# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208751Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY REVIEW

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| **NDA:** | 208751 |
| **Link to EDR:** | \\CDSESUB1\evsprod\NDA208751\208751.enx |
| **Submission Date(s):** | 29th March, 2017 (Resubmission)<br>Original NDA submission on 9th December, 2015 |
| **Submission Type; Code:** | NDA 505(b)(1); Standard |
| **Brand Name** | Fiasp |
| **Generic Name** | Insulin aspart |
| **Formulation; Strength(s)** | 100 Units/mL (U-100) in 10 mL vials and 3 mL FlexTouch pen |
| **Route of Administration:** | Subcutaneous, Intravenous |
| **Proposed Indication:** | To improve glycemic control in adults with diabetes mellitus |
| **Applicant:** | Novo Nordisk |
| **Clinical Pharmacology Reviewer:** | Shalini Wickramaratne Senarath Yapa, Ph.D. |
| **Clinical Pharmacology Team Leader:** | Manoj Khurana, Ph.D. |
| **OCP Division:** | Clinical Pharmacology -2 |
| **OND division:** | Metabolism and Endocrinology Products |

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## 1. Executive Summary

Novo Nordisk resubmitted NDA 208751 on 29th March, 2017 (Original NDA submitted on 9th December, 2015), seeking marketing approval for insulin aspart (proposed trade name Fiasp®) to improve glycemic control in adults with diabetes mellitus. Fiasp is developed as a meal time insulin with the claim of a 'greater early glucose lowering effect' when compared to the currently approved NovoLog® (insulin aspart injection 100 units/mL). The drug product intended for market (insulin aspart 100 units/mL) is a clear, colorless solution available as a 10 mL vial or 3 mL cartridge (assembled into a pre-filled disposable pen-injector).

During the review of original NDA 208751 submission, a Complete Response Letter was issued, in part due to the Office of Clinical Pharmacology concluding that the submitted clinical pharmacology data was unacceptable (refer to Complete Response Letter issued on 7th October, 2016). The unacceptability of the pharmacokinetic (PK) data was due to deficiencies in the bioanalytical method used (b) (4) in human serum. At the End-of-Review meeting (15th December, 2016), the Applicant agreed to characterize the PK of Fiasp using total insulin aspart concentrations.

Novo Nordisk resubmitted NDA 208751 on 29th March, 2017, having addressed the deficiencies identified by the Office of Clinical Pharmacology.

The clinical pharmacology program consists of 8 Phase 1 studies (euglycemic clamp and meal challenge studies) and 2 Phase 3a therapeutic confirmatory studies (pharmacodynamic (PD) data to supplement the clinical pharmacology data). The majority of the studies are conducted in in patients with Type 1 diabetes mellitus (T1DM). A Phase 1 study and a Phase 3a study are conducted in healthy subjects and patients with Type 2 diabetes mellitus (T2DM), respectively.

In the original NDA submission, in three Phase 1 studies, the PK of Fiasp based on total insulin aspart concentrations was reported as exploratory analysis (not primary PK endpoints). In the resubmission, retrospective analysis using total insulin aspart concentrations has been performed to characterize the PK of Fiasp in these studies. In one study, clinical samples were reanalyzed to quantify total insulin aspart concentrations. Results from a new meal challenge study characterizing the PK of Fiasp based on total insulin aspart concentrations have also been submitted. In all other studies, PD results following subcutaneous (SC) administration of Fiasp has only been reported.

The Clinical Pharmacology review reports total insulin aspart concentrations/PK parameters as insulin aspart concentrations/PK parameters.

### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted in support of NDA 208751 for insulin aspart

(Fiasp) and found it acceptable to support approval. OCP has the following recommendations and comments:

| Review Issue | Recommendations and Comments |
|---|---|
| Pivotal or supportive evidence of effectiveness | The PK and PD (glucose infusion rate from euglycemic clamp studies) of Fiasp in patients with T1DM provided supportive evidence of effectiveness.<br><br>Pharmacodynamic response from meal-challenge PK/PD studies showed post-prandial glucose (PPG) excursion was comparable between pre-meal Fiasp and pre-meal NovoLog in patients with T1DM supporting the effectiveness of Fiasp per se, however, reflecting no distinction from NovoLog. These results were in line with the conclusion of non-inferiority for pre-meal Fiasp versus pre-meal NovoLog® in patients with T1DM and T2DM in the Phase 3a study (see Clinical and Statistical Review for further details) with numerical differences for HbA1c reduction in the T1DM (sensitive population) and no difference in HbA1c reduction in T2DM (less sensitive population) between Fiasp and NovoLog.<br><br>Pharmacodynamic response from meal-challenge PK/PD studies for post-meal Fiasp showed higher PPG excursions (i.e., a smaller glucose lowering effect with respect to time of meal) for post-meal Fiasp when compared to pre-meal NovoLog. These observations were in line with the conclusion of non-inferiority for post-meal Fiasp versus pre-meal NovoLog in patients with T1DM in the Phase 3a study (see Clinical and Statistical Review for further details), with numerically lower HbA1c reduction than pre-meal NovoLog. |
| General dosing instructions | Individualized the dosage of Fiasp based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goals.<br><br>As tested in the Phase 3 clinical trials, Fiasp is recommended to be administered (b) (4) a meal or 20 minutes after starting a meal subcutaneously into the abdomen, upper arm, or thigh. Since clinical pharmacology data indicates differences in PPG control between pre-meal and post-meal use of Fiasp, preferably patients should choose |

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|---|---|
| | one of the times of administration from these two options to minimize the variability in their day-to-day and dose-to-dose variability in glycemic control.<br><br>Dose adjustments may be needed when switching from another insulin product, with changes in physical activity, changes in concomitant medications, changes in meal patterns (i.e., macronutrient content or timing of food intake), and changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia. |
| Dosing in patient subgroups | No separate dose/dosing regimen is recommended in any patients subgroups due to intrinsic and extrinsic factors. However, due to the potential increased risk of hypoglycemia, patients with renal or hepatic impairment may require more frequent Fiasp dose adjustment and more frequent blood glucose monitoring. |
| Labeling | (b) (4) |

**1.2 Post-Market Requirements and Commitments**

None.

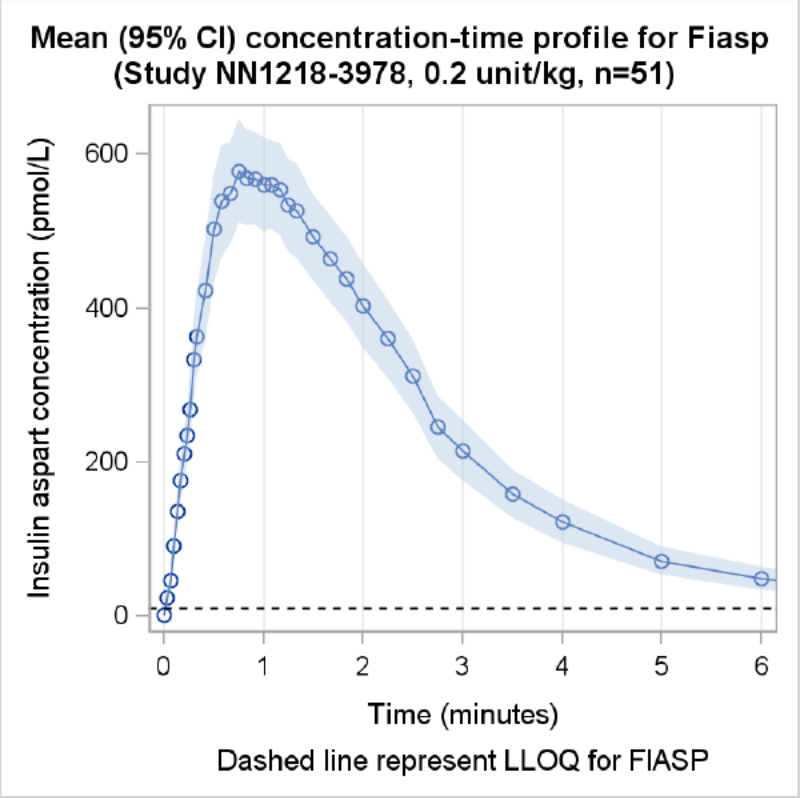
**2. Summary of Clinical Pharmacology Assessment**

**2.1 Pharmacology and Clinical Pharmacokinetics**

Fiasp is a meal time insulin aspart indicated to improve glycemic control in patients with diabetes mellitus (T1DM and T2DM).

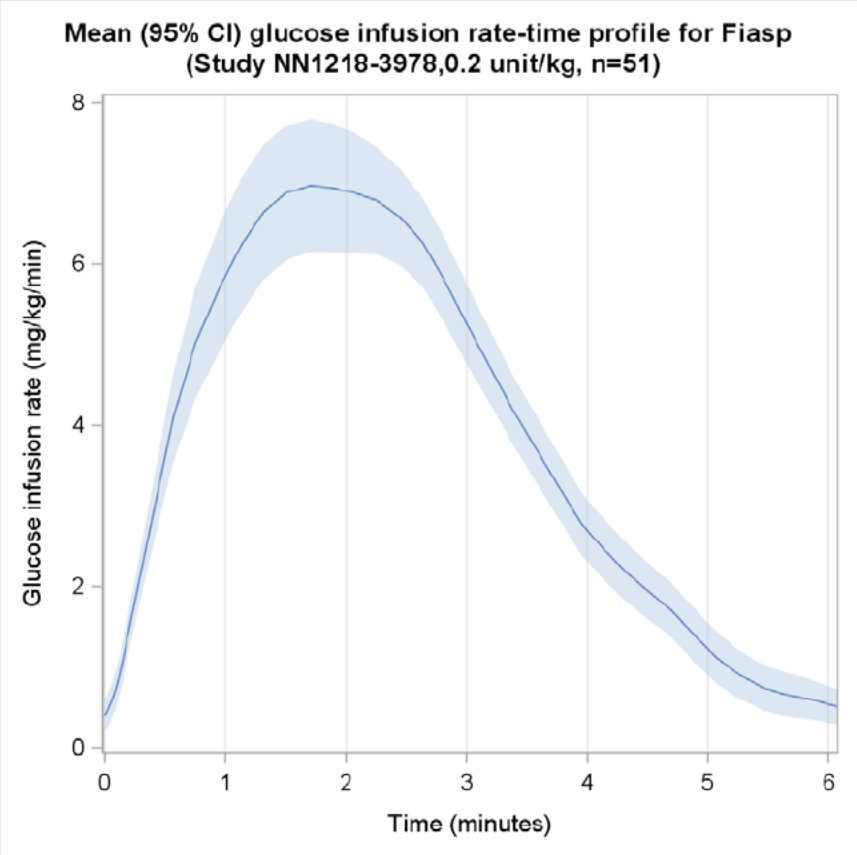
The following is a summary of the clinical pharmacology of Fiasp:

**Pharmacokinetics:**

| | |
|---|---|
| **Representative Mean PK** |  |
| **Absorption** | ▪ Following SC administration of 0.2 unit/kg single dose of Fiasp in patients with T1DM, the mean onset of appearance was ~2.5 minutes post-dose and mean time to maximum insulin aspart concentration was achieved ~63 minutes post-dose<br>▪ Following SC administration of single doses ranging from 0.06 to 0.28 unit/kg in patients with T1DM, a proportional increase in total insulin aspart exposure and maximum concentrations of insulin aspart was observed with an increase in Fiasp dose<br>▪ The absolute SC bioavailability of insulin aspart in healthy subjects following administration of a 0.2 unit/kg Fiasp dose in the abdomen, deltoid, and thigh was 85%, 76%, and 75%, respectively |
| **Distribution** | ▪ Following IV administration of 0.02 unit/kg Fiasp in healthy subjects, the geometric mean volume of distribution for insulin aspart was 0.15 L/kg<br>▪ Insulin aspart has a low binding affinity to plasma proteins (<10%), similar to that seen with regular human insulin |

| | |
|---|---|
| **Elimination** | ▪ Following SC administration of 0.2 unit/kg single dose of Fiasp in patients with T1DM, the geometric mean terminal half-life for Fiasp was 68.1 minutes (median: 65.5 minutes)<br>▪ Following IV administration of 0.02 unit/kg Fiasp in healthy subjects, the geometric mean clearance and elimination half-life was 0.90 (L/hr)/kg, and 7.2 minutes, respectively |

**Pharmacodynamics:**

| | |
|---|---|
| **Representative Mean PD** |  |
| **Pharmacodynamics of Fiasp** | ▪ In 3 euglycemic clamp studies, following SC administration of 0.2 unit/kg single dose of Fiasp in patients with T1DM, the geometric mean onset of action was 11 to 17 minutes (range) and time to maximum glucose lowering effect was 109 to 119 minutes (range). The geometric mean duration of action was 342 to 476 minutes (range) for Fiasp<br>▪ The total glucose lowering effect and maximum glucose lowering |

| | |
|---|---|
| | effect increased in slightly less than linear manner within increasing dose of Fiasp (0.1, 0.2, 0.4 unit/kg)<br>▪ Following SC administration of 0.2 unit/kg Fiasp, the within-subject variability for total glucose lowering effect and maximum glucose lowering effect was 18.3% and 19.3%, respectively |

**2.2 Outstanding Issues**

None.

**2.3 Summary of Labeling Recommendations**

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert:

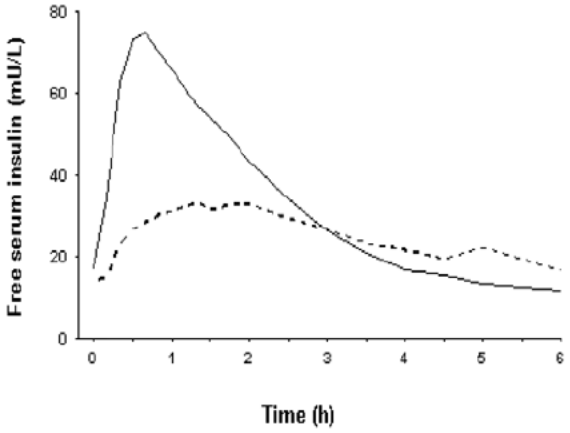
| Label Section | Recommendations |
|---|---|
| **Section 12.2 (Pharmacodynamics) and Section 12.3 (Pharmacokinetics)** | ▪ (b) (4) The PK and PD data of Fiasp is sufficient as the guiding principal for use of the product in the label. |
| **Section 12.2 (Pharmacodynamics)** | ▪ (b) (4) |
| **Section 12.3 Pharmacokinetics** | ▪ Include a representative PK and PD profile for Fiasp following SC administration at the 0.2 unit/kg dose<br>▪ Delete (b) (4)<br>▪ Include the following: "Age, Gender, BMI, Racial or Ethnic Groups: Age, gender, BMI, and racial or ethnic groups did not meaningfully affect the pharmacokinetics and pharmacodynamics of TRADENAME"<br>▪ Delete labelling language for renal and hepatic impairment. Replace with the following "*Patients with Renal and Hepatic Impairment*- Renal and hepatic impairment is not known to impact the pharmacokinetics of insulin aspart." |

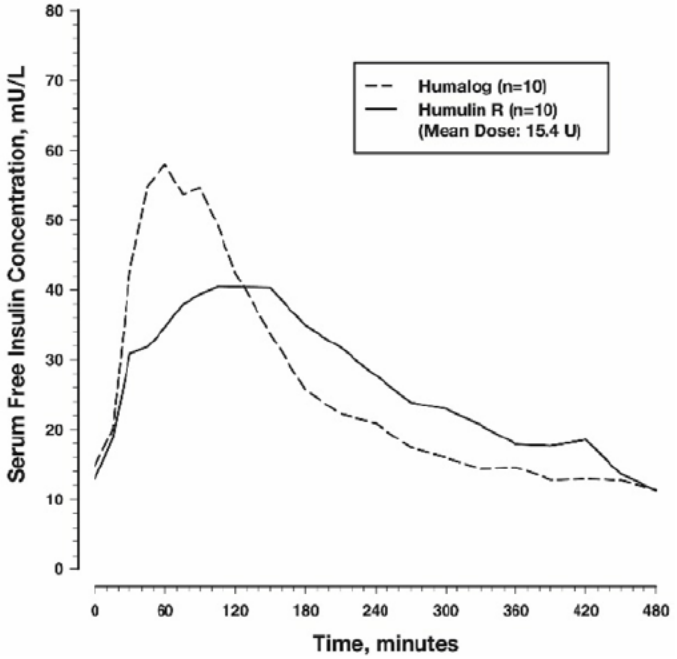
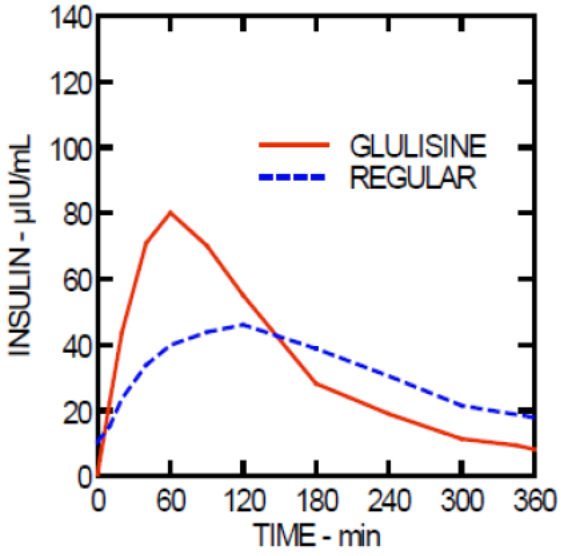
## 3. Comprehensive Clinical Pharmacology Review

### 3.1 Overview of the Product and Regulatory Background

***Meal Time Insulins***

Currently, the following insulin drug products are approved for meal time administration with their unique time of administration, as it relates to the PK/PD profile, and as specified in the Dosing and Administration section:

| Insulin Product | Recommended Use and PK Profile in the Current Label |
|---|---|
| Humulin® R (regular human insulin, NDA 018780) | To be administered subcutaneously approximately 30 minutes before meals |
| Novolin® R (regular human insulin, NDA 019938) | To be administered subcutaneously approximately 30 minutes prior to the start of a meal |
| NovoLog® (insulin aspart, NDA 020986) | To be administered subcutaneously within 5-10 minutes before a meal<br>  <br><br>**Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single 0.15 units/kg pre-meal dose of NOVOLOG (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.** |
| Humalog® (insulin lispro, NDA 020563) | To be administered subcutaneously within 15 minutes before a meal or immediately after a meal |

| | |
|---|---|
| |  <br>Figure 2: Serum HUMALOG and Insulin Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[9]. |
| Apidra®<br>(insulin glulisine, NDA 021629) | To be administered subcutaneously within 15 minutes before a meal or within 20 minutes after starting a meal<br>  <br>**Figure 2.** Pharmacokinetic profiles of insulin glulisine and regular human insulin in patients with type 1 diabetes after a dose of 0.15 Units/kg. |

***Developmental Rational for Fiasp and Clinical Program Pursed by the Applicant***

Fiasp is developed as a meal-time insulin with the claim of a 'greater early glucose lowering effect' compared to the currently approved NovoLog® (global trade name of NovoRapid® reflected in the Applicant's tables and figures; hereafter, comparator referred to as NovoLog in the review text). Compared to NovoLog, Fiasp formulation has 2 additional excipients, nicotinamide and L-arginine hydrochloride. The Applicant claims that the addition of nicotinamide results in a faster initial absorption of insulin aspart following SC injection, leading to a greater early glucose lowering effect when compared to NovoLog.

