 |
| Arthralgia | 9 | ( 2.3) | 10 5.4 | 6 | ( 1.6) | 6 3.3 | 5 | ( 1.3) | 6 3.2 | 20 | ( 1.7) | 22 3.9 |
| Musculoskeletal pain | 2 | ( 0.5) | 2 1.1 | 3 | ( 0.8) | 3 1.6 | 4 | ( 1.1) | 4 2.1 | 9 | ( 0.8) | 9 1.6 |
| Myalgia | 2 | ( 0.5) | 2 1.1 | 1 | ( 0.3) | 1 0.5 | 4 | ( 1.1) | 6 3.2 | 7 | ( 0.6) | 9 1.6 |
| Tendonitis | 2 | ( 0.5) | 2 1.1 | 2 | ( 0.5) | 2 1.1 | 4 | ( 1.1) | 4 2.1 | 8 | ( 0.7) | 8 1.4 |
| General disorders and administration site conditions | | | | | | | | | | | | |
| Fatigue | 10 | ( 2.6) | 13 7.0 | 8 | ( 2.1) | 8 4.4 | 5 | ( 1.3) | 5 2.6 | 23 | ( 2.0) | 26 4.7 |
| Pyrexia | 5 | ( 1.3) | 5 2.7 | 8 | ( 2.1) | 8 4.4 | 9 | ( 2.4) | 10 5.3 | 22 | ( 1.9) | 23 4.1 |
| Influenza like illness | 6 | ( 1.6) | 7 3.8 | 3 | ( 0.8) | 3 1.6 | 4 | ( 1.1) | 4 2.1 | 13 | ( 1.1) | 14 2.5 |
| Injection site reaction | 4 | ( 1.0) | 5 2.7 | 5 | ( 1.3) | 6 3.3 | 3 | ( 0.8) | 3 1.6 | 12 | ( 1.0) | 14 2.5 |
| Pain | 2 | ( 0.5) | 2 1.1 | 4 | ( 1.1) | 6 3.3 | 2 | ( 0.5) | 2 1.1 | 8 | ( 0.7) | 10 1.8 |
| Malaise | 4 | ( 1.0) | 5 2.7 | 2 | ( 0.5) | 2 1.1 | 1 | ( 0.3) | 2 1.1 | 7 | ( 0.6) | 9 1.6 |
| Chest pain | 0 | | | 4 | ( 1.1) | 4 2.2 | 1 | ( 0.3) | 1 0.5 | 5 | ( 0.4) | 5 0.9 |
| Respiratory, thoracic and mediastinal disorders | | | | | | | | | | | | |
| Oropharyngeal pain | 9 | ( 2.3) | 13 7.0 | 16 | ( 4.2) | 21 11.5 | 14 | ( 3.7) | 17 9.0 | 39 | ( 3.4) | 51 9.1 |
| Cough | 10 | ( 2.6) | 11 5.9 | 12 | ( 3.2) | 13 7.1 | 12 | ( 3.2) | 12 6.4 | 34 | ( 3.0) | 36 6.4 |
| Nasal congestion | 4 | ( 1.0) | 4 2.1 | 1 | ( 0.3) | 1 0.5 | 5 | ( 1.3) | 5 2.6 | 10 | ( 0.9) | 10 1.8 |

Continued next page

| | Faster aspart (meal) N | (%) | E | R | Faster aspart (post) N | (%) | E | R | NovoRapid (meal) N | (%) | E | R | Total N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metabolism and nutrition disorders | | | | | | | | | | | | | | | | |
| Hypoglycaemia | 8 | ( 2.1) | 10 | 5.4 | 11 | ( 2.9) | 11 | 6.0 | 5 | ( 1.3) | 5 | 2.6 | 24 | ( 2.1) | 26 | 4.7 |
| Hyperglycaemia | 4 | ( 1.0) | 4 | 2.1 | 1 | ( 0.3) | 1 | 0.5 | 1 | ( 0.3) | 1 | 0.5 | 6 | ( 0.5) | 6 | 1.1 |
| Eye disorders | | | | | | | | | | | | | | | | |
| Diabetic retinopathy | 3 | ( 0.8) | 3 | 1.6 | 10 | ( 2.7) | 10 | 5.5 | 4 | ( 1.1) | 4 | 2.1 | 17 | ( 1.5) | 17 | 3.0 |
| Reproductive system and breast disorders | | | | | | | | | | | | | | | | |
| Dysmenorrhoea | 2 | ( 0.5) | 10 | 5.4 | 5 | ( 1.3) | 5 | 2.7 | 1 | ( 0.3) | 1 | 0.5 | 8 | ( 0.7) | 16 | 2.9 |
| Immune system disorders | | | | | | | | | | | | | | | | |
| Seasonal allergy | 5 | ( 1.3) | 5 | 2.7 | 3 | ( 0.8) | 3 | 1.6 | 6 | ( 1.6) | 7 | 3.7 | 14 | ( 1.2) | 15 | 2.7 |
| Skin and subcutaneous tissue disorders | | | | | | | | | | | | | | | | |
| Rash | 6 | ( 1.6) | 6 | 3.2 | 3 | ( 0.8) | 3 | 1.6 | 2 | ( 0.5) | 2 | 1.1 | 11 | ( 1.0) | 11 | 2.0 |
| Vascular disorders | | | | | | | | | | | | | | | | |
| Hypertension | 5 | ( 1.3) | 5 | 2.7 | 3 | ( 0.8) | 3 | 1.6 | 3 | ( 0.8) | 3 | 1.6 | 11 | ( 1.0) | 11 | 2.0 |
| Psychiatric disorders | | | | | | | | | | | | | | | | |
| Insomnia | 0 | | | | 0 | | | | 4 | ( 1.1) | 4 | 2.1 | 4 | ( 0.3) | 4 | 0.7 |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0

Source, CSR 3852, Table 14.3.1.7

## Table 83: Trial 3852 – Most Frequently Reported (≥5%) Treatment Emergent AEs by System Organ Class and Preferred Term (SAS)

| | Faster aspart (meal) N | (%) | E | R | Faster aspart (post) N | (%) | E | R | NovoRapid (meal) N | (%) | E | R | Total N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of subjects | 386 | | | | 377 | | | | 380 | | | | 1143 | | | |
| Total exposure (yrs) | 186.36 | | | | 183.00 | | | | 188.88 | | | | 558.23 | | | |
| Infections and infestations | | | | | | | | | | | | | | | | |
| Nasopharyngitis | 78 | (20.2) | 103 | 55.3 | 90 | (23.9) | 111 | 60.7 | 74 | (19.5) | 93 | 49.2 | 242 | (21.2) | 307 | 55.0 |
| Upper respiratory tract infection | 35 | ( 9.1) | 40 | 21.5 | 28 | ( 7.4) | 31 | 16.9 | 29 | ( 7.6) | 38 | 20.1 | 92 | ( 8.0) | 109 | 19.5 |
| Influenza | 13 | ( 3.4) | 14 | 7.5 | 11 | ( 2.9) | 12 | 6.6 | 25 | ( 6.6) | 28 | 14.8 | 49 | ( 4.3) | 54 | 9.7 |
| Nervous system disorders | | | | | | | | | | | | | | | | |
| Headache | 29 | ( 7.5) | 45 | 24.1 | 26 | ( 6.9) | 41 | 22.4 | 32 | ( 8.4) | 50 | 26.5 | 87 | ( 7.6) | 136 | 24.4 |
| Gastrointestinal disorders | | | | | | | | | | | | | | | | |
| Nausea | 19 | ( 4.9) | 22 | 11.8 | 19 | ( 5.0) | 30 | 16.4 | 16 | ( 4.2) | 20 | 10.6 | 54 | ( 4.7) | 72 | 12.9 |
| Diarrhoea | 21 | ( 5.4) | 25 | 13.4 | 12 | ( 3.2) | 12 | 6.6 | 18 | ( 4.7) | 19 | 10.1 | 51 | ( 4.5) | 56 | 10.0 |
| Injury, poisoning and procedural complications | | | | | | | | | | | | | | | | |
| Wrong drug administered | 17 | ( 4.4) | 21 | 11.3 | 19 | ( 5.0) | 21 | 11.5 | 19 | ( 5.0) | 23 | 12.2 | 55 | ( 4.8) | 65 | 11.6 |
| Musculoskeletal and connective tissue disorders | | | | | | | | | | | | | | | | |
| Back pain | 20 | ( 5.2) | 23 | 12.3 | 15 | ( 4.0) | 17 | 9.3 | 13 | ( 3.4) | 13 | 6.9 | 48 | ( 4.2) | 53 | 9.5 |