The claimed changes to the time-action profile of Fiasp is reflected in the proposed labelling language under Dosage and Administration Section, which states the Fiasp should be administered at the start of a meal or post-meal (within 20 minutes after starting a meal) in comparison to NovoLog, which is recommended to be administered subcutaneously within 5-10 minutes before a meal.

The clinical pharmacology development program consists of 8 Phase 1 studies (euglycemic clamp and meal challenge studies), with the majority of the studies conducted in patients with T1DM (Figure 1). Two Phase 3a therapeutic confirmatory studies (NN1218-3852, NN1218-3853) was conducted in patients with T1DM and T2DM, respectively, and provides PD results to supplement the clinical pharmacology data. The Applicant reports that all studies were conducted with the final Fiasp formulation intended for the market.

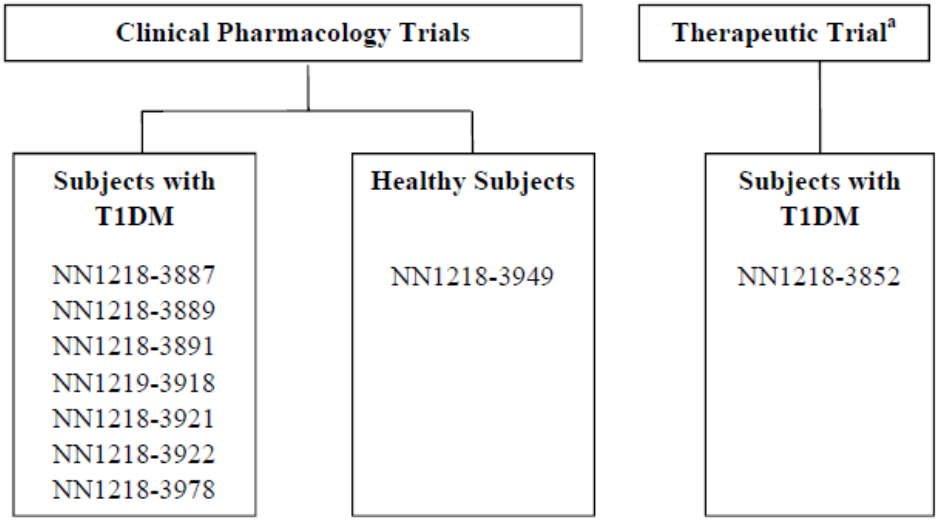



**Figure 1: Overview of studies contributing to the PK and PD evaulation of Fiasp**

(Source: Summary of clinical pharmacology studies, page14)

***Highlights of Fiasp Drug Product***

*Drug substance:* Insulin aspart is an analogue of human insulin where the amino acid proline has been replaced with aspartic acid in position B28. Insulin aspart is produced using recombinant

DNA technology in yeast (*Saccharomyces cerevisiae*). The structural formula of insulin aspart is shown in Figure 2.

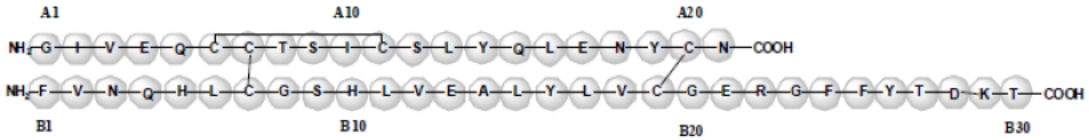



**Figure 2: Structural formula of insulin aspart**
(Source: Quality overall summary, Introduction, page 3)

*Drug product*: Fiasp drug product intended for market, insulin aspart 100 units/mL, is a clear, colorless solution. The solution is filled in a 10 mL vial or 3 mL cartridge (cartridge assembled into a pre-filled disposable pen-injector). The composition of Fiasp drug product is presented in Table 1.

**Table 1: Composition of Fiasp**

| Name of components | Quantity per ml | Function | Reference to standards |
|---|---|---|---|
| **Active substance** | | | |
| Insulin aspart | 600 nmol (100 U) | Drug substance | Novo Nordisk A/S |
| **Excipients** | | | |
| Phenol | 1.50 mg[a] | (b) (4) | Ph. Eur./USP/JP |
| Metacresol | 1.72 mg[a] | | Ph. Eur./USP |
| Glycerol | 3.3 mg | | Ph. Eur./USP/JP |
| Zinc (as zinc acetate) | 19.6 µg | | Ph. Eur./USP/JPE |
| Disodium phosphate dihydrate | 0.53 mg | | Ph. Eur./USP |
| Arginine (as L-arginine HCl) | 3.48 mg | Stabilising agent | Ph. Eur./USP/JP |
| Nicotinamide | 20. (b) (4) mg | Absorption modifier | Ph. Eur./USP/JP |
| Hydrochloric acid | q.s.[b] | pH adjusting agent | Ph. Eur./USP/JP |
| Sodium hydroxide | q.s.[b] | pH adjusting agent | Ph. Eur./USP/JP |
| Water for injections | (b) (4) | | Ph. Eur./USP/JP |
| (b) (4) | | | |

[b] To reach pH 7.1
(Source: Description and composition of the drug product, page 2)

### 3.2 Clinical Pharmacology Review Questions

#### 3.2.1 Does the pharmacokinetic/pharmacodynamic data support the Applicant's claim of "faster initial absorption of insulin leading to greater early glucose-lowering effect when compared to NovoLog"?

Pharmacokinetic data from euglycemic clamp studies and meal challenge study (pre-meal) support the Applicant's claim of faster initial absorption of insulin aspart following administration of Fiasp when compared to NovoLog in patients with T1DM. Overall the onset of

appearance was faster, time to 50% $C_{max}$ and $t_{max}$ occurred earlier, early insulin aspart exposure was greater for Fiasp when compared to NovoLog following SC administration.

Supporting the observed PK difference, the PD data from euglycemic clamp studies in patients with T1DM showed an earlier onset of action, time to 50% $GIR_{max}$ (glucose infusion rate) and $GIR_{max}$ occurred earlier, and a greater early glucose lowering effect was observed for Fiasp when compared to NovoLog. Thereby, the PD data from the euglycemic clamp studies support the Applicant's claim of greater early glucose lowering effect for Fiasp when compared to NovoLog. These findings along with the quantitative analysis submitted by the Applicant establish a link between the PK and PD data for Fiasp in patients with T1DM.

With regards to the clinical relevance of these PK/PD differences for Fiasp, postprandial glucose (PPG) excursion data from the Phase 1 meal challenge studies, which represent a more clinically relevant setting, showed that the PPG of pre-meal Fiasp was comparable to pre-meal NovoLog. Following post-meal dosing of Fiasp (20 min after start of intake of a standardized meal), PPG was on average higher than pre-meal NovoLog.

Overall, the PK data supports a faster initial absorption of insulin aspart following administration of Fiasp when compared to NovoLog. The faster initial absorption of insulin aspart leads to a greater early glucose-lowering effect for Fiasp compared to NovoLog in euglycemic clamp settings. However, under meal challenge settings, the magnitude of these PK and PD differences do not translate into a greater early glucose lowering effect for pre-meal and post-meal Fiasp when compared to pre-meal NovoLog and do not substantiate the Applicant's claims.

Pharmacokinetic and pharmacodynamic results from the Phase 1 studies are described below:

**Pharmacokinetics**

***Pharmacokinetics of Fiasp compared to NovoLog***

Pharmacokinetic properties of Fiasp were characterized in 2 euglycemic clamp studies (NN1218-3978, NN1218-3891) and in a meal challenge study (NN1218-3922). In Studies NN1218-3978, NN1218-3891, patients were administered a single dose of 0.2 unit/kg of Fiasp and NovoLog, and in Study NN1218-3922 the actual dose of Fiasp and NovoLog administered was in the range of 0.06 – 0.28 unit/kg (single dose, individualized dosing). Of the 3 studies, Study NN1218-3978 was the largest PK study, in terms of the number of patients and the number of PK sampling points. For Study NN1218-3891, only the PK of Fiasp and NovoLog in young adult patients with T1DM are reported below. Refer to Appendix 5.1 for description of the studies and Appendix 5.4 for information on the estimation of PK endpoints.

Pharmacokinetics of Fiasp and NovoLog is characterized based on insulin aspart concentrations (total insulin aspart concentrations) as discussed at the End-of-Review meeting (refer to Section 1). The reported PK of Fiasp and NovoLog are based on retrospective analysis. To enable comparison of PK endpoints between the 3 studies, the PK endpoints are consistent among the studies.

Mean insulin aspart serum concentration-time profiles for Fiasp and NovoLog stratified by study are presented in Figure 3. In all studies, a left shift in the PK profile of Fiasp compared to NovoLog was observed.

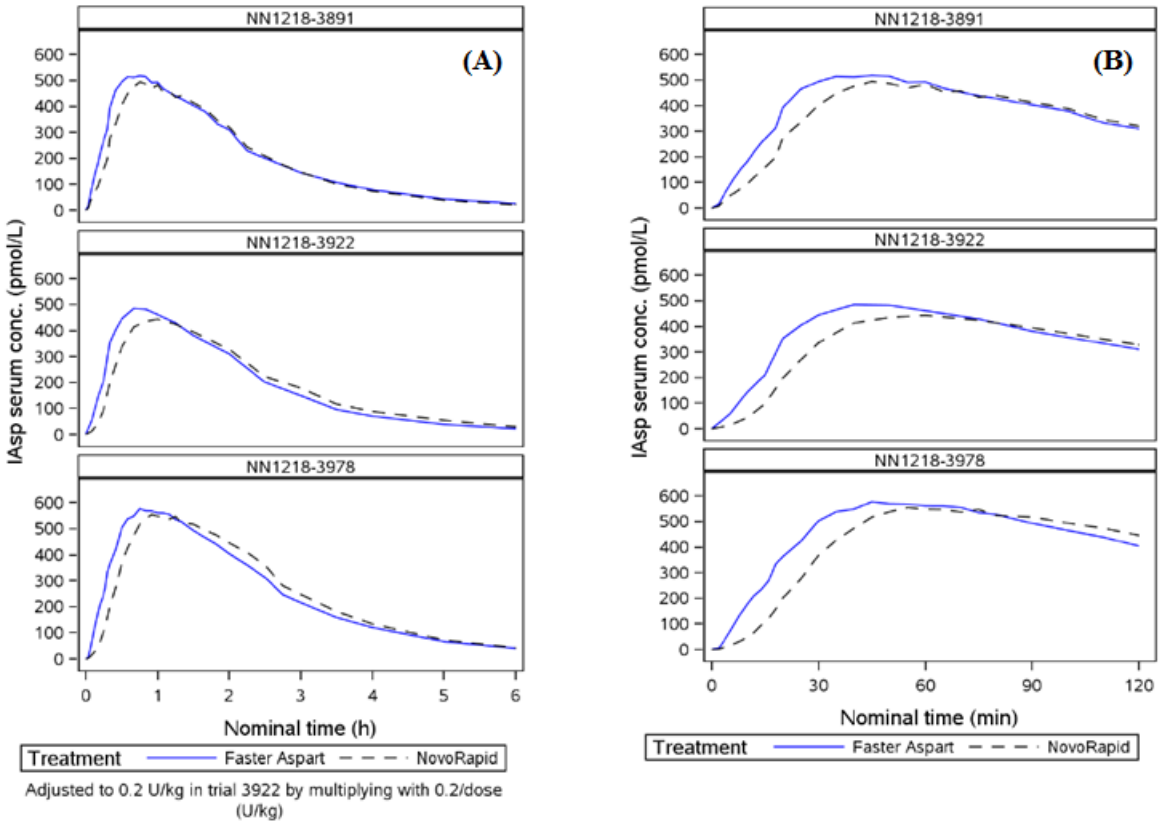



**Figure 3: Mean insulin aspart serum concentration-time profile for Fiasp (indicated as faster aspart in the Applicant's figures above) and NovoLog (indicated via global tradename of NovoRapid in the Applicant's figures above) following a 0.2 unit/kg dose, stratified by study (A) 0-6 hrs and (B) 0-2 hrs [In Studies NN1218-3978 and NN1218-3891 a 0.2 unit/kg dose was administered; in Study NN1218-3922 the administered actual dose ranged from 0.06-0.28 unit/kg (for this study, serum concentrations are adjusted to a dose of 0.2 unit/kg)]**

(Source: Summary of Clinical Pharmacology Studies, Appendix 5.2, page 9, 11)

Onset of insulin aspart exposure

Pharmacokinetics endpoints for assessment of 'onset of insulin aspart exposure' following administration of Fiasp and NovoLog are presented in Table 2 (refer to Appendix 5.2 for definition of PK endpoints).

A faster mean onset of appearance was observed for Fiasp when compared to NovoLog in all studies, with the mean onset of appearance for Fiasp (2.53 min) appearing to be twice as fast

compared to NovoLog (5.24 min) in Study NN1218-3978 (estimated mean treatment difference of -2.71 min [-3.26; -2.16]$_{95\%CI}$, statistically significant).

The mean time to 50% $C_{max}$ and mean time to $t_{max}$ was earlier for Fiasp compared to NovoLog in the 3 studies. For study NN1218-3978, the mean treatment difference for mean time to 50% $C_{max}$ and time to $t_{max}$ for Fiasp when compared to NovoLog was statistically significant (-9.41 min [-11.54; -7.29]$_{95\%CI}$ and -10.42 min [-18.52; -2.31]$_{95\%CI}$, respectively).

**Table 2: Onset of insulin aspart exposure following SC administration of single dose of Fiasp (indicated as faster aspart in the Applicant's table below) and NovoLog in adult patients with T1DM**

| Endpoint | Number of subjects | | Estimated mean (minutes) | | Treatment ratio [95% CI] | |
|---|---|---|---|---|---|---|
| | Faster aspart | NovoRapid® | Faster aspart | NovoRapid® | Faster aspart / NovoRapid® | |
| **Onset of appearance** | | | | | | |
| 3891[a] | 22 | 22 | 2.24 | 3.21 | 0.70 | [0.53;0.89] |
| 3922 | 40 | 40 | 3.98 | 7.52 | 0.53 | [0.41;0.66] |
| 3978 | 51 | 51 | 2.53 | 5.24 | 0.48 | [0.40;0.57] |
| **Pooled analysis** | **113** | **113** | **2.98** | **5.65** | **0.53** | **[0.45;0.60]** |
| **Time to 50%$C_{max,IAsp}$** | | | | | | |
| 3891[a] | 22 | 22 | 16.58 | 21.10 | 0.79 | [0.67;0.91] |
| 3922 | 40 | 40 | 17.04 | 24.79 | 0.69 | [0.61;0.77] |
| 3978 | 51 | 51 | 19.12 | 28.54 | 0.67 | [0.61;0.74] |
| **Pooled analysis** | **113** | **113** | **17.88** | **25.76** | **0.69** | **[0.65;0.74]** |
| **$t_{max,IAsp}$** | | | | | | |
| 3891[a] | 22 | 22 | 50.36 | 55.10 | 0.91 | [0.70;1.18] |
| 3922 | 40 | 40 | 49.90 | 64.25 | 0.78 | [0.68;0.88] |
| 3978 | 51 | 51 | 63.04 | 73.46 | 0.86 | [0.76;0.97] |
| **Pooled analysis** | **113** | **113** | **56.08** | **66.58** | **0.84** | **[0.77;0.92]** |

[a]Only younger adult subjects (18−35 years) were included.

**Number of subjects:** For the pooled analysis, the number of subjects should be read as the number of profiles contributing to the analysis. **Note:** NovoRapid® is known as NovoLog® in the U.S.

(Source: Summary of Clinical Pharmacology Studies, page 51)

Early insulin aspart exposure

Early insulin aspart exposure (up to 2 hr post-dose) for Fiasp compared to NovoLog following administration of a single SC dose of 0.2 unit/kg (for Study NN1218-3922 the exposure has been adjusted to a 0.2 unit/kg dose) is presented in Figure 4.

For Study NN1218-3978, insulin aspart exposure up to 90 min post-dose was statistically significantly larger for Fiasp compared to NovoLog. For Studies NN1218-3891 and NN1218-3922, the early insulin aspart exposure (up to 90 min post-dose) was also larger for Fiasp when compared to NovoLog. In all studies, the largest difference in insulin aspart exposure for Fiasp compared to NovoLog was observed in the initial 15 mins post-dose, with the estimated mean treatment ratio ranging from 1.93 to 3.55.

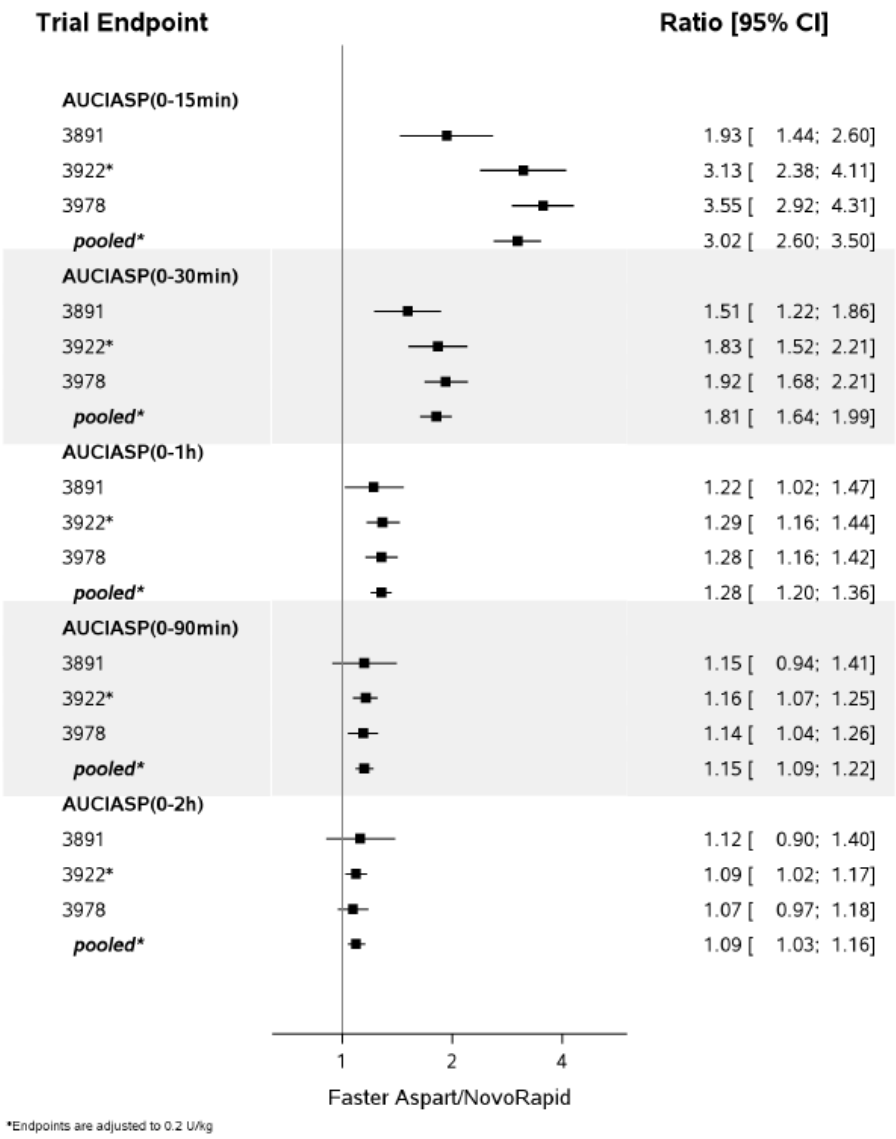



**Figure 4: Mean treatment ratios (95%CI) for early insulin aspart exposure (up to 2 hrs post-dose) for Fiasp (indicated as faster aspart in the Applicant's figures above) and NovoLog in adult patients with T1DM (for Study NN1218-3922, the endpoints have been adjusted to 0.2 unit/kg)**

(Source: Summary of Clinical Pharmacology Studies, page 54)

Duration of insulin aspart exposure and late insulin aspart exposure

Duration of insulin aspart exposure (time to late 50% $C_{max}$) and late insulin aspart exposure ($AUC_{2hr-t}$) following administration of Fiasp and NovoLog are presented in Table 3 (refer to Appendix 5.2 for description of PK endpoints).

In Study NN1218-3978, the mean estimated time to late 50% $C_{max}$ was 12.6 min shorter for Fiasp when compared to NovoLog (treatment difference of -12.65 min $[-26.41; 1.12]_{95\%CI}$), reflecting

the left shift observed in the early part of the profile. Late insulin aspart exposure was 14% lower for Fiasp compared to NovoLog (treatment ratio of 0.86 [0.70; 1.06]$_{95\%CI}$). The geometric mean terminal half-life for insulin aspart was 68.1 min (median: 65.5 min) and 67.8 min (median: 64.4 min) following SC administration of Fiasp and NovoLog, respectively.

For Study NN1218-3922, the mean estimated time to late 50% $C_{max}$ was shorter (22.9 min) for Fiasp when compared to NovoLog; a larger treatment difference was observed in this study compared to Study NN1218-3978. Late insulin aspart exposure was 17% lower for Fiasp when compared to NovoLog. For Study NN1218-3891, a profound treatment difference was not evident for both PK endpoints when compared to the other 2 studies; this may be attributed to the smaller sample size in this study.

**Table 3: Duration of exposure and late exposure for insulin aspart following administration of single SC dose of Fiasp (indicated as faster aspart in the Applicant's table below) and NovoLog in adult patients with T1DM (for Study NN1218-3922, exposure has been adjusted to 0.2 unit/kg)**

| Endpoint | Number of subjects | | Estimated mean | | Treatment difference [95% CI] |
|---|---|---|---|---|---|
| | Faster aspart | NovoRapid® | Faster aspart | NovoRapid® | Faster aspart-NovoRapid® |
| **Time to late 50%$C_{max,IAsp}$** (minutes) | | | | | |
| 3891[a] | 21 | 21 | 131.86 | 134.90 | -3.04 [-16.27; 10.19] |
| 3922 | 40 | 40 | 135.93 | 158.89 | -22.96 [-39.03; -6.88] |
| 3978 | 51 | 51 | 155.84 | 168.49 | -12.65 [-26.41; 1.12] |
| **Pooled analysis** | **112** | **112** | **144.23** | **158.75** | **-14.52 [-22.66; -6.37]** |
| | **Number of subjects** | | **Estimated mean** | | **Treatment ratio [95% CI]** |
| | Faster aspart | NovoRapid® | Faster aspart | NovoRapid® | Faster aspart/NovoRapid® |
| **$AUC_{IAsp,\ 2h\text{-}t}$** (pmol h/L) | | | | | |
| 3891[a] | 21 | 21 | 416.40 | 421.55 | 0.99 [0.82;1.19] |
| 3922[b] | 40 | 40 | 326.10 | 391.37 | 0.83 [0.75;0.92] |
| 3978 | 51 | 51 | 578.67 | 673.12 | 0.86 [0.70;1.06] |
| **Pooled analysis**[b] | **112** | **112** | **442.45** | **505.56** | **0.88 [0.82;0.93]** |

t: time of last assessment. [a]Only younger adult subjects (18−35 years) were included. [b]Adjusted to 0.2 U/kg

(Source: Summary of Clinical Pharmacology Studies, page 58)

Total insulin aspart exposure and maximum concentration of insulin aspart

In all 3 studies, the total exposure of insulin aspart ($AUC_{0\text{-}tlast}$) and $C_{max}$ was comparable for Fiasp and NovoLog (total exposure: Study NN1218-3978, NN1218-3891, NN1218-3922 (adjusted to dose of 0.2 unit/kg) mean treatment ratio of 0.98 [0.89; 1.09]$_{95\%CI}$, 1.13 [0.88; 1.43]$_{95\%CI}$, 0.99 [0.95; 1.03]$_{95\%CI}$, respectively; $C_{max}$: Study NN1218-3978, NN1218-3891, NN1218-3922 (adjusted to dose of 0.2 unit/kg) mean treatment ratio of 1.02 [0.93; 1.11]$_{95\%CI}$, 1.06 [0.90; 1.25]$_{95\%CI}$, 1.05 [0.97; 1.14]$_{95\%CI}$, respectively). The results indicate that for Fiasp the total exposure and maximum concentrations of insulin aspart are comparable to NovoLog despite

evidence of an earlier onset of exposure and larger initial exposure (0-90 min) when compared to NovoLog.

Overall the PK data from the 3 Phase 1 studies show a faster onset of insulin aspart exposure, a larger early insulin aspart exposure, a shorter duration of insulin aspart exposure (reflecting the left shift in the early part of the profile) following SC administration of Fiasp when compared to NovoLog. Total insulin aspart exposure and maximum concentrations were comparable for both treatments.

**Pharmacodynamics**

***Pharmacodynamics of Fiasp compared to NovoLog in Euglycemic Clamp Studies***

Pharmacodynamic properties of Fiasp were characterized in 3 euglycemic clamp studies. Overall the results from the euglycemic clamp studies show a greater early glucose lowering effect following single dose administration of Fiasp when compared to NovoLog in patients with T1DM. Despite these differences, the total and maximum glucose lowering effects are comparable for Fiasp and NovoLog.

Study NN1218-3978

Mean GIR profiles following administration of Fiasp (blue solid line) and NovoLog in patients with T1DM are presented in Figure 5. Of note, results for the exploratory formulation (FIA(R)) have not been reported in the Clinical Pharmacology review. A left shift in the mean GIR profile for Fiasp was observed when compared to NovoLog. Refer to Appendix 5.5 for blood glucose profiles following administration of Fiasp and NovoLog.

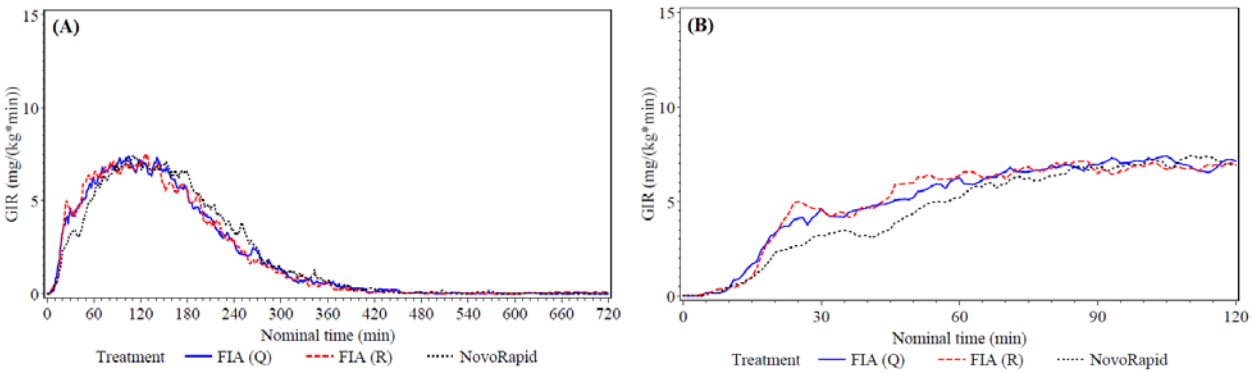



**Figure 5: Mean GIR profile (A) 0-12 hrs and (B) 0-2 hrs after a single SC dose (0.2 unit/kg) of Fiasp (FIA(Q)) and NovoLog in patients with T1DM in a euglycemic clamp setting (note FIA(R) (dash red line) is an exploratory formulation)**

(Source: NN1218-3978, Clinical study report, page 104-105)

The primary objective of the study was to compare the early PD response, defined by area under the GIR profile from 0-2 hrs ($AUC_{GIR,0-2hr}$), for Fiasp and NovoLog. The estimated treatment

ratio (Fiasp/NovoLog) for $AUC_{GIR,0\text{-}2hr}$ was 1.10 [1.00; 1.22]$_{95\%CI}$ (p=0.058), which suggests an approximately 10% greater early glucose lowering effect of Fiasp when compared to NovoLog.

The greater early glucose lowering effect for Fiasp compared to NovoLog was further supported by the following PD endpoints: $AUC_{GIR,0\text{-}30min}$ (Fieller treatment ratio: 1.48 [1.13; 2.02]$_{95\%CI}$), $AUC_{GIR,0\text{-}1hr}$ (treatment ratio: 1.31 [1.18; 1.46]$_{95\%CI}$, p<0.001), $AUC_{GIR,0\text{-}1.5hr}$ (treatment ratio: 1.17 [1.05; 1.30]$_{95\%CI}$, p=0.004)). The largest difference in early glucose lowering effect between the 2 treatments was observed in the first 30 mins, with an approximately 48% greater early glucose lowering effect for Fiasp compared to NovoLog.

No statistically significant difference for Fiasp and NovoLog was observed for onset of action (treatment difference of -2.58 min [-5.79; 0.63]$_{95\%CI}$, p=0.114), total glucose lowering effect ($AUC_{GIR,0\text{-}12hr}$, treatment ratio of 0.98 [0.87; 1.11]$_{95\%CI,}$ p=0.729), maximum GIR (treatment ratio of 1.02 [0.93; 1.12]$_{95\%CI}$, p=0.712), time to $GIR_{max}$ (treatment difference of -10.85 min [-23.09; 1.39]$_{95\%CI}$, p=0.082), and duration of action (treatment difference of -10.32 min [-40.85; 20.21]$_{95\%CI}$, p=0.504) (refer to Appendix 5.2 for definition of onset of action and duration of action).

For Fiasp, the mean onset of action was 13 min (SD 8) (geometric mean (CV%) 11 min (56)), mean time to $GIR_{max}$ was 125 min (SD 39) (geometric mean (CV%) 118 min (31)), and mean duration of action was 488 min (SD 114) (geometric mean (CV%) 476 min (23)). For NovoLog, the mean onset of action was 16 min (SD 10) (geometric mean (CV%) 12 min (63), mean time to $GIR_{max}$ was 135 min (SD 43) (geometric mean (CV%) 129 min (32)), and mean duration of action was 498 min (SD 123) (geometric mean (CV%) 484 min (25)).

However, the reviewer noted that for Fiasp and NovoLog, the blood glucose levels deviated from target clamp concentration after around 240-300 min post-dose (refer to Appendix 5.5) and are more reflective of the duration of action.

Study NN1218-3891

Mean GIR profiles following administration of Fiasp and NovoLog in young adult patients with T1DM are presented in Figure 6. The PD of Fiasp and NovoLog in young adult patients with T1DM are only reported below. A left shift in the mean GIR profile for Fiasp when compared to NovoLog was observed. Refer to Appendix 5.5 for blood glucose profiles following administration of Fiasp and NovoLog.

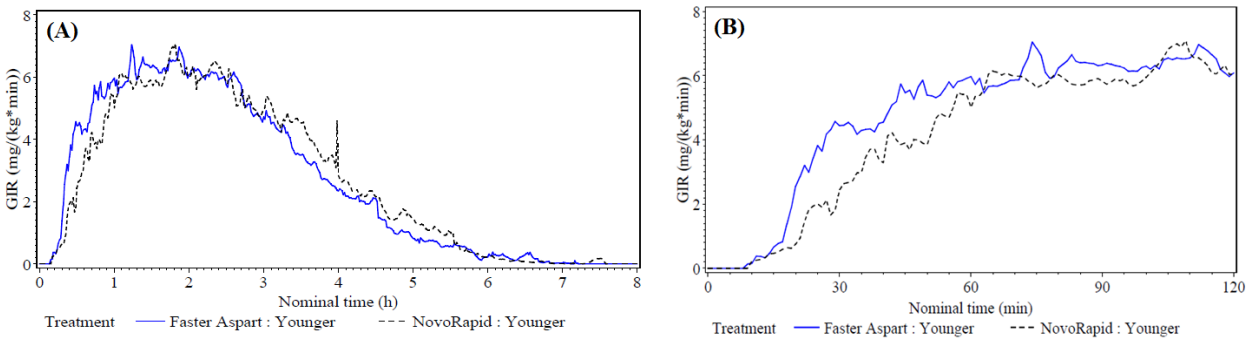



**Figure 6: Mean GIR profile (A) 0-8 hrs and (B) 0-2 hrs after a single SC dose (0.2 unit/kg) of Fiasp (indicated as faster aspart in the Applicant's figures above) and NovoLog in young adult patients with T1DM in a euglycemic clamp setting**

(Source: NN1218-3891, Clinical study report, page 101-102)

The onset of glucose lowering effect was characterized by the onset of action and time to 50% $GIR_{max}$ (refer to Appendix 5.2 for definition of onset of action). The estimated onset of action for glucose lowering effect was 33% earlier for Fiasp compared to NovoLog (Fieller age group/treatment ratio of 0.67 [0.49; 0.89]$_{95\%CI}$), with the treatment difference of 8.7 min being statistically significant. The estimated time to 50% $GIR_{max}$ was 25% shorter for Fiasp compared to NovoLog (Fieller age group/treatment ratio of 0.75 [0.65; 0.86]$_{95\%CI}$), with the treatment difference of -10.3 min being statistically significant.

The early glucose lowering effect was larger for Fiasp compared to NovoLog during the first 2 hr post-dose ($AUC_{GIR,0\text{-}30min}$ (Fieller age group/treatment ratio of 2.09 [1.31; 4.30]$_{95\%CI}$), $AUC_{GIR,0\text{-}1hr}$ (age group/treatment ratio of 1.55 [1.16; 2.07]$_{95\%CI}$), $AUC_{GIR,0\text{-}90min}$ (age group/treatment ratio of 1.26 [1.01; 1.57]$_{95\%CI,}$ $AUC_{GIR,0\text{-}2hr}$ (age group/treatment ratio of 1.19 [0.97; 1.46]$_{95\%CI}$ (not statistically significant)).

Comparable total glucose lowering effect ($AUC_{GIR,0\text{-}12hr}$, age group/treatment ratio of 1.03 [0.90; 1.17]$_{95\%CI}$) and maximum GIR (age group/treatment ratio of 1.04 [0.88; 1.22]$_{95\%CI}$) was observed for Fiasp and NovoLog in young adult patients with T1DM.

For Fiasp, the mean onset of action was 18 min (SD 6) (geometric mean 17 min), mean time to $GIR_{max}$ was 114 min (SD 36) (geometric mean 109 min), mean time to 50% $GIR_{max}$ was 31 min (SD 9) (geometric mean 30 min),and mean duration of action was 347 min (SD 59) (geometric mean 342 min).