N: Number of subjects, %: Percentage of subjects, E: Number of events
R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 17.0

Source: CSR 3852, Table 14.3.1.6

**Trial 3853:**

The most frequently reported AEs (≥1%) in the treatment groups that occurred more frequently in the (b) (4) group compared to NovoLog were the following events by SOC (Table 84):

- Infections and Infestations: urinary tract infection (5.9% versus 3.8%), gastroenteritis (1.8% versus 0.9%), bronchitis (1.5% versus 0.9%), pneumonia (1.2% versus 0.3%);
- Gastrointestinal disorders: diarrhea (4.4% versus 2.6%), toothache (2.3% versus 0.9%), nausea (2.1% versus 1.8%);
- Musculoskeletal and connective tissue: back pain (1.8% versus 0.9%), periarthritis (1.2% versus 0);
- Investigations: weight increased (3.2% versus 1.8%), C-reactive protein increased (1.8% versus 0.9%);
- Blood and lymphatic system disorders: anemia (3.5% versus 1.8%);
- Renal and urinary disorders: nephrolithiasis (1.2% versus 0.3%);
- Vascular disorders: hypertension (1.8% versus 0.6%);
- General disorders and administration site conditions: local swelling (1.5% versus 0.9%);
- Immune system disorders: seasonal allergy (1.2% versus 0.3%);
- Injury, poisoning, and procedural complications (1.2% versus 0.9%).

**Reviewer's comments: There was also a slight imbalance of 'nausea' and 'back pain' in the (b) (4) group compared to NovoLog in T1DM trial 3852 as well. However, the number of events for these AEs was very small and inconclusive.**

**Urinary tract infection** which was most frequently reported event at >5% with higher incidence in the (b) (4) group compared to the NovoLog group (20 subjects [5.9%] versus 13 subjects [3.8%]).

**Reviewer's comments: A slight imbalance in urinary tract infection not favoring mealtime (b) (4) compared to NovoLog was also seen in trial 3852 (9.1% versus 7.6%), although not seen with postmeal (b) (4) group (7.4%) (Table 82). The clinical significance of this small imbalance in urinary tract infection between treatment groups is unclear.**

**Table 84: Trial 3853 – Most Frequently Reported (≥1%) Treatment Emergent AEs by System Organ Class and Preferred Term (Safety Analysis Set)**

| | Faster aspart N (%) | E | R | NovoRapid N (%) | E | R |
|---|---|---|---|---|---|---|
| Number of subjects | 341 | | | 341 | | |
| Total exposure (yrs) | 159.81 | | | 162.26 | | |
| Infections and infestations | | | | | | |
| Nasopharyngitis | 17 ( 5.0) | 20 | 12.5 | 24 ( 7.0) | 27 | 16.6 |
| Upper respiratory tract infection | 16 ( 4.7) | 19 | 11.9 | 22 ( 6.5) | 27 | 16.6 |
| Urinary tract infection | 20 ( 5.9) | 27 | 16.9 | 13 ( 3.8) | 16 | 9.9 |
| Gastroenteritis | 6 ( 1.8) | 6 | 3.8 | 3 ( 0.9) | 6 | 3.7 |
| Sinusitis | 2 ( 0.6) | 2 | 1.3 | 6 ( 1.8) | 8 | 4.9 |
| Bronchitis | 5 ( 1.5) | 5 | 3.1 | 3 ( 0.9) | 3 | 1.8 |
| Influenza | 3 ( 0.9) | 3 | 1.9 | 5 ( 1.5) | 5 | 3.1 |
| Gastroenteritis viral | 1 ( 0.3) | 1 | 0.6 | 5 ( 1.5) | 5 | 3.1 |
| Pneumonia | 4 ( 1.2) | 4 | 2.5 | 1 ( 0.3) | 1 | 0.6 |
| Gastrointestinal disorders | | | | | | |
| Diarrhoea | 15 ( 4.4) | 15 | 9.4 | 9 ( 2.6) | 11 | 6.8 |
| Nausea | 7 ( 2.1) | 9 | 5.6 | 6 ( 1.8) | 7 | 4.3 |
| Vomiting | 6 ( 1.8) | 6 | 3.8 | 9 ( 2.6) | 9 | 5.5 |
| Toothache | 8 ( 2.3) | 8 | 5.0 | 3 ( 0.9) | 3 | 1.8 |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Arthralgia | 8 ( 2.3) | 9 | 5.6 | 8 ( 2.3) | 11 | 6.8 |
| Back pain | 6 ( 1.8) | 7 | 4.4 | 3 ( 0.9) | 3 | 1.8 |
| Pain in extremity | 2 ( 0.6) | 2 | 1.3 | 4 ( 1.2) | 4 | 2.5 |
| Musculoskeletal chest pain | 1 ( 0.3) | 1 | 0.6 | 4 ( 1.2) | 4 | 2.5 |
| Periarthritis | 4 ( 1.2) | 4 | 2.5 | 0 | | |
| Investigations | | | | | | |
| Weight increased | 11 ( 3.2) | 11 | 6.9 | 6 ( 1.8) | 6 | 3.7 |
| C-reactive protein increased | 6 ( 1.8) | 6 | 3.8 | 3 ( 0.9) | 3 | 1.8 |
| Nervous system disorders | | | | | | |
| Headache | 4 ( 1.2) | 5 | 3.1 | 8 ( 2.3) | 9 | 5.5 |
| Dizziness | 3 ( 0.9) | 5 | 3.1 | 4 ( 1.2) | 4 | 2.5 |
| Metabolism and nutrition disorders | | | | | | |
| Dyslipidaemia | 7 ( 2.1) | 7 | 4.4 | 14 ( 4.1) | 14 | 8.6 |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Cough | 3 ( 0.9) | 4 | 2.5 | 6 ( 1.8) | 8 | 4.9 |
| Oropharyngeal pain | 4 ( 1.2) | 5 | 3.1 | 4 ( 1.2) | 4 | 2.5 |
| Respiratory disorder | 0 | | | 4 ( 1.2) | 4 | 2.5 |
| Blood and lymphatic system disorders | | | | | | |
| Anaemia | 12 ( 3.5) | 12 | 7.5 | 6 ( 1.8) | 6 | 3.7 |
| Renal and urinary disorders | | | | | | |
| Nephrolithiasis | 4 ( 1.2) | 4 | 2.5 | 1 ( 0.3) | 1 | 0.6 |
| Vascular disorders | | | | | | |
| Hypertension | 6 ( 1.8) | 6 | 3.8 | 2 ( 0.6) | 2 | 1.2 |
| Ear and labyrinth disorders | | | | | | |
| Vertigo | 2 ( 0.6) | 2 | 1.3 | 4 ( 1.2) | 4 | 2.5 |
| General disorders and administration site conditions | | | | | | |
| Asthenia | 4 ( 1.2) | 4 | 2.5 | 5 ( 1.5) | 5 | 3.1 |
| Oedema peripheral | 4 ( 1.2) | 4 | 2.5 | 5 ( 1.5) | 5 | 3.1 |
| Local swelling | 5 ( 1.5) | 5 | 3.1 | 3 ( 0.9) | 3 | 1.8 |
| Immune system disorders | | | | | | |
| Seasonal allergy | 4 ( 1.2) | 4 | 2.5 | 1 ( 0.3) | 1 | 0.6 |
| Injury, poisoning and procedural complications | | | | | | |
| Fall | 4 ( 1.2) | 8 | 5.0 | 3 ( 0.9) | 4 | 2.5 |

N: Number of subjects, %: Percentage of subjects, E: Number of events R: Event rate per 100 patient years of exposure, yrs: Years.
Treatment-emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. MedDRA version 17.0.