For NovoLog, the mean onset of action was 26 min (SD 12) (geometric mean 24 min), mean time to $GIR_{max}$ was 125 min (SD 49) (geometric mean 116 min), mean time to 50% $GIR_{max}$ was 41 min (SD 11) (geometric mean (CV%) 40 min), and mean duration of action was 346 min (SD 48) (geometric mean 343 min).

However, the reviewer noted that for Fiasp and NovoLog, the blood glucose levels deviated from the target concentration after 240-300 min post-dose (refer to Appendix 5.5) and are more reflective of the duration of action.

Study NN1218-3887

Mean GIR profiles following administration of single doses of 0.1, 0.2, and 0.4 unit/kg of Fiasp and NovoLog in patients with T1DM are presented in Figure 7. For all 3 doses, a left shift in the mean GIR profile for Fiasp when compared to NovoLog was observed. Refer to Appendix 5.5 for blood glucose profiles following administration of Fiasp and NovoLog.

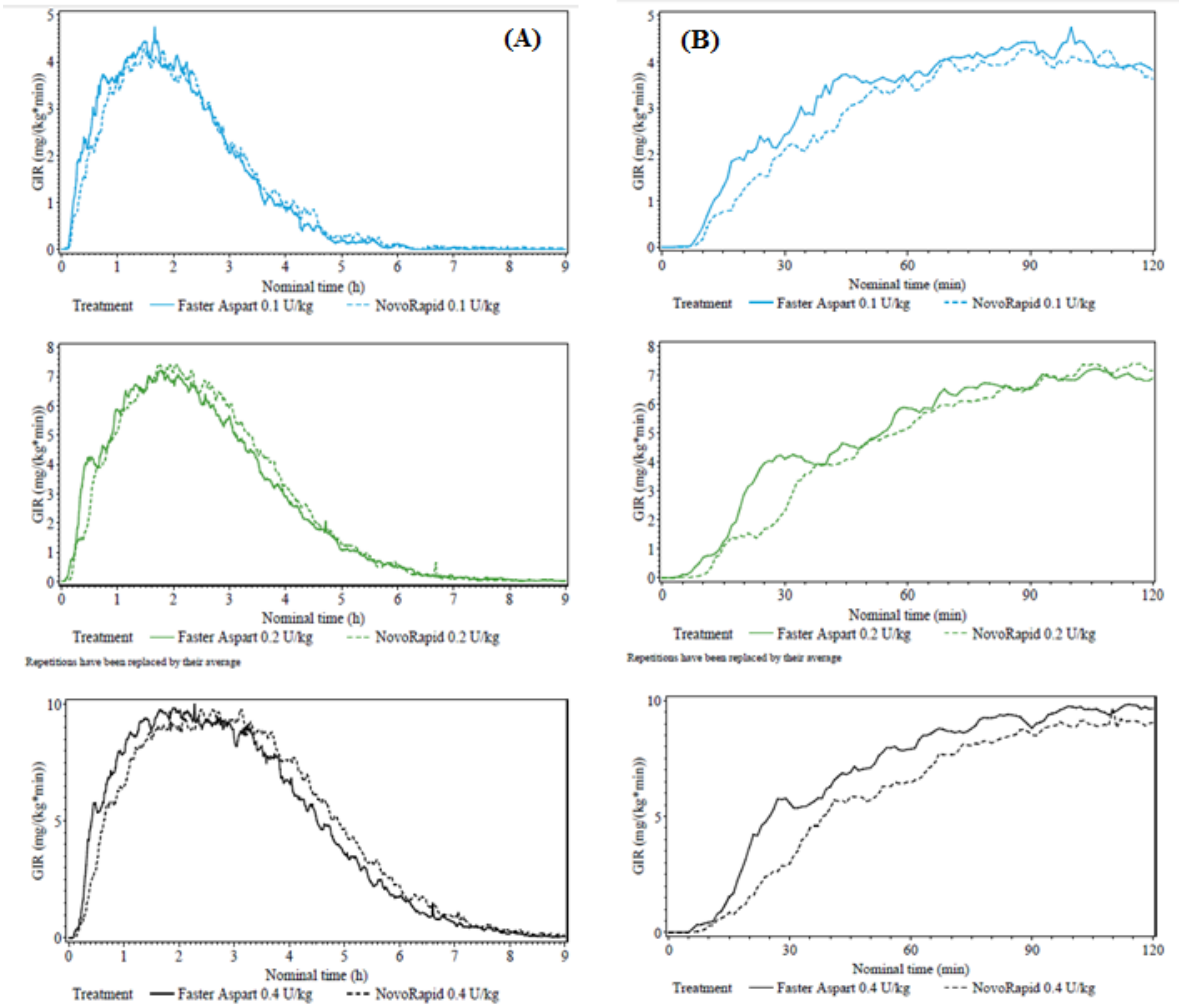



**Figure 7: Mean GIR profile (A) 0-9 hrs and (B) 0-2 hrs after single SC doses (0.1, 0.2, 0.4 unit/kg) of Fiasp (indicated as faster aspart in the Applicant's figures above) and NovoLog in patients with T1DM in a euglycemic clamp setting**

(Source: Study NN1218-3887, Clinical study report, page 104-105)

The onset of glucose lowering effect was characterized by the onset of action, time to 50% $GIR_{max}$, and time to $GIR_{max}$ (refer to Appendix 5.2 for definition of onset of action). For all 3

doses, the estimated onset of action for glucose lowering effect was 20-26% earlier for Fiasp when compared to NovoLog and the treatment differences ranging from 5.02 to 5.83 min was statistically significant. The estimated time to 50% $GIR_{max}$ for all doses was 22-25% earlier for Fiasp compared to NovoLog and the treatment differences ranging from 8.75 to 11.83 min was statistically significant. For all 3 doses, the estimated time to $GIR_{max}$ was 8-22% shorter for Fiasp when compared to NovoLog and the treatment differences ranging from 10.02 to 29.73 min was statistically significant.

For all doses, the early glucose lowering effect was larger for Fiasp when compared to NovoLog (up to 2 hr post-dose) (Table 4). At the 0.1 unit/kg dose level, the difference in exposure at the 0-30 min and 0-2 hr period was not statistically significant. In a sensitivity analysis, in which a number of GIR profiles were excluded, similar results to that observed in the original analysis was observed, except at the 0.1 unit/kg dose level where a statistically significant larger $AUC_{GIR,0\text{-}30min}$ was observed for Fiasp when compared to NovoLog.

**Table 4: Statistical analysis for $AUC_{GIR}$ (30 min, 1 hr, 90 min, 2 hr) for Fiasp (indicated as faster aspart in the Applicant's table below) and NovoLog in adult patients with T1DM**

| | N | Estimate | 95% CI | P-value |
|---|---|---|---|---|
| **$AUC_{GIR}$(0-30min) (mg/kg)** | | | | |
| Treatment ratio | | | | |
| 0.1 U/kg : Faster Aspart/NovoRapid | | 1.48 | [1.00;2.41] | |
| 0.2 U/kg : Faster Aspart/NovoRapid | | 1.92 | [1.51;2.58] | |
| 0.4 U/kg : Faster Aspart/NovoRapid | | 2.13 | [1.60;3.06] | |
| **$AUC_{GIR}$(0-1h) (mg/kg)** | | | | |
| Treatment ratio | | | | |
| 0.1 U/kg : Faster Aspart/NovoRapid | | 1.25 | [1.06;1.49] | |
| 0.2 U/kg : Faster Aspart/NovoRapid | | 1.28 | [1.17;1.41] | |
| 0.4 U/kg : Faster Aspart/NovoRapid | | 1.39 | [1.24;1.57] | |
| **$AUC_{GIR}$(0-90min) (mg/kg)** | | | | |
| Treatment ratio | | | | |
| 0.1 U/kg : Faster Aspart/NovoRapid | | 1.13 | [1.02;1.26] | 0.023 |
| 0.2 U/kg : Faster Aspart/NovoRapid | | 1.17 | [1.08;1.27] | <0.001 |
| 0.4 U/kg : Faster Aspart/NovoRapid | | 1.26 | [1.13;1.40] | <0.001 |
| **$AUC_{GIR}$(0-2h) (mg/kg)** | | | | |
| Treatment ratio | | | | |
| 0.1 U/kg : Faster Aspart/NovoRapid | | 1.10 | [0.99;1.22] | 0.073 |
| 0.2 U/kg : Faster Aspart/NovoRapid | | 1.11 | [1.03;1.20] | 0.009 |
| 0.4 U/kg : Faster Aspart/NovoRapid | | 1.18 | [1.07;1.31] | 0.002 |

N: Number of profiles contributing to analysis, CI: Confidence interval
The endpoints for $AUC_{GIR}$(0-30min) and $AUC_{GIR}$(0-1h) were analysed using a linear mixed model with period, treatment, dose and dose by treatment interaction as fixed effects and subject and the interaction between subject and dose as random effects. The between- and within-subject variances depend on dose. Ratios and the corresponding CIs were estimated using Fieller's method and p-values are therefore not calculated. Treatment differences with corresponding CIs and p-values are shown in EOT Table 14.2.49.
The endpoints for $AUC_{GIR}$(0-90min) and $AUC_{GIR}$(0-2h) were log-transformed and analysed using a linear mixed model with period, treatment, dose and dose by treatment interaction as fixed effects and subject as a random effect.

(Source: NN1218-3887, Clinical study report, page 110)

The total glucose lowering effect (tests for equal functional form of the dose-response relationship indicates that $AUC_{GIR,0-12hr}$ was similar for both treatments across all 3 dose levels (Refer to Section 3.2.5)) and maximum GIR (estimated treatment ratio ranging from 0.98 to 1.00) at all dose levels were similar for Fiasp and NovoLog in patients with T1DM.

At the 0.2 and 0.4 unit/kg dose levels, the duration of action was approximately 11-12 min shorter and at the 0.1 unit/kg dose level the duration of action was approximately 25 min shorter for Fiasp when compared to NovoLog. In a sensitivity analysis (post-hoc), which excluded GIR profile for 2 patients at the 0.1 unit/kg dose level, the duration of action for all doses was 10-12 min shorter following administration of Fiasp compared to NovoLog (refer to Appendix 5.2 for definition of duration of action).

For Fiasp, the mean onset of action was 20 min (SD 12) (geometric mean 16 min), 17 min (SD 8) (geometric mean 15 min), and 16 min (SD 6) (geometric mean 15 min) at the 0.1 unit/kg, 0.2 unit/kg, and 0.4 unit/kg dose, respectively. Mean time to $GIR_{max}$ was 91 min (SD 29) (geometric mean 87 min), 124 min (SD 37) (geometric mean 119 min), and 133 min (SD 36) (geometric mean 129 min) at the 0.1 unit/kg, 0.2 unit/kg, and 0.4 unit/kg dose, respectively. Mean time to $50\%GIR_{max}$ was 30 min (SD 10) (geometric mean 28 min), 37 min (SD 14) (geometric mean 34 min), and 35 min (SD 10) (geometric mean 34 min), at the 0.1 unit/kg, 0.2 unit/kg, and 0.4 unit/kg dose, respectively. Mean duration of action was 284 min (SD 64) (geometric mean 278 min), 364 min (SD 81) (geometric mean 355 min), and 432 min (SD 84) (geometric mean 424 min) at the 0.1 unit/kg, 0.2 unit/kg, and 0.4 unit/kg dose, respectively.

For NovoRapid, the mean onset of action was 25 min (SD 12) (geometric mean 22 min), 23 min (SD 10) (geometric mean 20 min), 22 min (SD 9) (geometric mean 19 min) at the 0.1 unit/kg, 0.2 unit/kg, and 0.4 unit/kg dose, respectively. Mean time to $GIR_{max}$ was 117 min (SD 76) (geometric mean 106 min), 130 min (SD 34) (geometric mean 126 min), and 163 min (SD 43) (geometric mean 157 min) at the 0.1 unit/kg, 0.2 unit/kg, and 0.4 unit/kg dose, respectively. Mean time to $50\%GIR_{max}$ was 38 min (SD 11) (geometric mean 37 min), 46 min (SD 16) (geometric mean 44 min), and 47 min (SD 13) (geometric mean 46 min) at the 0.1 unit/kg, 0.2 unit/kg, and 0.4 unit/kg dose, respectively. Mean duration of action was 309 min (SD 93) (geometric mean 299 min), 362 min (SD 73) (geometric mean 355 min), and 444 min (SD 81) (geometric mean 436 min) at the 0.1 unit/kg, 0.2 unit/kg, and 0.4 unit/kg dose, respectively.

The Reviewer notes that for Fiasp and NovoLog, the blood glucose levels deviated from the target concentration after 240-300 mins post-dose (refer to Appendix 5.5) and are more reflective of the duration of action.

Pharmacodynamic within-subject variability for $AUC_{GIR,0-12hr}$ and $GIR_{max}$ was assessed following administration of three single doses of either Fiasp or NovoLog at the 0.2 unit/kg dose level. The estimated within-subject variability (CV%) for $AUC_{GIR,0-12hr}$ was 18.3% and 18.4% for Fiasp and NovoLog, respectively. For $GIR_{max}$, the estimated within-subject variability (CV%)

was 19.3% and 21.0% for Fiasp and NovoLog, respectively. The results suggest low and overall comparable variability for the 2 treatments.

***Pharmacodynamics of Fiasp compared to NovoLog in Meal Challenge Studies***

Pharmacodynamic properties of Fiasp in relation to a meal were characterized in 3 Phase 1 meal challenge studies. Overall results are as follows:

- In the Phase 1 meal challenge studies, when Fiasp and NovoLog are administered immediately prior to a standardized meal, the early glucose lowering effect was not statistically significant different between the 2 treatments
- In the Phase 1 meal challenge study, when Fiasp was administered 20 min after start of a standardized meal when compared to NovoLog administered immediately prior to a standardized meal, a smaller glucose lowering effect was evident for Fiasp when compared to NovoLog.

Phase 1 Meal Challenge Studies

*Meal time dosing*

For Study NN1218-3889, the mean baseline adjusted plasma glucose profiles for Fiasp and NovoLog when administered immediately before a standardized meal in patients with T1DM is presented in Figure 8 (refer to Appendix 5.1 for description of study). The mean baseline adjusted plasma glucose profiles was comparable for Fiasp and NovoLog when administered immediately before a standardized meal.

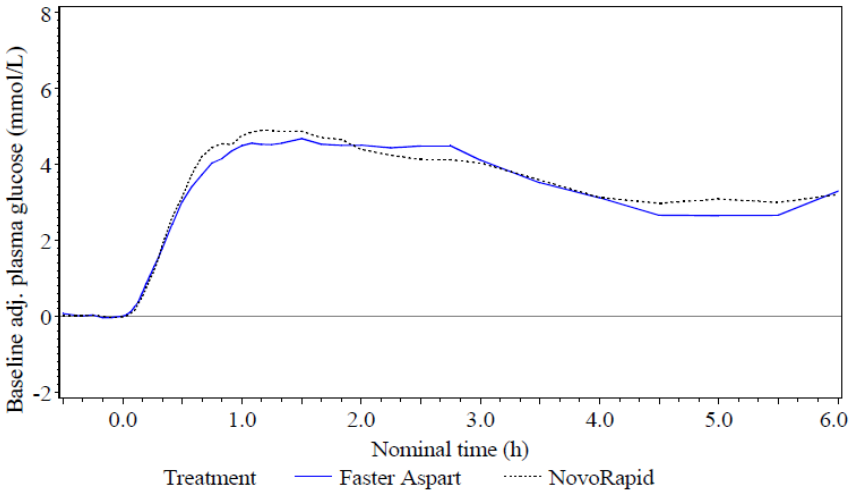



**Figure 8: Mean baseline adjusted plasma glucose profiles for Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog after a single SC dose (0.2 unit/kg) administered immediately before a standardized meal in patients with T1DM**

(Source: Study NN1218-3889, Clinical study report, page 75)

No statistically significant difference was observed for Fiasp and NovoLog for the primary endpoint of the study, the mean change in plasma glucose concentrations from 0 to 2 hr after dose administration ($\Delta PG_{av,0\text{-}2hr}$) (estimated treatment difference of -0.19 mmol/L [-0.77; 0.39]$_{95\%CI}$, p=0.508; estimated Fieller treatment ratio of 0.95 [0.81; 1.11]$_{95\%CI}$). Supporting the primary endpoint, no statistically significant differences between the 2 treatments was evident for the following PD endpoints: $\Delta PG_{av,0\text{-}1hr}$, $\Delta PG_{av,0\text{-}6hr}$ (total glucose lowering effect), $\Delta PG_{max}$, and $PG_{min}$.

For Study NN1218-3922, the mean baseline adjusted plasma glucose profiles for Fiasp and NovoLog when administered immediately before a standardized mixed meal in patients with T1DM is presented in Figure 9 (that meal duration was changed from 6 hr to 4 hr for all PD endpoints (change to the planned statistical analysis); refer to Appendix 5.1 for description of study). The mean baseline adjusted plasma glucose profile was lower for up to ~2.5 hr post-dose for Fiasp when compared to NovoLog when administered immediately before a standardized mixed meal.

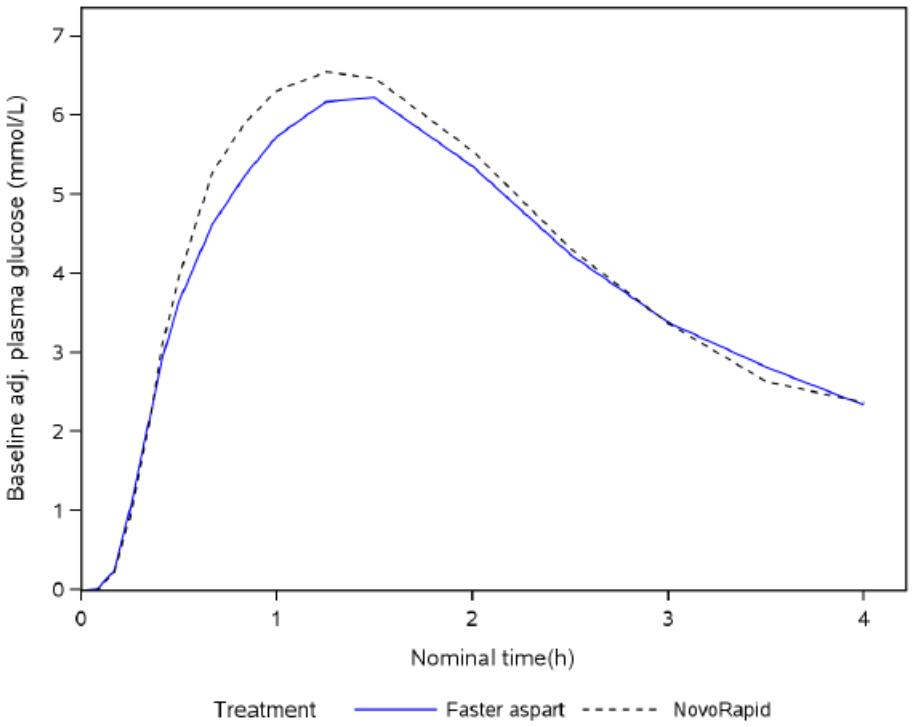



**Figure 9: Mean baseline adjusted plasma glucose profiles for Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog (0-4 hr) after individualized single SC dose (0.06-0.28 unit/kg) administered immediately before a standardized mixed meal in patients with T1DM**

(Source: Study NN1218-3922, Clinical study report, page 140)

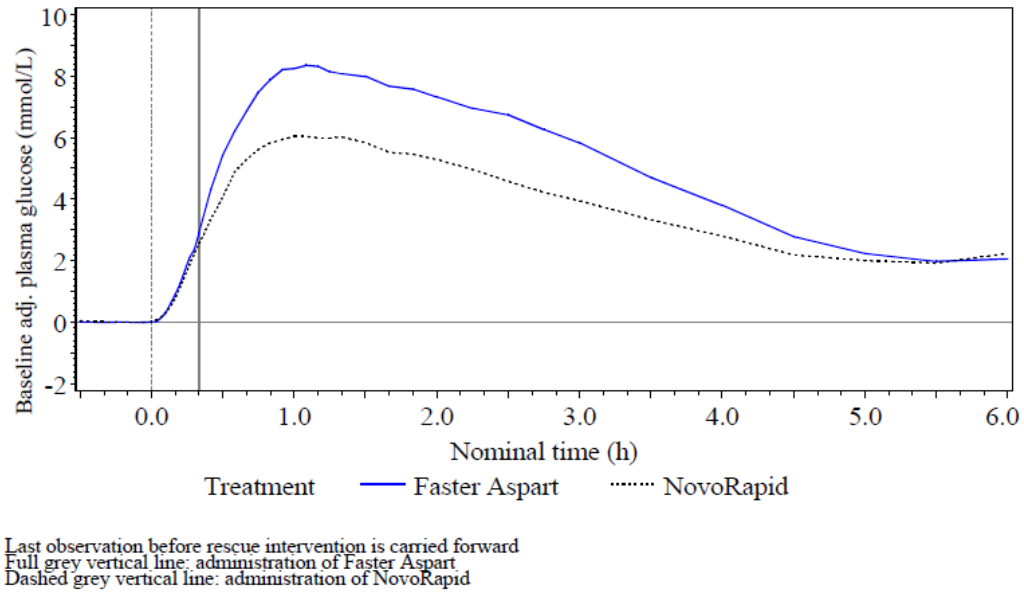
No statistically significant difference was observed for Fiasp and NovoLog for the primary endpoint of the study, mean change in plasma glucose concentrations from 0 to 1 hr after dose administration ($\Delta PG_{av,0\text{-}1hr}$) (estimated treatment difference of -0.31 mmol/L $[-0.66; 0.05]_{95\%CI}$, p=0.089; estimated Fieller treatment ratio of 0.91 $[0.81; 1.02]_{95\%CI}$). Additionally, no statistically significant treatment differences was observed for $\Delta PG_{1hr}$ (-0.59 mmol/L $[-1.19; 0.01]_{95\%CI}$, p=0.055), $\Delta PG_{2hr}$ (-0.19 mmol/L $[-1.05; 0.66]_{95\%CI}$, p=0.646), $\Delta PG_{av,0\text{-}2hr}$ (-0.31 mmol/L $[-0.84; 0.22]_{95\%CI}$, p=0.245), $\Delta PG_{av,0\text{-}4hr}$ (total glucose lowering effect, -0.14 mmol/L $[-0.73; 0.46]_{95\%CI}$, p=0.649), and $\Delta PG_{max}$ (-0.44 mmol/L $[-1.16; 0.28]_{95\%CI}$, p=0.224).

The Reviewer notes that under the meal challenge setting, where Fiasp was administered immediately prior to a standardized meal, the observed PD effects was not different to that of pre-meal NovoLog. The results from the meal challenge PK/PD study are in contrast to findings from the euglycemic clamp PK/PD studies which showed a greater early glucose lowering effect following administration of Fiasp compared to NovoLog. The clinical pharmacology data shows that magnitude of differences evident in the PK/PD profile from clamp studies is not large enough to translate to significant impact on PPG control as anticipated when Fiasp and NovoLog are administered in identical manner.

The overall clinical pharmacology results show that despite the faster onset of exposure and greater early exposure of insulin aspart after administration of Fiasp when compared to NovoLog, Fiasp does not appear to improve the PPG control towards the claimed early glucose lowering effect of Fiasp when compared to NovoLog following identical pre-meal dosing. The glucose lowering effect is undoubtedly demonstrated for both Fiasp and NovoLog in clinical pharmacology studies.

*Post-meal dosing*

For Study NN1218-3921, the mean baseline adjusted plasma glucose profiles (LOCF) for Fiasp and NovoLog when administered 20 min after the start of intake of a standardized meal and administered immediately before a standardized meal, respectively, in patients with T1DM is presented in Figure 10. The mean baseline adjusted plasma glucose profiles for Fiasp administered post-meal was higher when compared to NovoLog administered pre-meal.




Last observation before rescue intervention is carried forward
Full grey vertical line: administration of Faster Aspart
Dashed grey vertical line: administration of NovoRapid

**Figure 10: Mean baseline adjusted plasma glucose profiles after a single SC dose (0.2 unit/kg) of Fiasp (indicated as faster aspart in the Applicant's figure above) administered 20 min after the start of intake of a standardized meal and NovoLog administered immediately before a standardized meal in patients with T1DM (LOCF) (dashed vertical line indicates the start of the standardized meal)**

(Source: Study NN1218-3921, Clinical study report, page 100)

The primary endpoint of the study, mean plasma glucose concentrations from 0-6 hr after the start of intake of a standardized meal ($PG_{av,0-6hr}$), was 13% higher for post-meal Fiasp when compared to pre-meal NovoLog (estimated treatment ratio of 1.13 $[1.06; 1.21]_{90\%CI}$, p=0.002). This suggests a smaller glucose lowering effect for post-meal Fiasp when compared to pre-meal NovoLog.

Supporting the primary endpoint, other PD endpoints showed a smaller glucose lowering effect for post-meal Fiasp when compared to pre-meal NovoLog: $PG_{av,0-1hr}$ (estimated treatment ratio of 1.12 $[1.08;1.16]_{90\%CI}$), $PG_{av,0-2hr}$ (estimated treatment ratio of 1.17 $[1.11;1.22]_{90\%CI}$), $PG_{1hr}$ (estimated treatment ratio of 1.20 $[1.14; 1.26]_{90\%CI}$), $PG_{2hr}$ (estimated treatment ratio of 1.19 $[1.09; 1.30]_{90\%CI}$), and $PG_{max}$ (estimated treatment ratio of 1.14 $[1.09; 1.19]_{90\%CI}$).

The Reviewer notes that despite the faster onset of exposure and greater early exposure of insulin aspart after dosing with Fiasp when compared to NovoLog, when administered 20 minutes post-meal when compared to NovoLog administered pre-meal a smaller glucose lowering effect for post-meal Fiasp was observed when compared to pre-meal NovoLog.

### 3.2.2 Does the pharmacokinetic/pharmacodynamic data establish that Fiasp is different to NovoLog with regards to the key clinically relevant difference from NovoLog – "time of administration"?

NovoLog is recommended to be administered subcutaneously within 5-10 minutes before a meal. Fiasp seems to be designed to shift the PK and PD profile of insulin aspart from that of NovoLog, sufficiently rapid enough to provide a better early control on PPG versus NovoLog when used identically (pre-meal) and also render it suitable for post-meal administration with PPG control similar if not better than NovoLog. Pharmacokinetic data from euglycemic clamp PK/PD studies does establish that Fiasp is different to NovoLog in terms of PK and PD profile to pursue a different time of administration.

An earlier onset of insulin aspart exposure was observed with the mean onset of appearance twice as fast for Fiasp when compared to NovoLog, and the mean time to achieve 50% $C_{max}$ and $t_{max}$ was approximately 10 min earlier for Fiasp when compared to NovoLog. Exposure of insulin aspart, up to 90 min post-dose, was larger for Fiasp compared to NovoLog, with the largest difference observed in the first 15 mins post-dose (treatment ratio range: 3.55).

When Fiasp is compared with NovoLog upon SC administration immediately prior to meal (time window covered by the recommended use of NovoLog) in PK/PD studies, pharmacodynamic data from meal challenge studies does not establish pre-meal Fiasp to be different from pre-meal NovoLog for almost similar time of administration. No statistically significant difference in early PPG excursion ($\Delta PG_{av,0\text{-}1hr}$, $\Delta PG_{av,0\text{-}2hr}$) was observed for pre-meal Fiasp and NovoLog, suggesting that despite the faster initial absorption of Fiasp, this does not translate into differences in early PPG control.

When Fiasp is administered 20 min after the start of intake of a meal, the total PPG excursion ($\Delta PG_{av,0\text{-}6hr}$) was 13% higher when compared to pre-meal NovoLog. This suggests that the faster initial absorption properties of Fiasp result in somewhat lower PPG control when administered 20 minutes post-meal compared to NovoLog administered pre-meal, although not compared to NovoLog post-meal administration, which would have provided the complete clinical scenario for PPG control in comparison to reference.

Therefore, the post-meal PD data does point to some extent that differences in PK/PD profile of Fiasp from NovoLog are close but not optimal for post-meal use as the time of administration, as it comes at a cost of lesser control on PPG excursion for post-meal Fiasp when compared to pre-meal NovoLog and even pre-meal Fiasp. The Reviewer recommends that patients preferably stick to one of the times of administration, i.e. either pre-meal or 20 minutes from start of the meal to minimize variability in glycemic control and label to reflect the anticipated differences from these two times of administration.

### 3.2.3 What is the relevance of Fiasp pharmacokinetic/pharmacodynamic data to the observations from the efficacy evaluation of Fiasp in comparison to NovoLog?

The PK/PD data from Phase 1 meal challenge studies showed comparable early glucose lowering effect for both pre-meal Fiasp and NovoLog in patients with T1DM. In the Phase 3a study, the treatment difference for estimated change from baseline in 2 hr PPG increment after 26 weeks of treatment during a standardized meal test was statistically significant in favor of pre-meal Fiasp when compared to pre-meal NovoLog (-0.67 mmol/L $[-1.29; -0.04]_{95\%CI}$) in patients with T1DM. However, in a sensitivity analysis (excluding confounding factors), this treatment difference for change from baseline in 2 hr PPG increment was not statistically significant (-0.57 mmol/L $[-1.26; 0.13]_{95\%CI}$). A statistically significant treatment difference for change from baseline in 1 hr PPG increment was also evident in favor of pre-meal Fiasp when compared to observations in the Phase 1 studies. An explanation for the observed difference in PPG excursion between the Phase 1 and 3a studies is not known at the present time. Overall, noninferiority was concluded for pre-meal Fiasp versus pre-meal NovoLog since the estimated treatment difference for change from baseline in HbA1c after 26 weeks of treatment was -0.15% points $[-0.23; -0.07]_{95\%CI}$.

For post-meal Fiasp, the PK/PD data from Phase 1 meal challenge study showed higher PPG excursion (i.e., a relatively smaller early glucose lowering effect) for Fiasp when compared to pre-meal NovoLog in patients with T1DM. In the Phase 3a study in patients with T1DM, early PPG excursion (change from baseline in 1 hr PPG increment) following a standardized meal was statistically significant in favor of pre-meal NovoLog when compared to post-meal Fiasp, and thereby supports the findings from the Phase 1 study. Despite this, noninferiority was concluded for post-meal Fiasp versus pre-meal NovoLog based on change from baseline in HbA1c after 26 weeks of treatment (estimated treatment difference of 0.04% points $[-0.04; 0.12]_{95\%CI}$) in the Phase 3a study.

In patients with T2DM, a statistically significant treatment difference for change from baseline in 1 hr PPG increment after 26 weeks of treatment during a standardized meal test was observed in favor of pre-meal Fiasp when compared to pre-meal NovoLog. However, the similar decline in HbA1c from baseline renders the magnitude of 1 hr PPG difference clinically irrelevant thus, indicating that Fiasp did not demonstrate any unique advantage over NovoLog with respect to the claimed higher early glucose lowering effect in T2DM population, when tested for identical method of use (pre-meal administration).

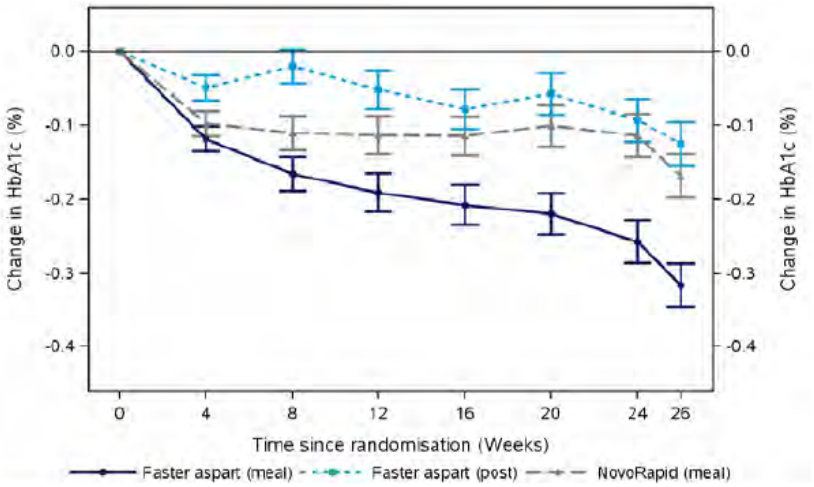
Efficacy and PPG excursion results from the Phase 3a studies are described below:

***Study NN1218-3852 in patients with T1DM***

<u>HbA1c after 26 weeks of treatment</u>

The Phase 3a study (Study NN1218-3852, refer to Appendix 5.1 for description of study) in patients with T1DM assessed the estimated change from baseline in HbA1c after 26 weeks of treatment for pre-meal Fiasp versus pre-meal NovoLog and for post-meal Fiasp versus pre-meal

NovoLog. The estimated change from baseline in HbA1c stratified by treatment in patients with T1DM is presented in Figure 11.




Full analysis set. Least-square mean values are obtained from a mixed-effect model for repeated measurements for change from baseline in $HbA_{1c}$. Error bars: ± standard error from the mixed-effect model for repeated measurements.

**Figure 11: Estimated change from baseline in HbA1c for pre-meal Fiasp, post-meal Fiasp (indicated as faster aspart in the Applicant's figure above), and pre-meal NovoLog in patients with T1DM**

(Source: Study NN1218-3852, Clinical study report, page 140)

The estimated change from baseline in HbA1c after 26 weeks of treatment was -0.32% points and -0.17% points for pre-meal Fiasp and NovoLog, respectively. Noninferiority was concluded for pre-meal Fiasp versus NovoLog since the estimated treatment difference (pre-meal Fiasp-pre-meal NovoLog) after 26 weeks of treatment was -0.15% points $[-0.23; -0.07]_{95\%CI}$. For further details refer to the Clinical Review.

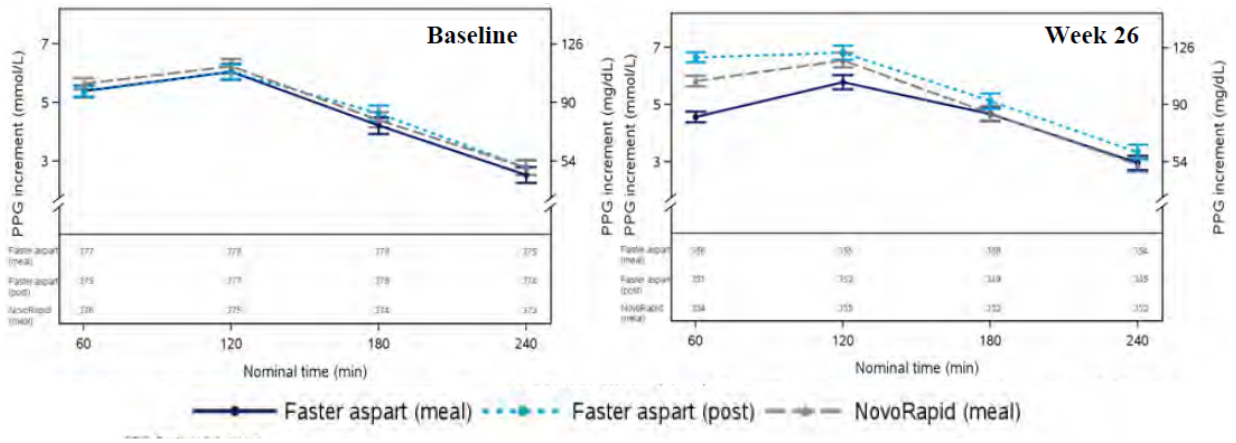
The estimated change from baseline in HbA1c after 26 weeks of treatment was -0.13% points for post-meal Fiasp. The estimated treatment difference (post-meal Fiasp-pre-meal NovoLog) after 26 weeks of treatment was 0.04% points $[-0.04; 0.12]_{95\%CI}$. Noninferiority was concluded for post-meal Fiasp versus pre-meal NovoLog since the upper boundary of the 2-sided 95%CI was ≤0.4% points and previous steps in the testing hierarchy were statistically significant. For further details refer to the Clinical Review.