Source: CSR 3853, Table 12-3

**Trial 4049 – T1DM**

The AEs (>2%) in the treatment groups that occurred more frequently in the (b) (4) plus basal group compared to basal group were:

- Cough: 3.5% (4) versus 0.8% (1)
- Toothache: 3.5% (4) versus 2.5% (3)
- Nausea: 2.6% (3) versus none
- Vomiting: 2.6% (3) versus none
- Arthralgia: 2.6% (3) versus 0.8% (1)
- Pain in extremity: 2.6% (3) versus 0.8% (1)
- Paresthesia: 2.6% (3) versus none

**Reviewer's comment: Imbalance in nausea not favoring (b) (4) treatment arm was seen in both 3852 and 3853 trials as well. However, the number of reported events are very few in each trials.**

**Also, although back pain occurred less frequently with (b) (4) treatment arm, there was an imbalance in other musculoskeletal events such as arthralgia and pain in extremity not favoring (b) (4) treatment arm. The clinical significance of this is unclear, and the number of reported events was very small to make conclusion.**

**Table 85: Trial 4049 – Most Frequently Reported (≥1%) Treatment Emergent AEs by System Organ Class and Preferred Term (SAS)**

| | Faster aspart + Basal | | | Basal | | |
|---|---|---|---|---|---|---|
| | N | (%) | E R | N | (%) | E R |
| Number of subjects | 115 | | | 120 | | |
| Total exposure (yrs) | 38.40 | | | 40.75 | | |
| Infections and infestations | | | | | | |
| Urinary tract infection | 4 | ( 3.5) | 4 10.4 | 4 | ( 3.3) | 6 14.7 |
| Pharyngitis | 2 | ( 1.7) | 3 7.8 | 2 | ( 1.7) | 4 9.8 |
| Respiratory tract infection | 2 | ( 1.7) | 2 5.2 | 2 | ( 1.7) | 3 7.4 |
| Bronchitis | 1 | ( 0.9) | 1 2.6 | 3 | ( 2.5) | 3 7.4 |
| Influenza | 0 | | | 4 | ( 3.3) | 4 9.8 |
| Nasopharyngitis | 1 | ( 0.9) | 1 2.6 | 2 | ( 1.7) | 2 4.9 |
| Cellulitis | 2 | ( 1.7) | 2 5.2 | 0 | | |
| Fungal infection | 0 | | | 2 | ( 1.7) | 2 4.9 |
| Upper respiratory tract infection | 0 | | | 2 | ( 1.7) | 2 4.9 |
| Gastrointestinal disorders | | | | | | |
| Diarrhoea | 2 | ( 1.7) | 4 10.4 | 6 | ( 5.0) | 6 14.7 |
| Toothache | 4 | ( 3.5) | 4 10.4 | 3 | ( 2.5) | 3 7.4 |
| Nausea | 3 | ( 2.6) | 3 7.8 | 0 | | |
| Vomiting | 3 | ( 2.6) | 3 7.8 | 0 | | |
| Odynophagia | 0 | | | 2 | ( 1.7) | 2 4.9 |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Arthralgia | 3 | ( 2.6) | 9 23.4 | 1 | ( 0.8) | 1 2.5 |
| Back pain | 1 | ( 0.9) | 2 5.2 | 2 | ( 1.7) | 2 4.9 |
| Musculoskeletal pain | 2 | ( 1.7) | 2 5.2 | 2 | ( 1.7) | 2 4.9 |
| Pain in extremity | 3 | ( 2.6) | 3 7.8 | 1 | ( 0.8) | 1 2.5 |
| Nervous system disorders | | | | | | |
| Headache | 3 | ( 2.6) | 3 7.8 | 3 | ( 2.5) | 3 7.4 |
| Paraesthesia | 3 | ( 2.6) | 3 7.8 | 0 | | |
| Injury, poisoning and procedural complications | | | | | | |
| Fall | 2 | ( 1.7) | 2 5.2 | 1 | ( 0.8) | 1 2.5 |
| Eye injury | 0 | | | 2 | ( 1.7) | 2 4.9 |
| Metabolism and nutrition disorders | | | | | | |
| Hypertriglyceridaemia | 2 | ( 1.7) | 2 5.2 | 1 | ( 0.8) | 1 2.5 |
| Hypoglycaemia | 2 | ( 1.7) | 2 5.2 | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Cough | 4 | ( 3.5) | 4 10.4 | 1 | ( 0.8) | 1 2.5 |
| Ear and labyrinth disorders | | | | | | |
| Vertigo | 1 | ( 0.9) | 1 2.6 | 2 | ( 1.7) | 2 4.9 |
| Investigations | | | | | | |
| Eosinophil count increased | 2 | ( 1.7) | 2 5.2 | 1 | ( 0.8) | 1 2.5 |
| Eye disorders | | | | | | |
| Visual impairment | 2 | ( 1.7) | 2 5.2 | 0 | | |
| Hepatobiliary disorders | | | | | | |
| Hepatic steatosis | 0 | | | 2 | ( 1.7) | 2 4.9 |
| Psychiatric disorders | | | | | | |
| Insomnia | 2 | ( 1.7) | 2 5.2 | 0 | | |
| Renal and urinary disorders | | | | | | |
| Microalbuminuria | 2 | ( 1.7) | 2 5.2 | 0 | | |

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 exposure years, yrs: Years

Source: CSR 4049, Table 12-3

**Trial 3931 – CSII**

All TEAEs during trial 3931 are presented in Table 86. The AEs that occurred more than once and more frequently in the (b) (4) group compared to NovoLog group were nasopharyngitis (3 versus 1), influenza like illness (2 versus none), and back pain (2 versus none). There were also two instances of rheumatism-related AEs in the (b) (4) group (one each of rheumatoid arthritis and rheumatic disorder) compared to none in the NovoLog group; rheumatoid arthritis also led to study discontinuation and this subject is briefly described in section 7.3.3. Infusion-site AEs were also more seen under General disorders and administration site conditions SOC with (b) (4) compared to NovoLog; infusion site reactions are further discussed in section 7.3.5.3.

## Table 86: Trial 3931 – Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

| | Faster aspart N | (%) | E | R | NovoRapid N | (%) | E | R |
|---|---|---|---|---|---|---|---|---|
| Number of subjects | 25 | | | | 12 | | | |
| Total exposure (yrs) | 2.91 | | | | 1.41 | | | |
| Events | 15 | ( 60.0) | 26 | 894 | 6 | ( 50.0) | 15 | 1064 |
| Infections and infestations | 7 | ( 28.0) | 7 | 241 | 4 | ( 33.3) | 5 | 355 |
| Nasopharyngitis | 3 | ( 12.0) | 3 | 103 | 1 | ( 8.3) | 1 | 71 |
| Ear infection | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Otitis media | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Pyelonephritis acute | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Sinusitis | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Tonsillitis | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Tooth abscess | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Upper respiratory tract infection | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Urinary tract infection | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Respiratory, thoracic and mediastinal disorders | 2 | ( 8.0) | 2 | 69 | 4 | ( 33.3) | 6 | 426 |
| Cough | 1 | ( 4.0) | 1 | 34 | 2 | ( 16.7) | 2 | 142 |
| Oropharyngeal pain | 0 | | | | 2 | ( 16.7) | 2 | 142 |
| Rhinitis allergic | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Sinus congestion | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Upper respiratory tract congestion | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| General disorders and administration site conditions | 5 | ( 20.0) | 7 | 241 | 1 | ( 8.3) | 1 | 71 |
| Influenza like illness | 2 | ( 8.0) | 2 | 69 | 0 | | | |
| Pyrexia | 1 | ( 4.0) | 1 | 34 | 1 | ( 8.3) | 1 | 71 |
| Infusion site erythema | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Infusion site induration | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Infusion site pruritus | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Infusion site reaction | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Musculoskeletal and connective tissue disorders | 3 | ( 12.0) | 5 | 172 | 0 | | | |
| Back pain | 2 | ( 8.0) | 3 | 103 | 0 | | | |
| Rheumatic disorder | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Rheumatoid arthritis | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Gastrointestinal disorders | 2 | ( 8.0) | 3 | 103 | 0 | | | |
| Abdominal discomfort | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Diarrhoea | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Vomiting | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Skin and subcutaneous tissue disorders | 0 | | | | 1 | ( 8.3) | 2 | 142 |
| Pruritus | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Rash | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Eye disorders | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Diabetic retinopathy | 0 | | | | 1 | ( 8.3) | 1 | 71 |
| Nervous system disorders | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Headache | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Injury, poisoning and procedural complications | 1 | ( 4.0) | 1 | 34 | 0 | | | |
| Laceration | 1 | ( 4.0) | 1 | 34 | 0 | | | |

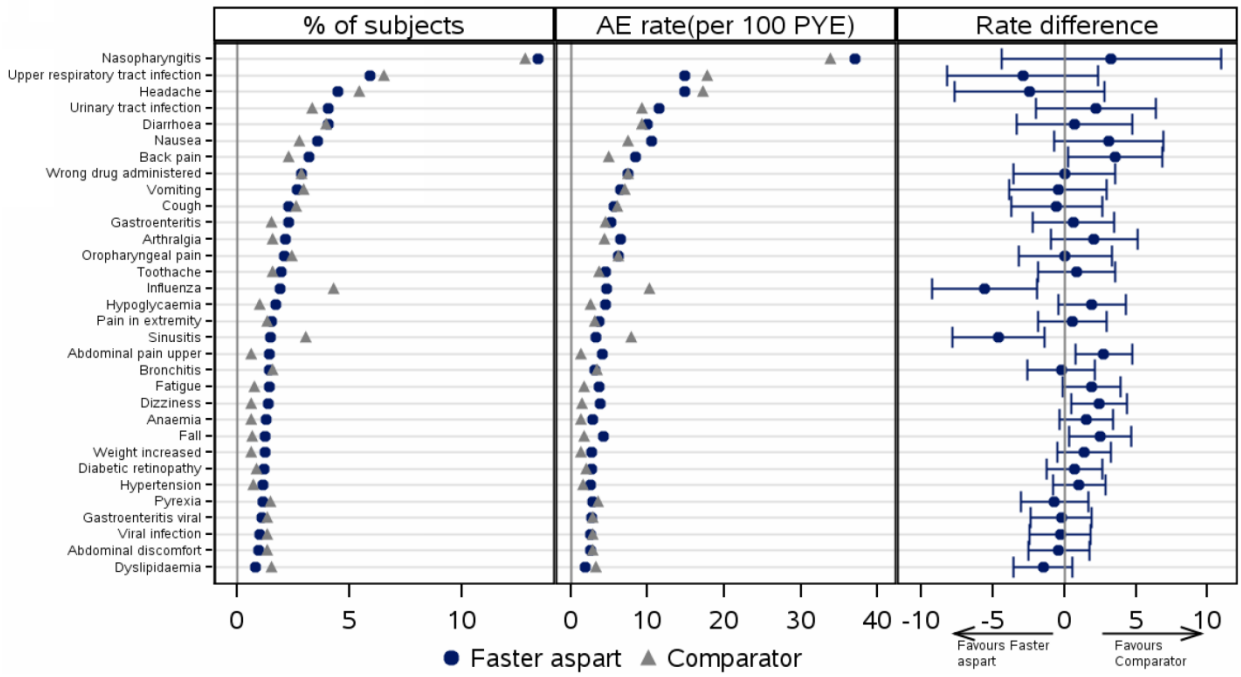
N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 exposure years, yrs: Years

Source: CSR 3931, Table 14.3.1.11

**Diabetes Pool:**

Figure 49 displays the AEs that occurred ≥1% in either (b) (4) or comparator in the diabetes pool, sorted by frequency in the (b) (4) group. Rate differences with associated 95% confidence intervals were calculated using the Cochran-Mantel-Haenszel method to account for different exposures in the trial.

**Figure 49: Diabetes Pool of AEs Occurring ≥1% in Either Treatment Group by PTs**




Source: SCS, Figure 2-4

In the diabetes pool, the AEs (≥1%) that occurred more frequently with (b) (4) (N=1244) versus comparator (N=853) included the following events, with calculated rate difference (RD) if it did not include 0 shown (thus not favoring (b) (4)

- Infections and Infestations:
  - Nasopharyngitis: 13.4% (189) versus 12.8% (101)
  - Urinary tract infection: 4.1% (48) versus 3.4% (29)
  - Gastroenteritis: 2.3% (30) versus 1.5% (12)
- Gastrointestinal Disorders:
  - Nausea: 3.6% (48) versus 2.8% (22)
  - **Abdominal pain upper:** 1.5% (20) versus 0.6% (5); **RD was 2.72 (95% CI: 0.74, 4.70)**
  - Toothache: 2.0% (23) versus 1.6% (13)
- Neurological Disorders:
  - **Dizziness:** 1.4% (19) versus 0.6% (6); **RD was 2.42 (95% CI: 0.49, 4.36)**

- Musculoskeletal Disorders:
  - **Back pain:** 3.2% (44) versus 2.3% (18); **RD was 3.54 (95% CI: 0.29, 6.80)**
  - Arthralgia: 2.1% (26) versus 1.6% (14)
- Injury, Poisoning and Procedural Complications SOC:
  - **Fall:** 1.3% (15) versus 0.7% (6); **RD was 2.5 (95% CI: 0.36, 4.65)**
  - Hypoglycemia: 1.7% (23) versus 1.0% (8)
- General Disorders and Administration Site Conditions:
  - Fatigue: 1.4% (20) versus 0.8% (6)
- Eye Disorders:
  - Diabetic retinopathy: 1.2% (16) versus 0.9% (7)
- Vascular Disorders:
  - Hypertension: 1.2% (14) versus 0.7% (6)
- Blood and Lymphatic System Disorders:
  - Anemia: 1.3% (13) versus 0.6% (6)
- Investigations:
  - Weight increased: 1.2% (12) versus 0.6% (6)

Since 'fall' and 'dizziness' can be related to hypoglycemia, the relationship of these events were evaluated.

In trial 3852, 11 subjects reported 15 falls (one was serious) and 17 subjects reported 19 events of dizziness (all non-serious). Five falls in 3 subjects did take place on the same day as hypoglycemia, and 5 dizziness occurred on the same day as hypoglycemia.