PPG excursion during a standardized meal test

A standardized meal test was performed at baseline (before randomization at the randomization visit) and at week 26 of the study. At the baseline meal test, all patients received 0.1 unit/kg of NovoLog 0-2 min before the meal and at week 26 patients were administered 0.1 unit/kg of either NovoLog 0-2 min before the meal or Fiasp 0-2 min before the meal or Fiasp 20 min after the start of the meal (based on the treatment arm).

Mean PPG increments during the meal test at baseline and week 26 stratified by treatment arm in patients with T1DM is presented in Figure 12.






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.

**Figure 12: Mean postprandial glucose increments (up to 4 hr) at baseline and Week 26 during the meal test stratified by treatment arm in patients with T1DM (Fiasp indicated as faster aspart in the Applicant's figures above)**

(Source: Study NN1218-3852, Clinical study report, page 146)

A confirmatory secondary endpoint of the study was to confirm superiority of pre-meal Fiasp compared to pre-meal NovoLog both in combination with insulin detemir after 26 weeks of treatment in terms of change from baseline in 2 hr PPG increment (meal test). Mean PPG increments was comparable between treatment arms at baseline. The estimated change from baseline in 2 hr PPG increment after 26 weeks of treatment was -0.29 mmol/L for pre-meal Fiasp and +0.38 mmol/L for pre-meal NovoLog. The estimated treatment difference (pre-meal Fiasp-pre-meal NovoLog) was statistically significant in favor of pre-meal Fiasp (-0.67 mmol/L [-1.29; -0.04]$_{95\%CI}$). The Applicant reports superiority of pre-meal Fiasp when compared to pre-meal NovoLog for this PD endpoint.

In a sensitivity analysis, the treatment difference after 26 weeks of treatment for change from baseline in 2 hr PPG increment for pre-meal Fiasp was not found to be statistically significant to pre-meal NovoLog (estimated treatment difference of -0.57 mmol/L [-1.26; 0.13]$_{95\%CI}$). The sensitivity analysis set excluded patients that did not consume the full amount of meal, did not consume the full amount of meal in 12 min, not fasted, received rescue medications during the first 2 hr of the meal test, actual bolus dose deviated from the planned dose by a defined value, discontinued treatment and the meal test was performed while treated with non-trial insulin product, or experienced a severe or blood glucose confirmed hypoglycemic episode on the day of the meal test prior to start of the meal.

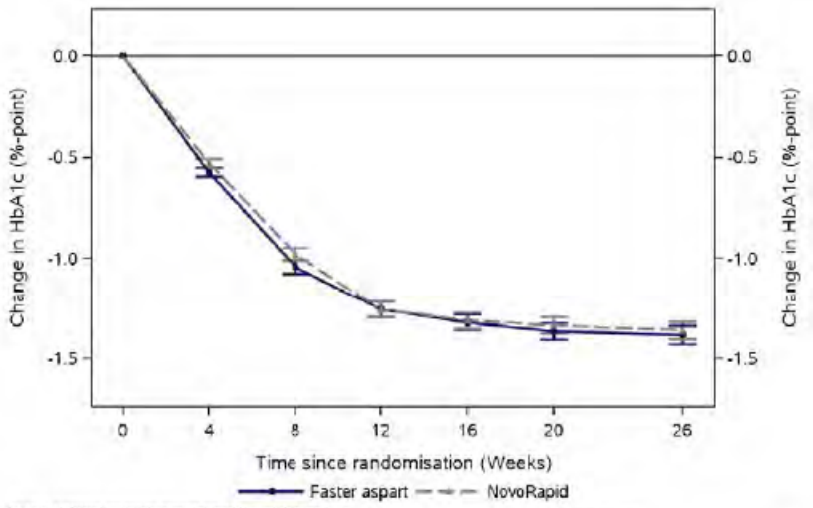
For estimated change from baseline in 1 hr PPG increment after 26 weeks of treatment, the estimated treatment difference was statistically significant in favor of pre-meal Fiasp when compared to pre-meal NovoLog in both the primary analysis (estimated treatment difference (pre-meal Fiasp-pre-meal NovoLog) -1.18 mmol/L $[-1.65; -0.71]_{95\%CI}$) and sensitivity analysis (estimated treatment difference -1.09 mmol/L $[-1.60; -0.58]_{95\%CI}$).

For post-meal Fiasp, the estimated change from baseline in 1 hr PPG increment after 26 weeks of treatment was +1.27 mmol/L compared to +0.34 mmol/L for pre-meal NovoLog. The estimated treatment difference (post-meal Fiasp-pre-meal NovoLog) was statistically significant in favor of pre-meal NovoLog (0.93 mmol/L $[0.46; 1.40]_{95\%CI}$). No statistically significant treatment difference was observed in PPG increments at 2 hr after start of the meal test.

***Study NN1218-3853 in patients with T2DM***

HbA1c after 26 weeks of treatment

The Phase 3a study (Study NN1218-3853, refer to Appendix 5.1 for description of study) in patients with T2DM assessed the estimated change from baseline in HbA1c after 26 weeks of treatment for pre-meal Fiasp versus pre-meal NovoLog. The estimated change from baseline in HbA1c stratified by treatment in patients with T2DM is presented in Figure 13.




Least-square mean values are obtained from a mixed-effect model for repeated measurements for change from baseline in $HbA_{1c}$.
Error bars: ± standard error from the mixed-effect model for repeated measurements.

**Figure 13: Estimated change from baseline in HbA1c for pre-meal Fiasp (indicated as faster aspart in the Applicant's figure above), and pre-meal NovoLog in patients with T2DM**

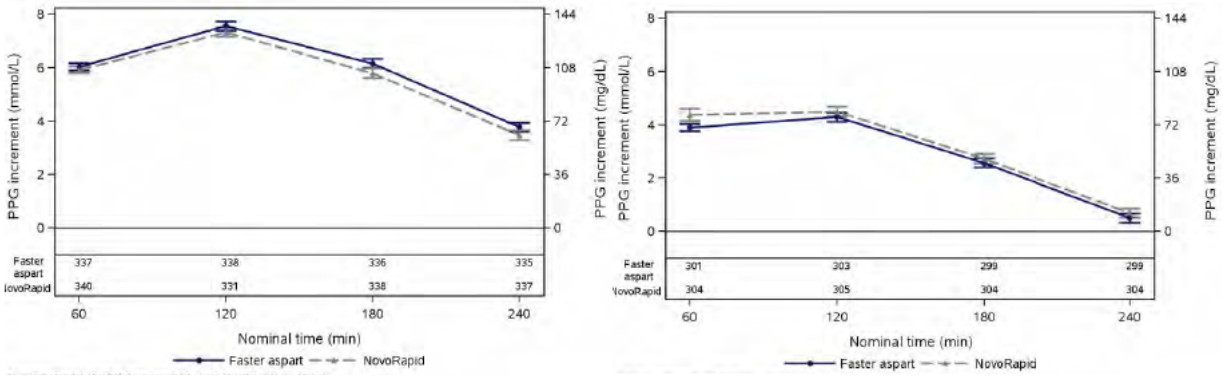
(Source: Study NN1218-3853, Clinical study report, page 128)

At baseline, the mean HbA1c was 7.96% and 7.89% in the pre-meal Fiasp and pre-meal NovoLog treatment groups, respectively. After 26 weeks of treatment, the mean HbA1c decreased to 6.63% (estimated reduction of 1.38% points) and to 6.59% (estimated reduction of

1.36% points) in the pre-meal Fiasp and pre-meal NovoLog treatment groups, respectively. Noninferiority was concluded for pre-meal Fiasp versus pre-meal NovoLog since the estimated treatment difference for change from baseline in HbA1c after 26 weeks of treatment for Fiasp versus NovoLog was -0.02% points [-0.15; 0.10]$_{95\%CI}$. For further details refer to the Clinical Review.

PPG excursion during a standardized meal test

Mean PPG increments during the meal test at baseline and week 26 stratified by treatment in patients with T2DM is presented in Figure 14.




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.

**Figure 14: Mean postprandial glucose increments (up to 4 hr) at baseline (left) and Week 26 (right) during the meal test stratified by treatment arm in patients with T2DM (Fiasp indicated as faster aspart in the Applicant's figures above)**

(Source: Study NN1218-3853, Clinical study report, page 134)

A confirmatory secondary endpoint of the study was change from baseline in 2 hr PPG increment after 26 weeks of treatment (meal test) to confirm superiority of pre-meal Fiasp to pre-meal NovoLog. At baseline, the mean 2 hr PPG increment was 7.57 mmol/L and 7.34 mmol/L for pre-meal Fiasp and pre-meal NovoLog, respectively. The estimated change from baseline in 2 hr PPG increment after 26 weeks of treatment was -3.24 mmol/L for pre-meal Fiasp and -2.87 mmol/L for pre-meal NovoLog. The estimated treatment difference in change from baseline in 2 hr PPG increment for pre-meal Fiasp versus pre-meal NovoLog was -0.36 mmol/L [-0.81; 0.08]$_{95\%CI}$. Superiority of pre-meal Fiasp versus pre-meal Novolog was not confirmed for this endpoint since the treatment difference was not statistically significant.

However, a statistically significant treatment difference in favor of pre-meal Fiasp was observed for change from baseline in 1 hr PPG increment after 26 weeks of treatment. The estimated treatment difference for change from baseline in 1 hr PPG increment after 26 weeks of treatment for pre-meal Fiasp versus pre-meal NovoLog was -0.59 mmol/L [-1.09; -0.09]$_{95\%CI}$.

The Reviewer notes that following 26 weeks of treatment with pre-meal Fiasp, an early glucose lowering effect, in PPG excursion at 1 hr after start of intake of a standardized meal, was observed when compared to pre-meal NovoLog in patients with T1DM. This is in contrast to observations in the Phase 1 meal challenge studies (NN1218-3889, NN1218-3922) of no statistically significant difference in early glucose lowering effect for pre-meal Fiasp compared to pre-meal NovoLog after single dose administration in the same patient population.

In the Phase 3a study (Study NN1218-3852), overall no difference in the administered bolus insulin dose was evident in the Fiasp and NovoLog treatment arms (insulin dose ratio (unit) (Fiasp/NovoLog) after 26 weeks of 0.97). The total insulin dose was also comparable in both treatment arms (insulin dose ratio (unit) after 26 weeks of 0.95). An explanation for the observed differences in PPG excursion for Fiasp (pre-meal) between the Phase 1 and Phase 3a studies is not known at the present time.

Similar to observations in patients with T1DM, in patients with T2DM following 26 weeks of treatment with pre-meal Fiasp, an early glucose lowering effect, in terms of PPG excursion at 1 hr after start of intake of a standardized meal, was observed when compared to pre-meal NovoLog. The magnitude of 1 hr PPG differences is likely not clinically relevant considering the decrease in HbA1c was non-inferior for Fiasp compared to NovoLog.

**3.2.4 If and to what extent the established pharmacokinetic-pharmacodynamic relationship allow for leveraging of pharmacodynamic data from studies lacking the pharmacokinetic data for total insulin aspart?**

In this unique situation, the established PK-PD relationship following single dose SC administration of Fiasp and NovoLog allows for leveraging of PD data from some key Phase 1 studies that (b) (4) lacked the PK data from total insulin aspart (referred to as insulin aspart in the Clinical Pharmacology review).

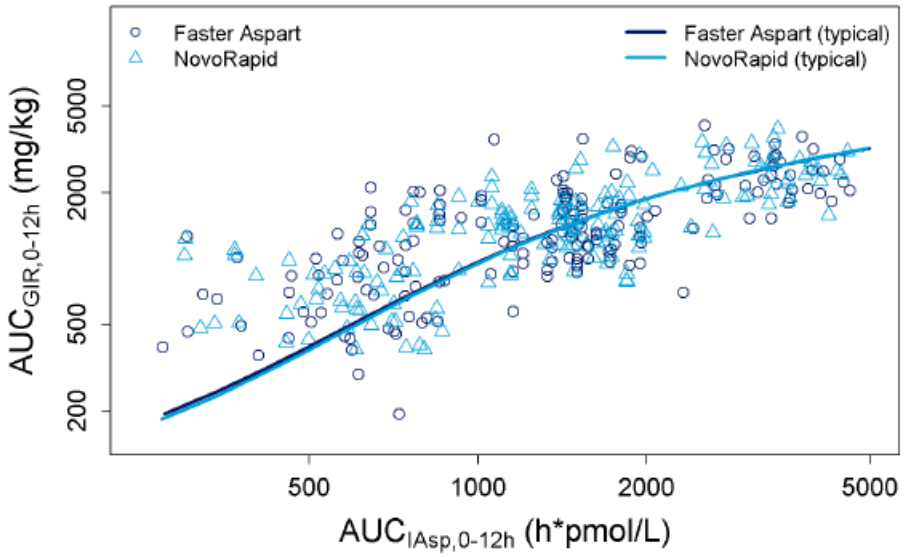
A one-compartment model with first-order absorption through 3 transit compartments and first-order elimination was used to describe the PK of insulin aspart and an effect compartment model driven by concentration profiles predicted from the PK model, and a sigmoidal $E_{max}$-type relationship between the effect compartment concentration and the GIR response was used to describe the PD of insulin aspart following SC administration of Fiasp and NovoLog. Refer to Appendix 5.3 for details on the PK-PD and exposure-response analysis.

The exposure-response relationship for total exposure of insulin aspart (predicted) and total glucose lowering effect (observed) for Fiasp and NovoLog following SC administration in patients with T1DM is presented in Figure 15. The observed $AUC_{GIR0\text{-}12hr}$ data for individual patients were obtained from Study NN1218-3887, and given that this study had no PK data for insulin aspart (total insulin aspart), the total exposure of insulin aspart ($AUC_{0\text{-}12hr}$) was predicted using the PK model (based on actual dose levels and demographics of subjects). The individual

data shows an increase in total glucose lowering effect with an increase in total insulin aspart exposure across the dose range of 0.1 to 0.4 unit/kg for both treatments.

The relationship between total glucose lowering effect and total insulin aspart exposure for a typical patient (population mean) is shown by the solid lines in Figure 15. Using the combined PK-PD model, an increase in total glucose lowering effect with an increase in total insulin aspart exposure was observed for a typical patient following SC administration of Fiasp and NovoLog. The model predicted relationship provides further support for the established PK-PD relationship.

Therefore, the established PK-PD relationship for Fiasp and NovoLog following SC dosing enables leveraging of PD data from Phase 1 studies to answer clinically relevant question of dose-response for Fiasp.




Data points are individual subject values from trial 3887 (n=46, 8-way cross-over) and the lines are typical subject relationships obtained from the combined PK-PD model.

**Figure 15: Relationship between predicted total exposure ($AUC_{0\text{-}12hr}$) and observed total glucose lowering effect ($AUC_{GIR,0\text{-}12hr}$) for Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog following SC administration in patients with T1DM**

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 12)

### 3.2.5 What is the dose-exposure and dose-response relationship for Fiasp?

***Dose-exposure relationship of Fiasp and NovoLog***

In Study NN1218-3922, the dose-exposure ($AUC_{0\text{-}8hr}$ and $C_{max}$) relationship for Fiasp and NovoLog was assessed following administration of individualized single doses ranging from 0.06 to 0.28 unit/kg. Of note, insulin aspart serum concentrations were below the LLOQ after 6

hr post-dose (Figure 3), however $AUC_{0\text{-}8hr}$ was estimated since this was a pre-specified PK endpoint. The dose-exposure analysis was a retrospective analysis conducted by the Applicant.

Scatter profiles for $AUC_{0\text{-}8hr}$ and $C_{max}$ versus insulin aspart dose for Fiasp and NovoLog is presented in Figure 16, and shows an increase in $AUC_{0\text{-}8hr}$ and $C_{max}$ with an increase in dose for both treatments.

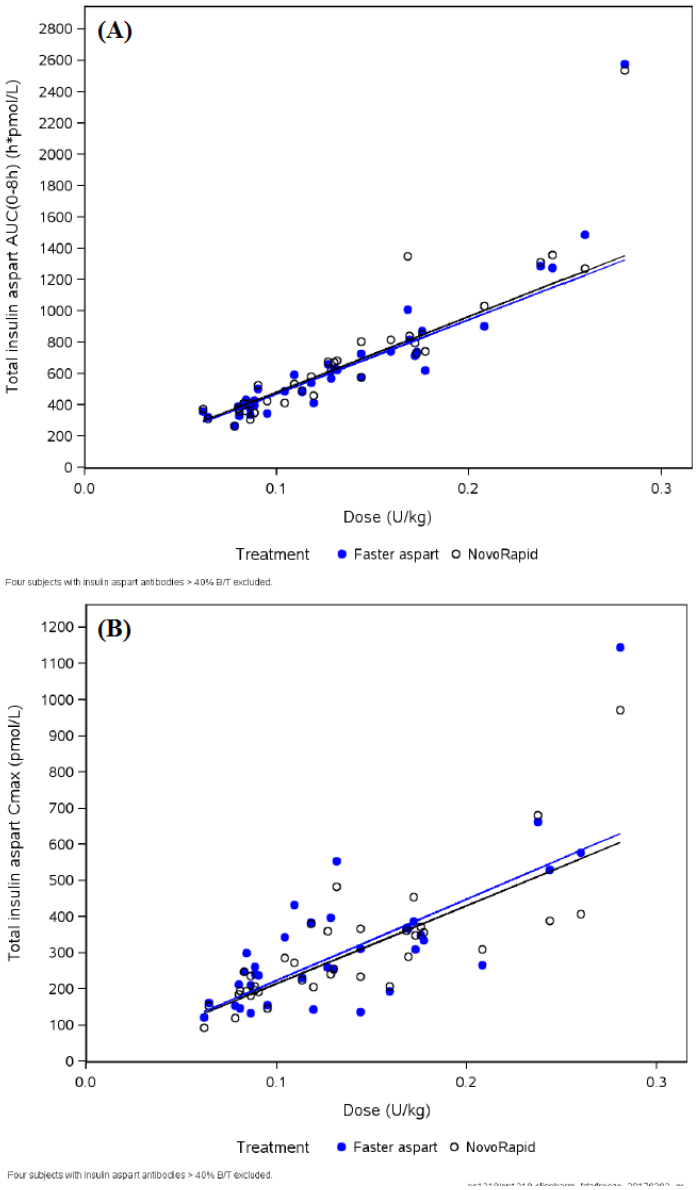



**Figure 16: Scatter plots of insulin aspart exposure (A) $AUC_{0\text{-}8hr}$ and (B) $C_{max}$ versus doses for Fiasp (indicated as faster aspart in the Applicant's figures above) and NovoLog in patients with T1DM**

(Source: Summary of Clinical Pharmacology Studies, page 80)

For Fiasp, statistical analysis for dose-proportionality showed a proportional increase in $AUC_{0\text{-}8hr}$ and $C_{max}$ with an increase in dose (estimated slope of 1.14 $[0.99; 1.29]_{95\%CI}$ and 0.91 $[0.65; 1.17]_{95\%CI}$, respectively) (Table 5). For NovoLog, dose-proportionality was shown for $C_{max}$ (estimated slope of 0.96 $[0.70; 1.22]_{95\%CI}$), however a slightly greater than proportional increase in $AUC_{0\text{-}8hr}$ was evident with an increase in dose (estimated slope of 1.20 $[1.05; 1.35]_{95\%CI,}$ p=0.009).