In trial 3853, 7 subjects experienced 12 falls, none of them on the same day as hypoglycemia episode; 7 subjects reported 9 dizziness (all non-serious) where 5 were reported on the same day as hypoglycemia episode.

In trial 4049, 3 episodes of fall and 1 episode of dizziness was reported, and none occurred with hypoglycemic episodes. In the CSII trials, no falls were reported, (b) (4)

**Reviewer's comment: It is highly possible that fall and dizziness can occur with hypoglycemia, but current data is inconclusive given the small number of observed correlations.**

### 7.4.2 Laboratory Findings

The laboratory parameters evaluated and timing of these evaluations for all trials are summarized in Table 87. In addition, trial 3852 analyzed anti-insulin antibodies (see section 7.4.6).

Urine pregnancy testing was done locally, and all other laboratory analyses were done by central laboratories. Trials 3852, 3852, 4049, and 3931 all used the same central laboratory.

**Table 87: Overview of Timing for Laboratory Parameters in All Trials**

| Trial | | Screening | Baseline | Week 12 | End of each 14 day treatment period | End of trial |
|---|---|---|---|---|---|---|
| Clinical pharmacology trials[a] | Biochemistry, haematology, urine analysis and lipid analysis | x | | | | x |
| 3852, 3853 and 4049 | Biochemistry, haematology and urine analysis[b] | x | x | x | | x |
| 3852 and 3853 | Lipid analysis | | x | x[c] | | x |
| 4049 | Lipid analysis | | x | | | x |
| 3852 | Insulin antibody assessment | | x | x | | x |
| 3931 | Biochemistry, haematology and urine analysis | x | x | | | x |
| | Lipid analysis | | x | | | x |
| (b) (4) | | | | | | |

[a] Trials 3887, (b) (4) 3889, (b) (4) 3891, 3918, 3921 and 3978. Trial 3949 differed from the other trials in that some of the biochemistry parameters and urine analysis were only measured at screening and glucose was only measured at follow-up (Trial 3949 (M 5.3.1.1), Table 9.5).

[b] Trial 4049 did not measure urine at screening.

[c] Trial 3852 did not measure lipids at week 12.

Source: SCS, Table 3-1

Biochemistry parameters included albumin, ALT, AST, ALP, creatinine, sodium potassium, total bilirubin, and total protein. Hematology parameters included hemoglobin, hematocrit, erythrocytes, thrombocytes, leukocytes, and differentials.

Subjects with extra low/extra high laboratory values during Phase 3 trials were evaluated, with the range defined in Table 88. Also further surveillance was done to identify possible cases of drug-induced liver injury (Hy's law) in trials 3852, 3853, and 4049.

**Table 88: Range Specifications for Clinically Relevant Safety Laboratory Parameters for Extra Low or Extra High Values for Trials 3852, 3853, 4049, 3931, (b) (4)**

| Category | Parameter | SI unit | Conventional unit | LLN (SI unit) | ULN (SI unit) | Extra low (SI unit) | Extra high (SI unit) |
|---|---|---|---|---|---|---|---|
| Biochemistry | Alanine aminotransferase (ALAT(SGPT)) | U/L | | 0 | 47 | NA | >3xULN |
| | Albumin (serum) | g/dL | | 3.7 | 4.9 | <30 | NA |
| | Alkaline phospatase (AP) | U/L | | 40 | 135 | NA | >2.5xULN |
| | Aspartate aminotransferase (ASAT(SGOT)) | U/L | | 0 | 37 | NA | >3xULN |
| | Bilirubin (total) | umol/L | mg/dL | 0.0 | 19.0 | NA | >1.5xULN |
| | Creatinine (female) | umol/L | mg/dL | 45 | 84 | NA | >1.5xbaseline |
| | Creatinine (male) | umol/L | mg/dL | 59 | 104 | NA | >1.5xbaseline |
| Haematology | Potassium | mmol/L | mEq/L | 3.6 | 5.2 | <3.0 | >5.5 |
| | Sodium | mmol/L | mEq/L | 134 | 146 | <130 | >150 |
| | Haemoglobin (female) | mmol/L | g/dL | 7.1 | 9.6 | <6.2 | NA |
| | Haemoglobin (male) | mmol/L | g/dL | 8.2 | 10.5 | <6.2 | NA |
| | Leucocytes | 10^9/L | | 3.5 | 11.1 | <3 | NA |
| | Lymphocytes-Abs. | 10^9/L | | 1.2 | 4 | < 0.8 | NA |
| | Neutrophils-Abs. | 10^9/L | | 1.8 | 7 | < 1.5 | NA |
| | Thrombocytes | 10^9/L | | 150 | 400 | <75 | NA |

[a] Based on severity grade given in the Common Terminology Criteria for Adverse Events)[24]. Ranges are identical for both genders except where specified. Abs: Absolute; LLN: Lower limit normal; NA: Not applicable; ULN: Upper limit normal; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamate-pyruvate transaminase; SI: International system of units. See Appendix 7.7, List 145 for the list of subjects with extra low or high safety laboratory values across trials.
Source: SCS, Table 3-2

There were no significant findings in terms of changes in biochemistry and hematology assessments in clinical pharmacology trials.

In trials 3852, 3853, and 4049, the mean values for biochemistry, hematology, and urinalysis remained stable during the trial without apparent differences between the treatment groups in mean values or changes during the trial. The majority of subjects also had normal values during treatment and few subjects had changes from normal to high or low, with no major differences observed across treatment groups (not shown

here; for trial 3852, see CSR Tables 14.3.5.4, 14.3.5.26, 14.3.5.88 and 14.3.5.92 to 14.3.5.94; for trial 3853, see CSR Tables 14.3.5.4, 14.3.5.28, 14.3.5.90 and 14.3.5.94 to 14.3.5.96; for trial 4049, see CSR Tables 14.3.5.4, 14.3.5.28, 14.3.5.76, and 14.3.5.80 to 14.3.5.82).

Also, no notable differences between treatment groups were seen in the mean of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides at baseline or end of the trial after 26 weeks of treatment in trials 3852 and 3853, and after 18 weeks of treatment in trial 4049.

There were no notable significant findings with regard to change in laboratory values after 14 days of treatment in CSII trials 3931 (b) (4).

### 7.4.3 Vital Signs

The mean blood pressure and pulse at baseline and after 26 weeks of treatment from trial 3852 are shown in Table 89. The small observed changes in blood pressure and pulse in treatment groups are small and would not be considered clinically meaningful changes.

**Table 89: Summary of Vital Signs in Trial 3852**

| | Faster aspart (meal) | | Faster aspart (post) | | NovoRapid® (meal) | |
|---|---|---|---|---|---|---|
| | BP (S/D) (mmHg) | Pulse (beats/min) | BP (S/D) (mmHg) | Pulse (beats/min) | BP (S/D) (mmHg) | Pulse (beats/min) |
| **Mean value at baseline** | 125.0/73.8 | 72.7 | 124.6/75.2 | 74.9 | 124.2/74.8 | 73.3 |
| **Mean value at end of trial** | 123.4/73.4 | 71.7 | 123.6/74.3 | 73.7 | 123.2/75.2 | 72.8 |
| **Mean change from baseline to end of trial** | -1.6/-0.4 | -0.9 | -0.9/-0.9 | -1.2 | -1.1/0.4 | -0.4 |

Safety analysis set. End of trial contains last available measurement

BP: blood pressure; S: systolic; D: diastolic

Source: CSR 3852, Table 12-14

In trials 3853, and 4049, the mean blood pressure and pulse remained stable in all treatment groups at baseline and at the end of study period with very minimal change (<1 mmHg in both systolic and diastolic pressure, and less than 1 beat per minute; not shown).

Vital signs also remained stable in CSII trials 3931 (b) (4).