In a sensitivity analysis in which 4 patients that were excluded in the original analysis (patients with insulin aspart antibodies >40 %B/T) were included in the analysis, the overall results were similar to that of the original analysis ($AUC_{0\text{-}8hr}$: estimated slope of 1.10 $[0.77; 1.43]_{95\%CI}$, 1.18 $[0.85; 1.50]_{95\%CI}$ for Fiasp and NovoLog, respectively; $C_{max}$: estimated slope of 0.89 $[0.57; 1.22]_{95\%CI}$, 0.94 $[0.62; 1.26]_{95\%CI}$ for Fiasp and NovoLog, respectively).

**Table 5: Statistical analysis for insulin aspart exposure ($AUC_{0\text{-}8hr}$ and $C_{max}$) versus dose for Fiasp (indicated as faster aspart in the Applicant's table below) and NovoLog in patients with T1DM**

| | N | Estimate | 95% CI | P-value¤ |
|---|---|---|---|---|
| AUCIASP(0-8h) (pmol*h/L) | | | | |
| Slope | | | | |
| Faster aspart | 36 | 1.14 | [0.99;1.29] | 0.068 |
| NovoRapid | 36 | 1.20 | [1.05;1.35] | 0.009 |
| Cmax (pmol/L) | | | | |
| Slope | | | | |
| Faster aspart | 36 | 0.91 | [0.65;1.17] | 0.513 |
| NovoRapid | 36 | 0.96 | [0.70;1.22] | 0.765 |

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was log-transformed and analysed using a linear regression model with log(dose) as covariate and treatment-dependent intercept and slope.
P-value for test of slope=1 corresponding to dose proportionality.
Four subjects with insulin aspart antibodies > 40 %B/T excluded.

(Source: Summary of Clinical Pharmacology Studies, Appendix 5.2, page 80)

Overall the results for the dose-exposure relationship suggest that total insulin aspart exposure ($AUC_{0\text{-}8hr}$) and maximum insulin aspart concentrations increase in a proportional manner with increasing doses of Fiasp. For NovoLog, a slightly greater than proportional increase in total insulin aspart exposure was evident with an increase in dose; a proportional increase in maximum insulin aspart concentrations was observed with increase in dose for NovoLog.

***Dose-response relationship of Fiasp®***

In Study NN1218-3887, the dose-response ($AUC_{GIR,0\text{-}12hr}$ and $GIR_{max}$) relationship for Fiasp was assessed following administration of single doses of 0.1, 0.2, and 0.4 unit/kg. Mean GIR profiles for the 3 doses following administration of Fiasp in patients with T1DM is presented in Figure 17, which shows an increase in mean glucose lowering effect with increasing dose. Refer to Appendix 5.5 for blood glucose profiles following administration of Fiasp.

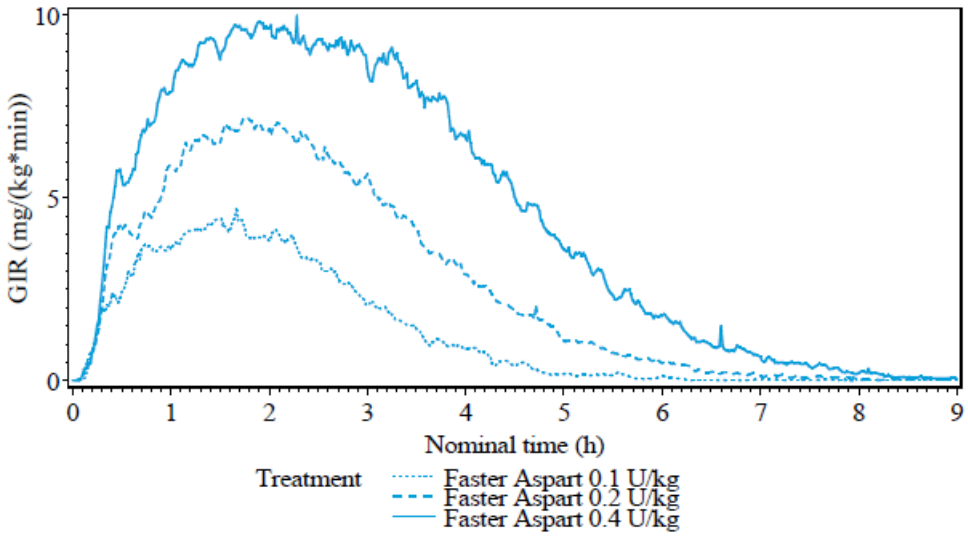



**Figure 17: Mean GIR profiles (0-9 hr) following administration of Fiasp (0.1, 0.2, 0.4 unit/kg) (indicated as faster aspart in the Applicant's figure above) in patients with T1DM**

(Source: Study NN1218-3887, Clinical study report, page 88)

Statistical analysis for $AUC_{GIR,0\text{-}12hr}$ (primary endpoint) showed that total glucose lowering effect was approximately 110% greater at the 0.2 unit/kg dose level compared to the 0.1 unit/kg dose level (estimated dose ratio of 2.09 $[1.92; 2.28]_{95\%CI}$). The $AUC_{GIR,0\text{-}12hr}$ was approximately 73% greater at the 0.4 unit/kg dose level compared to the 0.2 unit/kg dose level (estimated dose ratio of 1.73 $[1.59; 1.88]_{95\%CI}$). The Applicant reports that this indicates that some patients had exceeded the linear part of the s-shaped dose-response curve before the 0.4 unit/kg dose level.

The estimated mean and confidence interval based on the statistical model for $AUC_{GIR0\text{-}12hr}$ and $GIR_{max}$ versus insulin aspart dose profiles for Fiasp in patients with T1DM are presented in Figure 18. Overall, an increase in $AUC_{GIR,0\text{-}12hr}$ and $GIR_{max}$ was observed with an increase in dose.

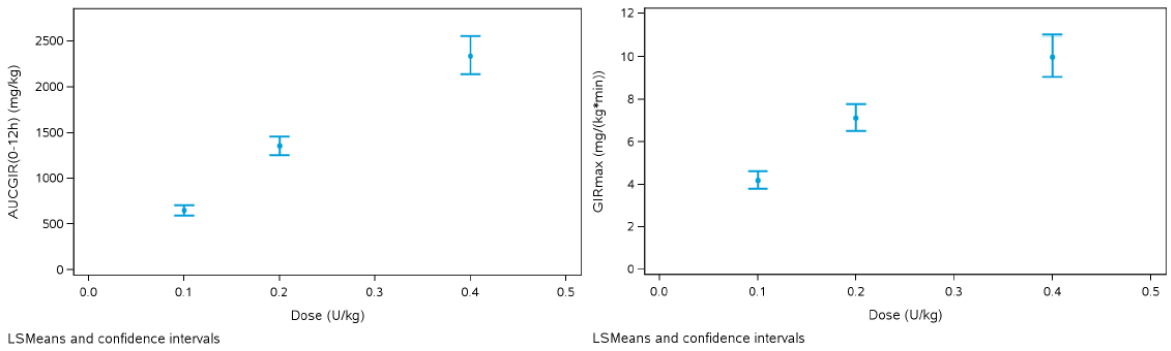



**Figure 18: Mean total glucose lowering effect ($AUC_{GIR,0\text{-}12hr}$) and maximum glucose lowering effect ($GIR_{max}$) versus dose for Fiasp in patients with T1DM**

(Source: Study NN1218-3887, Clinical study report, page 90)

Statistical analysis for dose-linearity of $AUC_{GIR,0\text{-}12hr}$ and $GIR_{max}$ for Fiasp is presented in Table 6. For both PD endpoints, the second order coefficient was statistically significantly lower than 0 which indicates that the increase in $AUC_{GIR,0\text{-}12hr}$ and $GIR_{max}$ for Fiasp was slightly less than linear.

**Table 6: Statistical analysis for dose-linearity of $AUC_{GIR,0\text{-}12hr}$ and $GIR_{max}$ for Fiasp (indicated as faster aspart in the Applicant's table below) in patients with T1DM**

| | N | Estimate | 95% CI | P-value |
|---|---|---|---|---|
| **AUCGIR(0-12h) (mg/kg)** | | | | |
| Faster Aspart, functional parameters | | | | |
| Intercept | 180 | -205 | [-397;-13] | |
| First order coefficient | 180 | 9354 | [7092;11616] | |
| Second order coefficient | 180 | -7226 | [-11915;-2538] | 0.003 |
| NovoRapid, functional parameters | | | | |
| Intercept | 176 | -233 | [-432;-34] | |
| First order coefficient | 176 | 9775 | [7426;12123] | |
| Second order coefficient | 176 | -7646 | [-12520;-2772] | 0.003 |
| Test for equal functional form | | | | |
| Faster Aspart vs NovoRapid: | | | | 0.786 |
| **GIRmax (mg/(kg*min))** | | | | |
| Faster Aspart, functional parameters | | | | |
| Intercept | 180 | 0.25 | [-0.81;1.32] | |
| First order coefficient | 180 | 45.65 | [33.73;57.58] | |
| Second order coefficient | 180 | -51.54 | [-75.16;-27.92] | <0.001 |
| NovoRapid, functional parameters | | | | |
| Intercept | 176 | -0.12 | [-1.20;0.97] | |
| First order coefficient | 176 | 50.03 | [37.70;62.36] | |
| Second order coefficient | 176 | -60.15 | [-84.48;-35.81] | <0.001 |
| Test for equal functional form | | | | |
| Faster Aspart vs NovoRapid: | | | | 0.944 |

N: Number of profiles contributing to analysis, CI: Confidence interval,
The endpoint was log-transformed and analysed using a non-linear mixed model with response depending on a quadratic function of dose on the original scale with coefficients depending on treatment, period as a fixed effect and subject as a random effect.

(Source: Study NN1218-3887, Clinical study report, page 91)

Overall the results for the dose-response relationship indicates an increase in total and maximum glucose lowering effect with an increase in dose for Fiasp, however this increase in PD effect was slightly less than linear.

### 3.2.6 What is the effect of intrinsic factors on the pharmacokinetics and pharmacodynamics of insulin aspart following administration of Fiasp?

In patients with T1DM, the total exposure and maximum concentrations of insulin aspart following administration of Fiasp was comparable between different age groups (younger adult and geriatric patients) and between genders (male and females). Following administration of Fiasp, the total exposure of insulin aspart was comparable between different body mass index (BMI) categories, however maximum concentrations of insulin aspart increased with decreasing

BMI category. Renal impairment and race/ethnicity overall showed no clinically meaningful impact on the PK of Fiasp. A trend for an increase in total insulin aspart exposure with an increase in the level of total anti-insulin aspart antibodies was observed following administration of Fiasp.

Overall, the total and maximum glucose lowering effect of insulin aspart following administration of Fiasp was similar between different age groups (young adult and geriatric patients) and between genders. Total glucose lowering effect for Fiasp did not appear to be affected by the level of total anti-insulin aspart antibodies. Total and maximum glucose lowering effect decreased with increasing BMI category.

Given that Fiasp is an insulin drug product, the dosing regimen will be individualized based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goals.

**Pharmacokinetics**

Assessments to evaluate the effect of age, body mass index (BMI), gender, anti-insulin aspart antibodies, race/ethnicity, renal impairment on the PK of insulin aspart following administration of Fiasp and NovoLog was conducted. To assess the effect of intrinsic factors on the PK of insulin aspart following administration of Fiasp and NovoLog, retrospective analysis with insulin aspart concentrations (total insulin aspart concentrations) was conducted.

The assessment for the effect of age, BMI, gender, anti-insulin aspart antibodies on the PK of insulin aspart is reported in the Clinical Pharmacology review based on the results from the cross-trial analysis (Studies NN1218-3978, NN1218-3891 (young adult patients), NN1218-3922) since the Phase 1 studies provide rich source of data.

The effect of renal impairment (normal renal function, mild and moderate renal impairment) and race/ethnicity (Black, White, Hispanic, non-Hispanic, North American and European patients) on the PK of insulin aspart was assessed based on the Phase 3a study (Study NN1218-3852). Findings from the Phase 3a study has limitations in that the total exposure of insulin aspart was predicted based on 2 sampling points collected at 1 and 2 hr after the start of meal during the standardized meal test (not based on sparse sampling throughout the study) using a prediction model (not a compartmental population PK model). For this reason, a comprehensive review of the PK data from the Phase 3a study was not conducted, although this data showed that renal impairment and race/ethnicity overall showed no clinically meaningful impact on PK of Fiasp. Additionally, based on historical data, both renal impairment and hepatic impairment have not shown to have an impact on the PK of insulin aspart. Since Fiasp is an insulin product, the dose will be individualized for individual patient response.

***Age***

Pharmacokinetic data from Study NN1218-3891 was used to assess the effect of age on PK of insulin aspart following administration of a single dose of 0.2 unit/kg of Fiasp and NovoLog (not

cross-trial analysis). Young adult patients (18-35 years) and geriatric patients (≥65 years) with T1DM was enrolled in the study.

In geriatric patients, an earlier onset of exposure (Table 7) and larger early insulin aspart exposure (Table 8) was observed for Fiasp when compared to NovoLog. The onset of appearance was approximately twice as fast for Fiasp when compared to NovoLog. The early insulin aspart exposure was 1.13 to 2.53 fold higher for Fiasp when compared to NovoLog in the first 90 min post-dose. Total insulin aspart exposure and maximum insulin aspart concentrations were comparable for both treatments in geriatric patients.

**Table 7: PK parameters for onset of exposure in geriatric patients with T1DM following administration of Fiasp and NovoLog**

| PK Parameter | Fieller age group/treatment ratio (Fiasp/NovoLog)[1] | |
|---|---|---|
| | Point estimate | 95%CI |
| Onset of appearance (min) | 0.53 | 0.37; 0.70 |
| $t_{max}$ (min) | 0.94 | 0.76; 1.15 |
| Time to 50% $C_{max}$ (min) (interpolated) | 0.74 | 0.65; 0.83 |

[1]Endpoints were analyzed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and residual variance depends on age group

(Source: Summary of clinical pharmacology studies, Appendix 5.2, page 86-87)

**Table 8: Treatment ratios and 95%CI[1] for early and total insulin aspart exposure, and $C_{max}$ in geriatric patients with T1DM following administration of Fiasp (indicated as faster aspart in the Applicant's table below) and NovoLog**

| Endpoint | Number of subjects | | Estimated mean | | Treatment ratio [95% CI] |
|---|---|---|---|---|---|
| | Faster aspart | NovoRapid® | Faster aspart | NovoRapid® | Faster aspart/NovoRapid® |
| $AUC_{IAsp(0\text{-}15\ min)}$ (pmol*h/L) | 22 | 22 | 31.99 | 12.64 | 2.53 [1.97;3.26] |
| $AUC_{IAsp(0\text{-}30\ min)}$ (pmol*h/L) | 22 | 22 | 125.85 | 77.72 | 1.62 [1.32;1.99] |
| $AUC_{IAsp(0\text{-}1\ h)}$ (pmol*h/L) | 22 | 22 | 384.74 | 316.98 | 1.21 [1.05;1.40] |
| $AUC_{IAsp(0\text{-}90\ min)}$ (pmol*h/L) | 22 | 22 | 628.33 | 558.06 | 1.13 [1.00;1.27] |
| $AUC_{IAsp(0\text{-}2\ h)}$ (pmol*h/L) | 22 | 22 | 828.31 | 757.47 | 1.09 [0.99;1.21] |
| $AUC_{IAsp(0\text{-}12\ h)}$ (pmol*h/L) | 22 | 22 | 1320.24 | 1290.73 | 1.02 [0.98;1.07] |
| $C_{max,IAsp}$ | 22 | 22 | 580.41 | 552.29 | 1.05 [0.94;1.18] |

**Note:** NovoRapid® is known as NovoLog® in the U.S.

[1]Endpoint was log-transformed and analyzed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and residual variance depends on age group

(Source: Summary of clinical pharmacology studies, page 98)

Following administration of Fiasp, total insulin aspart exposure (estimated treatment ratio (geriatric/young) of 1.09 $[0.86; 1.38]_{95\%CI}$) and maximum insulin aspart concentrations (estimated treatment ratio (geriatric/young) of 1.06 $[0.88; 1.28]_{95\%CI}$) was comparable between young adult and geriatric patients. Therefore, total exposure and maximum concentrations of insulin apart are comparable across the age group studied.