### 7.4.4 Electrocardiograms (ECGs)

A 12-lead ECG was performed locally and was interpreted by the investigator at screening/baseline and at the end of trial in trials 3852, 3853, and 4049. No clinically relevant difference was seen between two treatment groups in ECG measurements at baseline or at the end of trial (not shown, see Table 14.3.6.14 in CSR 3852 and 3853).

In trial 3852, 3 subjects had a change in ECG from 'normal' or 'abnormal, not clinically significant' at baseline to 'abnormal, clinically significant' after 26 weeks ((b) (6) from mealtime (b) (4) and (b) (6) from postmeal (b) (4) None of these events led to related clinical events.

In trial 3853, 1 subject in the (b) (4) group and 4 subjects in the NovoLog group had a change in ECG to 'abnormal, clinically significant' after 26 weeks of treatment in trial 3852. One subject in the (b) (4) group who had an 'abnormally significant' ECG at baseline was later withdrawn from the trial due to a non-serious AE of "post infarction angina" and the ECG measurement at Week 26 was not available.

In trial 4049, 1 subject with 'normal' and 2 subjects with 'abnormal, not clinically significant' baseline ECG shifted to 'abnormal, clinically significant' at the end of the trial in the (b) (4) plus basal group; also, 2 subjects in the Fasonsi plus basal group with 'abnormal, clinically significant' baseline ECG shifted to 'abnormal, not clinically significant' at the end of trial. In the basal group, 1 subject with baseline 'abnormal, clinically significant' shifted to 'abnormal, not clinically significant' at the end of trial.

In CSII trials 3931 (b) (4), there were no 'abnormal, clinically significant' ECGs reported at the end of the trial.

### 7.4.5 Special Safety Studies/Clinical Trials

None.

### 7.4.6 Immunogenicity

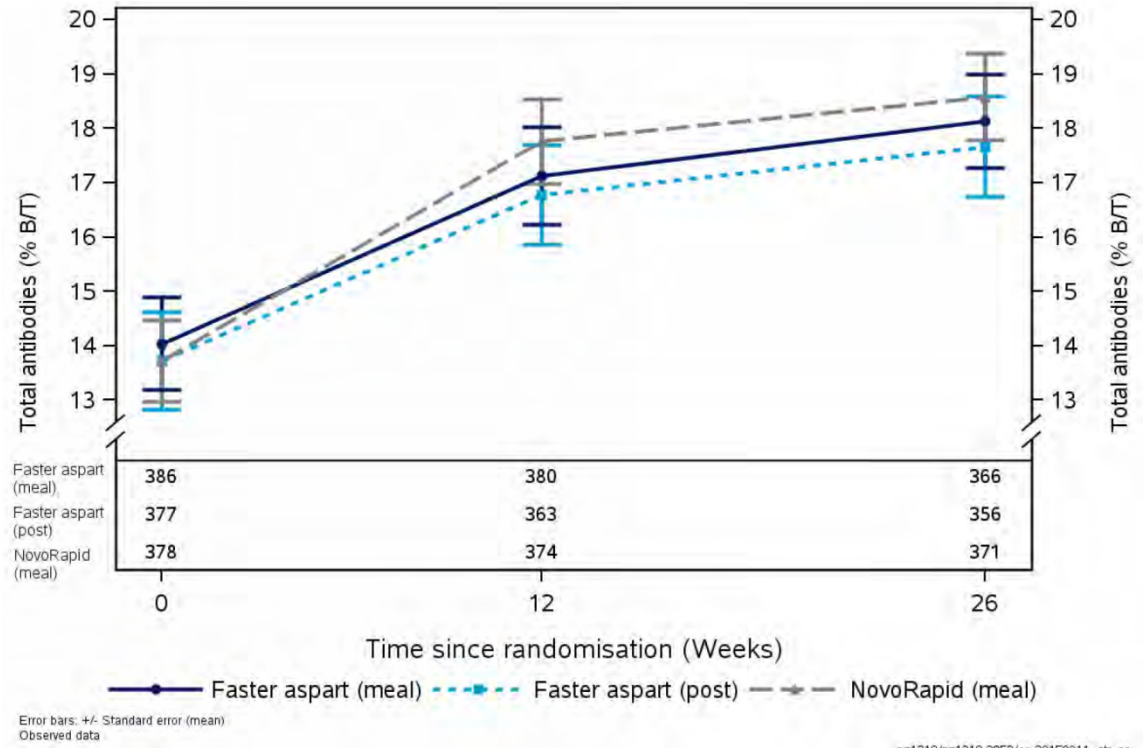
Development of antibodies with any new insulin therapy may potentially lead to reduced drug exposure and affect glycemic efficacy by neutralizing the effect of the drug, and sometimes may lead to requiring higher insulin doses to maintain glycemic control. To assess this, antibodies specific to insulin aspart and antibodies cross-reacting to human insulin were measured in trial 3852 at baseline, Week 12, and Week 26. The results are presented as the percent of bound radioactivity (B) out of total amount of radioactivity (T) (%B/T) on three time points of measurements, which are proportional to the amount of anti-insulin antibody present in the sample.

At baseline, most subjects across three treatment groups had insulin antibodies because they've previously received insulin treatment, with a mean level of 1.5%B/T for specific anti-insulin aspart antibodies and 12.3 %B/T for anti-insulin aspart antibodies cross-reacting with human insulin, with a total antibody level of 13.8%.

The mean plot of total insulin antibodies, cross-reacting antibodies, and insulin aspart specific antibodies are shown in Figure 50, Figure 51, and Figure 52 respectively.

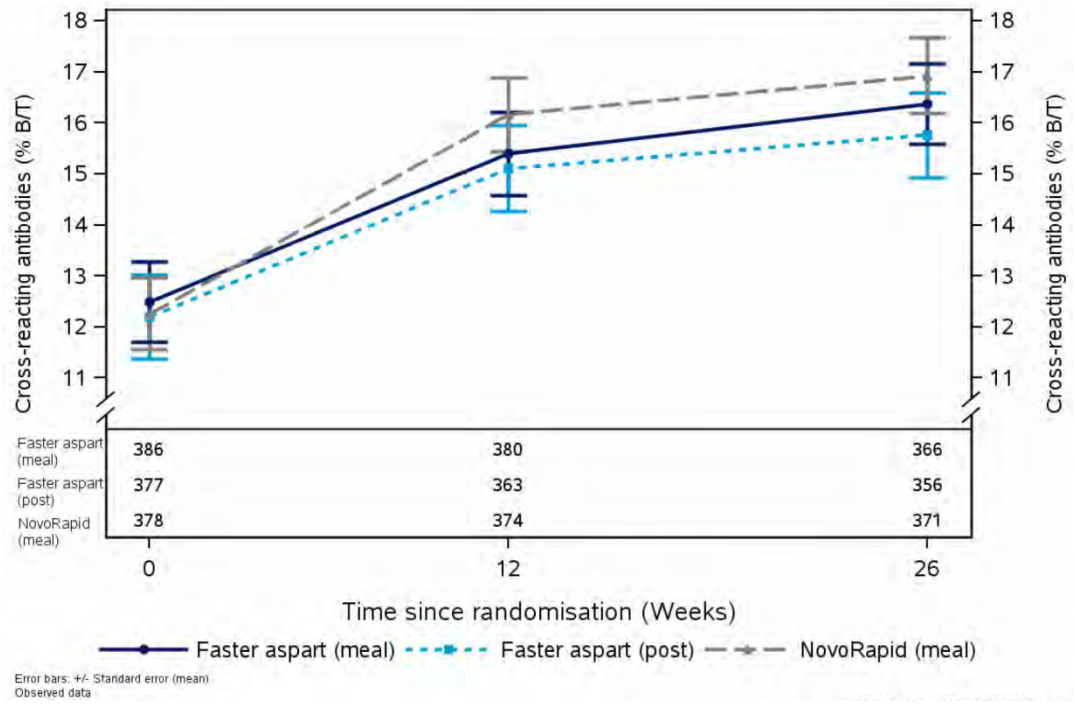
The mean level of total anti-insulin aspart antibody was low at baseline and increased slightly during the trial, and this increase was slightly larger in the NovoLog treatment group compared to (b) (4) treatment groups (Figure 50). This slightly larger increase in total anti-insulin aspart with NovoLog appears to correlate with the increase in the cross-reacting antibodies seen during treatment period (Figure 51). There was a slightly larger increase in insulin aspart specific antibodies in the postmeal (b) (4) compared to NovoLog (Figure 52), but the increase appear to be very small and the clinical significance of this finding is unclear.

**Figure 50: Mean Plot of Total Insulin Antibodies in Trial 3852**



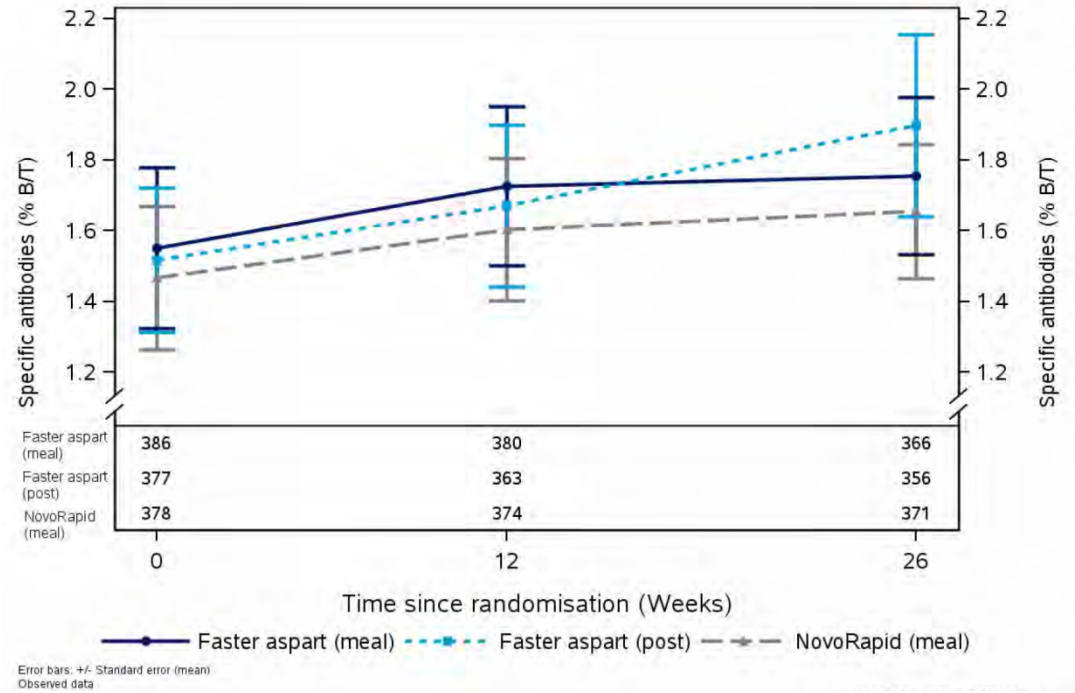

Source: CSR 3852, 14.3.6.24

**Figure 51: Mean Plot of Cross-Reacting Antibodies in Trial 3852**




Source: CSR 3852, Figure 14.3.6.22

**Figure 52: Mean Plot of Insulin Aspart Specific Antibodies in Trial 3852**




Source: CSR 3852, Figure 14.3.6.20

***Antibodies and Glycemic Effect***

The relationship between lack of glycemic effect and antibody development was evaluated, but there was no apparent relationship (not shown; see Figures 14.3.6.38 and 14.3.6.39; 14.3.6.26 and 14.3.6.27; 14.3.6.32 and 14.3.6.33 in CSR 3852). There was also no apparent correlation between the level of antibodies and the total insulin aspart exposure based on 1 and 2 hour PK samples during the standardized meal test at baseline and after 26 weeks of treatment (not shown; see Figures 14.3.6.40, 14.3.6.28, and 14.3.6.34 in CSR 3852).

***Antibodies and Injection Site Reactions and Allergic Reactions:***

The potential impact of anti-insulin antibody development on safety was evaluated by looking at the relationship between the occurrence of injection site reactions and immunogenicity-related AEs in relation to total anti-insulin aspart antibodies, anti-insulin aspart antibodies, and cross-reacting anti-insulin antibodies in scatter plots. The pre-defined MedDRA searches for identifying injection site reactions and immunogenicitiy-related AEs (i.e., allergic reactions) are described in sections 7.3.5.3 and 7.3.5.4 respectively.

In the scatter plots of titers of anti-insulin aspart antibodies cross-reacting to human insulin in subjects with and without injection site reactions, there did not appear to be a correlation between injection site reactions and an increase in antibody titers from baseline to 26 weeks of treatment (not shown; see Figure 5-7 of SCS), or between allergic reactions (not shown; see Figure 5-8 of SCS). It should be noted that the number of injection site reactions or allergic reactions were small overall.

**Reviewer's comments: There does not seem to be an increased risk of immunogenicity associated with (b) (4) compared to NovoLog that may affect glycemic efficacy or safety based on the available data at this time.**

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Dose-dependent AEs related to insulin are hypoglycemia and body weight gain. Hypoglycemic episodes are discussed in section 7.3.4 and changes in body weight were discussed for each trial in section 6.

### 7.5.2 Time Dependency for Adverse Events

Time dependency for hypoglycemia was discussed in section 7.3.4.

### 7.5.3 Drug-Demographic Interactions

The potential effect of some demographic characteristics (gender, age, baseline BMI, ethnicity and race) on the safety profile of (b) (4) was evaluated by the applicant using results from trials 3852 and 3853. The effect of these characteristics on safety was done by comparing the AEs in (b) (4) group against those in the NovoLog group. No formal statistical analyses were done, and in some subgroup the number of subjects or frequency of AEs were very low. The mealtime and postmeal (b) (4) group in trial 3852 were pooled for these subgroup analyses, which is acceptable.

The following differences were noted (other subgroups were too small to evaluate differences between treatment groups):

Age: The event rates of AEs were numerically lower for (b) (4) compared to NovoLog in the elderly group ≥65 years of age (414 versus 554 events per 100 PYE) and 65 to <75 years of age (433 versus 538 events per 100 PYE) in T1DM. This difference appeared to have been largely driven by a higher rate of 'nasopharyngitis' in elderly subjects in the NovoLog group compared to (b) (4) group (18.2 versus 57.5 events per 100 PYE in (b) (4) versus NovoLog group in ≥65 years of age).

Ethnicity: The event rates of AEs in Hispanic or Latino subjects were higher for (b) (4) compared to NovoLog in T1DM (359 versus 235 events per 100 PYE) and T2DM (481 versus 281 events per 100 PYE). The difference in AE rates between treatment groups in trial 3852 was largely due to more events in Infections and Infestations SOC (106 versus 74.2 events per 100 PYE, with largest imbalance of 'nasopharyngitis') and Gastrointestinal disorders (61.5 versus 0 events per 100 PYE; 'abdominal pain', 'vomiting', and 'nausea' most commonly reported with 10 events per 100 PYE). However more Hispanic/Latino subjects were exposed to (b) (4) compared to NovoLog in both trials.

Race: The overall event rate of AEs for African Americans were numerically higher in the (b) (4) compared to NovoLog for T1DM (328 [25 events in 9 subjects] versus 135 [6 events in 3 subjects] events per 100 PYE) and T2DM (425 [39 events in 10 subjects] versus 338 [27 events in 12 subjects] events per 100 PYE). However, the overall number of reported events was small.

**Reviewer's comments: Given the multiple comparisons, these noted differences may have occurred by chance. Also, the number of events is very small for some of these comparisons. Thus these results are considered exploratory.**

### 7.5.4 Drug-Disease Interactions

No clinically relevant interactions between treatment and intrinsic factors related to concomitant disease were identified in subgroup analysis of all AEs for baseline disease factors (see section 5.3.1 of SCS).

### 7.5.5 Drug-Drug Interactions

For detailed discussion of drug-disease interactions, see the Clinical Pharmacology Review. Insulin aspart is not expected to directly interact with other drugs because it is a peptide.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

The number and types of cancers reported in each trial under Neoplasm Benign, Malignant and Unspecified (including cysts and polyps) SOC were reviewed. The reported events under this SOC were very small in each trial and there was no apparent trend/grouping in the types of cancer subjects reported or with either (b) (4) or NovoLog. Thus there was no suggestion of any safety signal related to cancer with the insulin treatment. However, the studies in this clinical development are too short in duration (~6 months or shorter) to evaluate carcinogenicity potential with a product.

### 7.6.2 Human Reproduction and Pregnancy Data

(b) (4) has not been studied during pregnancy and lactation in clinical studies.

In the clinical development program for (b) (4) women of childbearing potential were required to use contraceptive methods, and pregnancy or intent to become pregnant were exclusion and withdrawal criteria.

Five pregnancies were reported in trial 3852. Two subjects were run-in failures and three of these subjects withdrew during the trial. No pregnancy complications were reported in these subjects to date. One of three subjects who withdrew were reported to have delivered without complications (subject (b) (6) postmeal (b) (4) another subject had an induced abortion voluntarily (subject (b) (6) NovoLog), and the outcome of pregnancy in the remaining subject is unknown at the data cut-off date (subject (b) (6) NovoLog) but the information in the safety database as of July 9, 2015 documented that she delivered without complications.

Additional 3 pregnancies (blinded) were reported from the additional, ongoing part of trial 3852. These pregnancies were reported to be term with a healthy child.

No pregnancies were reported in other trials.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

There are no completed pediatric studies for review with the use of (b) (4) The sponsor submitted an agreed-upon Pediatric Study Plan (iPSP) with the submission.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The following MedDRA PTs were used to search for events of overdose in the diabetes pool: accidental overdose, intentional overdose, suicide attempt, completed suicide, overdose, and prescribed overdose.

Twelve overdose events were reported in 12 subjects (9 with (b) (4) and 3 with comparator). Eleven of the events were reported as 'accidental overdose' (8 with (b) (4) and 3 with comparator) and the remaining event (with (b) (4) was reported as 'overdose'. This 'overdose' event was serious and was related to an overdose of pain medication and not related to the insulin aspart. The other 'accidental overdose' events were non-serious, but 2 events of accidental overdose (one with postmeal (b) (4) and one with NovoLog) were associated with an episode of severe hypoglycemia. The outcome of all events was recovered/resolved.

There is no drug abuse potential with insulin aspart.

No rebound effect has been observed for insulin products.

### 7.7 Additional Submissions / Safety Issues

## 8 Postmarket Experience

As (b) (4) is not yet marketed, no postmarketing experience exists for this product.

# 9 Appendices

## 9.1 Literature Review/References

## 9.2 Labeling Recommendations

Labeling recommendations are contained within this review as appropriate. Labeling is not finalized at the time of this review.

## 9.3 Advisory Committee Meeting

No advisory committee meeting was convened for this application.

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

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/s/

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HYON J KWON
10/06/2016

LISA B YANOFF
10/07/2016

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 208751** **Applicant: Novo Nordisk** **Stamp Date: December 8, 2015**

**Drug Name: insulin aspart** **NDA/BLA Type: 505(b)(1)**

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **FORMAT/ORGANIZATION/LEGIBILITY** | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD). | | | | eCTD |
| 2. | Is the clinical section legible and organized in a manner to allow substantive review to begin? | X | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | X | | | |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)? | X | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | X | | | |
| **LABELING** | | | | | |
| 6. | Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm | X | | | |
| **SUMMARIES** | | | | | |
| 7. | Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)? | X | | | |
| 8. | Has the applicant submitted the integrated summary of safety (ISS)? | X | | | |
| 9. | Has the applicant submitted the integrated summary of efficacy (ISE)? | X | | | |
| 10. | Has the applicant submitted a benefit-risk analysis for the product? | X | | | |
| 11. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). | | | | 505(b)(1) |
| **505(b)(2) Applications** | | | | | |
| 12. | If appropriate, what is the relied upon listed drug(s)? | | | | |
| 13. | Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature? | | | | |
| 14. | Describe the scientific bridge (e.g., BA/BE studies) | | | | |
| **DOSAGE** | | | | | |
| 15. | If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)?<br>Study Number:<br>Study Title:<br>Sample Size:<br>Treatment Arms:<br>Location in submission: | X | | | Clin pharm trials include dose-response trial (3887), mealtime dosing (3889), postmeal dosing (3921) |
| **EFFICACY** | | | | | |
| 16. | Do there appear to be the requisite number of adequate and | X | | | |

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | well-controlled studies in the application?<br><br>Pivotal Study #1: 3852 (Basal-bolus in T1DM)<br><br>Pivotal Study #2: 3853 (Basal-bolus in T2DM)<br><br>Supportive Study: 4049 (Basal-bolus vs basal in T2DM)<br><br>(b) (4)<br><br>Indication: To improve glycemic control in adults with diabetes mellitus | | | | |
| 17. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | |
| 18. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | No previous agreements, but HbA1c is an acceptable primary endpoint for diabetes products |
| 19. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | X | | |
| **SAFETY** | | | | | |
| 20. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 21. | Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | | | X | |
| 22. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 23. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious? | X | | | |
| 24. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | X | |
| 25. | Has the applicant submitted the coding dictionary[2] used for | X | | | MedDRA version 17.0 |

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | mapping investigator verbatim terms to preferred terms? | | | | used for coding in pivotal Phase 3 trials and CSII trials |
| 26. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 27. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | |
| **OTHER STUDIES** | | | | | |
| 28. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | | | X | |
| 29. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)? | | | X | |
| **PEDIATRIC USE** | | | | | |
| 30. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | |
| **PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE** | | | | | |
| 31. | For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)? | | X | | This should be requested in 74 letter; they only referenced NovoLog PI for proposed labeling for pregnancy and lactation section of labeling. |
| **ABUSE LIABILITY** | | | | | |
| 32. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | X | |
| **FOREIGN STUDIES** | | | | | |
| 33. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | X | | Request a rationale in the 74 day letter. |
| **DATASETS** | | | | | |
| 34. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | Defer to stats for final acceptability of datasets |
| 35. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 36. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | |
| 37. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 38. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | | | X | |
| **CASE REPORT FORMS** | | | | | |
| 39. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| 40. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | X | |
| **FINANCIAL DISCLOSURE** | | | | | |
| 41. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| **GOOD CLINICAL PRACTICE** | | | | | |
| 42. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

- Request sources of clinical information (literature review, postmarketing cases), summary of clinical information and justification for proposed PLLR format.
- Provide justification for the applicability of study results to the US population for the trials conducted outside the US.

Hyon Kwon 2/8/2016

Reviewing Medical Officer Date

Lisa Yanoff 2/12/2016

Clinical Team Leader Date

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

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/s/

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HYON J KWON
02/12/2016

LISA B YANOFF
02/16/2016