***Body mass index***

The effect of BMI on the PK of insulin aspart following administration of Fiasp and NovoLog was assessed in a cross-trial analysis. Body mass index was used as a marker of fat layer thickness. The BMI range in patients with T1DM from the 3 studies was 18.9 to 28.7 $kg/m^2$ (median 24.2 $kg/m^2$) Lean, normal, and overweight was defined as having a BMI of 20 $kg/m^2$, BMI of 24 $kg/m^2$, and BMI of 28 $kg/m^2$, respectively. The effect of BMI category on insulin aspart exposure and $C_{max}$ for Fiasp and NovoLog are presented in Figure 19. In all BMI categories, a larger early insulin aspart exposure was evident for Fiasp when compared to NovoLog in the first 1 hr post-dose.

Comparable total insulin aspart exposure was observed for both treatments in all 3 BMI categories and comparable maximum concentrations were observed between the 2 treatments in normal and overweight patients. In lean patients (BMI 20 $kg/m^2$) the maximum concentrations were 17% higher for Fiasp when compared to NovoLog. A statistically significant interaction between treatment and BMI category for $C_{max}$ was observed where the difference between the 2 treatments decreased with increasing BMI category.

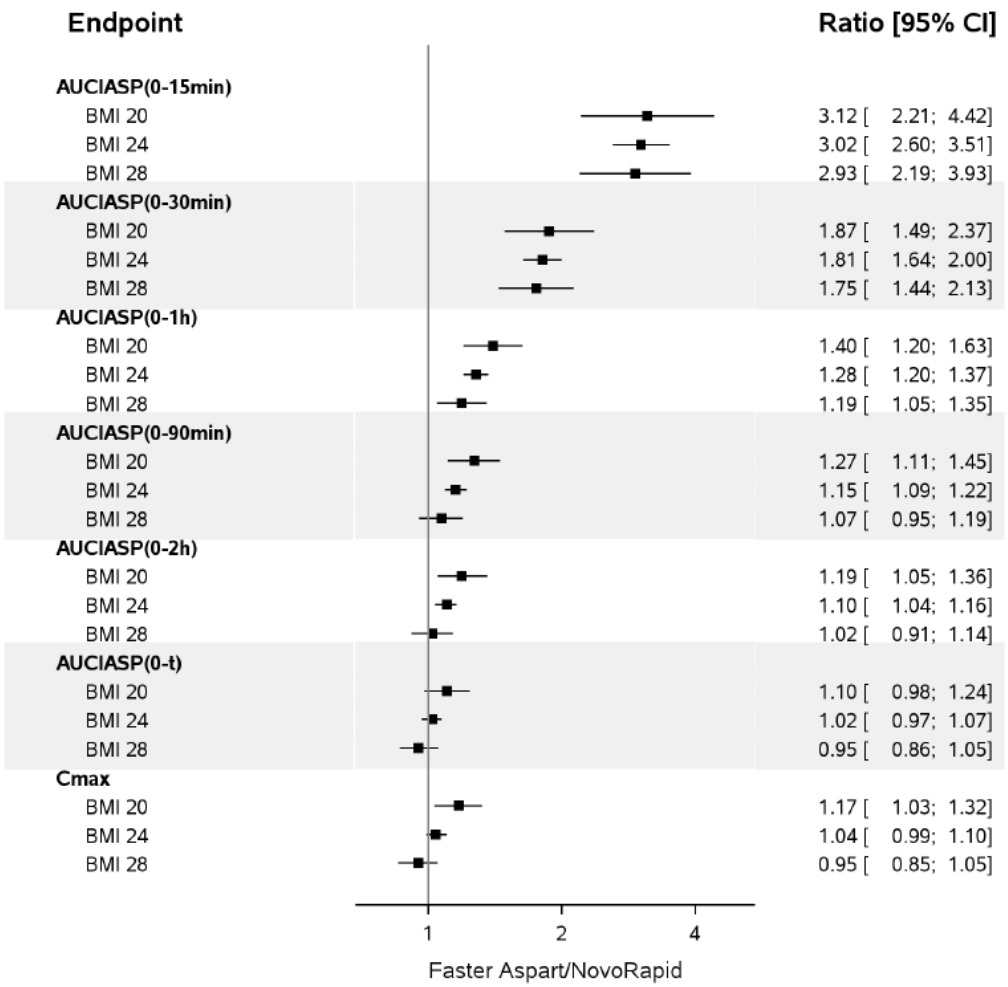



**Figure 19: Mean treatment ratios (95%CI)[1] for dose-adjusted insulin aspart exposure (early and total) and $C_{max}$ by BMI category in patients with T1DM following administration of Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog in the pooled analysis (Studies NN1218-3978, -3922, -3891 (young adult patients))**

[1]Endpoints were log-transformed and analyzed in a linear mixed model with treatment, period (trial), treatment*log(BMI) and treatment as fixed effects and subject as a random effect

t is the time of last observation

(Source: Summary of clinical pharmacology studies, page 94; Appendix 5.2, page 24)

Following administration of Fiasp, a higher dose-adjusted insulin aspart exposure ($AUC_{0\text{-}15min}$, $AUC_{0\text{-}30min}$, $AUC_{0\text{-}1hr}$) and dose-adjusted $C_{max}$ was observed with lower BMI (Table 9). The Applicant reports that no statistically significant difference for dose-adjusted total insulin aspart exposure ($AUC_{0\text{-}t}$) was observed across the BMI categories. The data suggests that overall total exposure of insulin aspart following administration of Fiasp is similar across the BMI categories, however higher early exposure and maximum concentrations of insulin aspart were observed with lower BMI category.

**Table 9: BMI ratio (95%CI)[1] for dose-adjusted insulin aspart exposure and $C_{max}$ by BMI category in patients with T1DM in the pooled analysis (Studies NN1218-3978, -3922, -3891 (young adult patients))**

| | BMI ratio for insulin aspart endpoints [95% CI] | | | |
|---|---|---|---|---|
| **Endpoint** | Faster aspart | | NovoRapid® | |
| **Dose-adjusted $AUC_{IAsp, 0\text{-}15\ min}$** | | | | |
| BMI 20/BMI 24 | 2.07 | [1.60;2.68] | 2.00 | [1.55;2.59] |
| BMI 20/BMI 28 | 3.84 | [2.39;6.17] | 3.61 | [2.25;5.79] |
| BMI 24/BMI 28 | 1.85 | [1.49;2.30] | 1.80 | [1.45;2.24] |
| **Dose-adjusted $AUC_{IAsp, 0\text{-}30\ min}$** | | | | |
| BMI 20/BMI 24 | 1.88 | [1.54;2.29] | 1.81 | [1.48;2.21] |
| BMI 20/BMI 28 | 3.19 | [2.21;4.61] | 2.99 | [2.07;4.31] |
| BMI 24/BMI 28 | 1.70 | [1.44;2.01] | 1.65 | [1.40;1.95] |
| **Dose-adjusted $AUC_{IAsp, 0\text{-}1\ hour}$** | | | | |
| BMI 20/BMI 24 | 1.67 | [1.43;1.96] | 1.53 | [1.31;1.80] |
| BMI 20/BMI 28 | 2.59 | [1.93;3.47] | 2.20 | [1.64;2.95] |
| BMI 24/BMI 28 | 1.55 | [1.35;1.77] | 1.44 | [1.26;1.64] |
| **Dose-adjusted $AUC_{IAsp, 0\text{-}t\ hours}$** | | | | |
| BMI 20/BMI 24 | 1.12 | [0.97;1.29] | 1.03 | [0.90;1.20] |
| BMI 20/BMI 28 | 1.23 | [0.94;1.61] | 1.06 | [0.82;1.39] |
| BMI 24/BMI 28 | 1.10 | [0.97;1.24] | 1.03 | [0.91;1.16] |
| **Dose-adjusted $C_{max,IAsp}$** | | | | |
| BMI 20/BMI 24 | 1.51 | [1.32;1.74] | 1.35 | [1.17;1.55] |
| BMI 20/BMI 28 | 2.15 | [1.66;2.78] | 1.74 | [1.34;2.25] |
| BMI 24/BMI 28 | 1.42 | [1.26;1.60] | 1.29 | [1.14;1.45] |

**Number of profiles:** Faster aspart = 113, NovoRapid® = 113. **Note:** NovoRapid® is known as NovoLog® in the U.S.

[1]Endpoints were log-transformed and analyzed in a linear mixed model with treatment, period (trial), treatment*log(BMI) and treatment as fixed effects and subject as a random effect

t is the time of last observation; Fiasp indicated as faster aspart in the Applicant's table above

(Source: Summary of clinical pharmacology studies, page 95; Appendix 5.2, page 24)

## Gender

The effect of gender on the PK of insulin aspart following administration of Fiasp and NovoLog was assessed in a cross-trial analysis. The effect of gender (male, female) on insulin aspart exposure and $C_{max}$ for Fiasp and NovoLog in patients with T1DM is presented in Figure 20. Both male and female patients had a greater early insulin aspart exposure (range for male: 1.08 to 3.05-fold higher; range for female: 1.12 to 2.94-fold higher) following administration of Fiasp when compared to NovoLog in the first 2 hr post-dose (when dosed per kg body weight). Total insulin aspart exposure and maximum insulin aspart concentrations were comparable between the 2 treatments in both male and female patients.

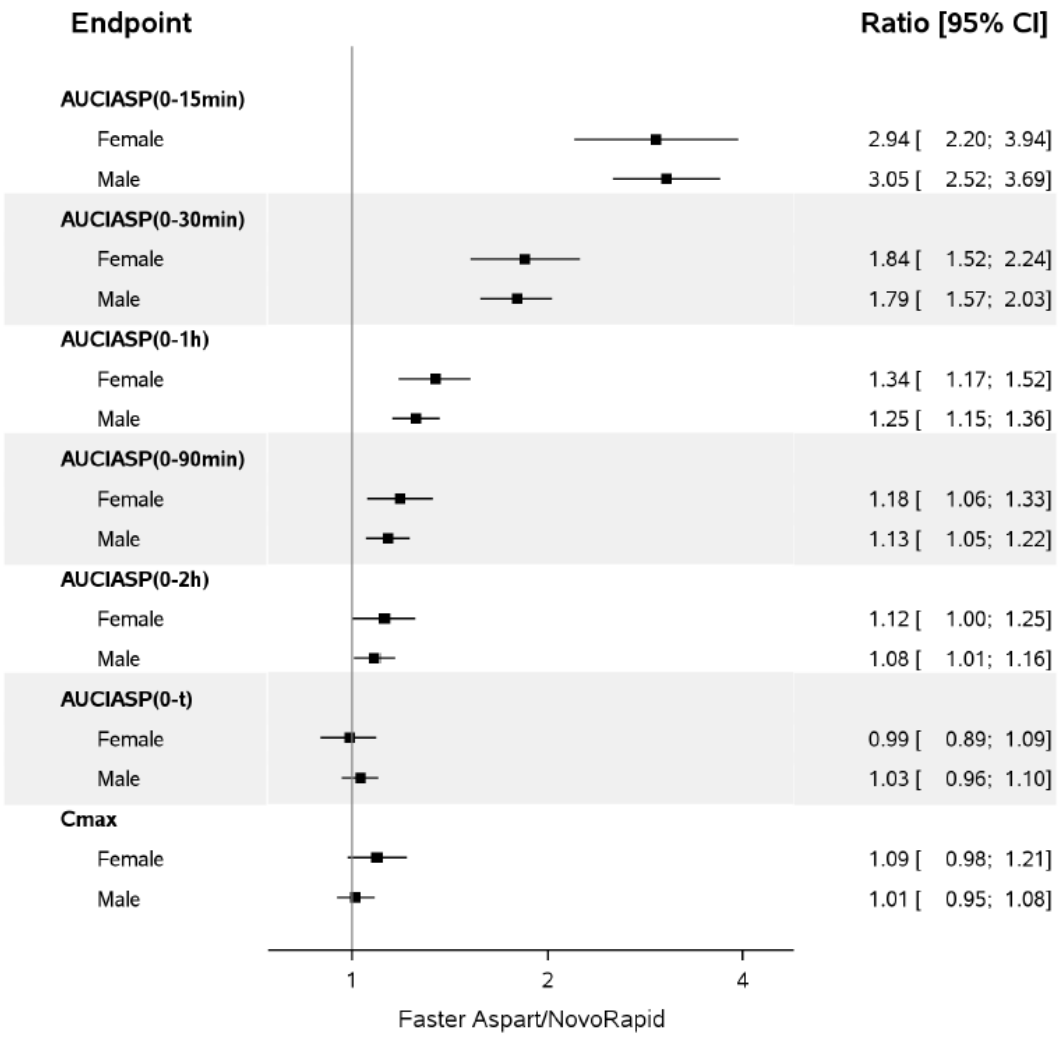



**Figure 20: Mean treatment ratios (95%CI)[1] for insulin aspart exposure (early and total) and $C_{max}$ by gender in patients with T1DM following administration of Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog in the pooled analysis (Studies NN1218-3978, -3922, -3891 (young adult patients)) (endpoints adjusted to 0.2 unit/kg, treatment ratios adjusted for body weight (75 kg))**

[1]Endpoints were log-transformed and analyzed in a linear mixed model with period (trial), treatment*dose, treatment*sex, bodyweight as fixed effects and subject as a random effect

t is the last observation time

(Source: Summary of clinical pharmacology studies, page 104; Appendix 5.2, page 27)

Following administration of Fiasp, the early insulin aspart exposure was approximately 3-20% lower in female patients when compared to male patients (Table 10). Total insulin aspart exposure and maximum insulin aspart concentrations were comparable between both genders for Fiasp. The data suggests that total insulin aspart exposure following administration of Fiasp was comparable in male and female patients with T1DM.

**Table 10: Sex differences and 95%CI[1] for insulin aspart exposure (early and total) and $C_{max}$ adjusted for body weight in patients with T1DM (Studies NN1218-3978, -3922, -3891 (young adult patients))**

| Endpoint | | Number of profiles | | Sex differences ratio (95 % CI) | |
|---|---|---|---|---|---|
| | | Female | Male | Female/Male | |
| $AUC_{IAsp,0\text{-}15\ min}$ | Faster aspart | 38 | 75 | 0.80 | [0.58;1.09] |
| | NovoRapid®/NovoLog® | 38 | 75 | 0.83 | [0.61;1.13] |
| $AUC_{IAsp,0\text{-}30\ min}$ | Faster aspart | 38 | 75 | 0.83 | [0.66;1.06] |
| | NovoRapid®/NovoLog® | 38 | 75 | 0.81 | [0.64;1.02] |
| $AUC_{IAsp,0\text{-}1\ hr}$ | Faster aspart | 38 | 75 | 0.91 | [0.75;1.09] |
| | NovoRapid®/NovoLog® | 38 | 75 | 0.85 | [0.70;1.02] |
| $AUC_{IAsp,0\text{-}90\ min}$ | Faster aspart | 38 | 75 | 0.95 | [0.80;1.12] |
| | NovoRapid®/NovoLog® | 38 | 75 | 0.91 | [0.76;1.07] |
| $AUC_{IAsp,0\text{-}2\ hr}$ | Faster aspart | 38 | 75 | 0.97 | [0.83;1.15] |
| | NovoRapid®/NovoLog® | 38 | 75 | 0.94 | [0.80;1.11] |
| $AUC_{IAsp,0\text{-}12\ hr}$ | Faster aspart | 38 | 75 | 1.00 | [0.84;1.20] |
| | NovoRapid®/NovoLog® | 38 | 75 | 1.05 | [0.88;1.25] |
| $C_{max,IAsp}$ | Faster aspart | 38 | 75 | 0.96 | [0.81;1.13] |
| | NovoRapid®/NovoLog® | 38 | 75 | 0.89 | [0.75;1.04] |

**Note:** NovoRapid® is known as NovoLog® in the U.S.

[1]Endpoints were log-transformed and analyzed in a linear mixed model with period (trial), treatment*dose, treatment*sex, bodyweight as fixed effects and subject as a random effect

Endpoints adjusted to 0.2 unit/kg, sex ratios adjusted for body weight (75 kg)

Fiasp indicated as faster aspart in the Applicant's table above

(Source: Summary of clinical pharmacology studies, page 105; Appendix 5.2, page 27)

### Anti-insulin aspart antibodies

In Phase 1 studies, the total level of anti-insulin aspart antibodies was determined prior to administration of Fiasp and NovoLog. The total insulin aspart antibody levels in Studies N1218-3978, NN1218-3922, and NN1218-3891 ranged from 0.27 to 66.94 %B/T (median: 7.68 %B/T). The impact of total anti-insulin aspart antibodies on the PK of insulin aspart was assessed in a cross-trial analysis using 3 fixed levels of total anti-insulin aspart antibodies based on the 25, 50, 75 percentile (6.0, 13.1, 24.6 %B/T, respectively) of anti-insulin aspart antibody levels observed in the Phase 3a study (NN1218-3852) after 26 weeks of treatment.

A larger early insulin aspart exposure was observed at all levels of total anti-insulin aspart antibodies following administration of Fiasp when compared to NovoLog in the first 1 hr post-dose (Table 11). Comparable total insulin aspart exposure was observed between the 2 treatments at all levels of total anti-insulin aspart antibodies. The Applicant reports that a slightly larger $C_{max}$ was observed for Fiasp when compared to NovoLog at the 75$^{th}$ percentile of total anti-insulin aspart antibodies.

**Table 11: Mean treatment ratio (95%CI)[1] for insulin aspart exposure and $C_{max}$ versus total anti-insulin aspart antibodies percentiles following administration of Fiasp (indicated as faster aspart in the Applicant's table below) and NovoLog in patients with T1DM (Studies NN1218-3978, -3922, -3891 (young adult patients))**

| Endpoint | | Treatment ratio (95 % CI) Faster aspart/NovoRapid® | |
|---|---|---|---|
| $AUC_{IAsp,0\text{-}30\ min}$ | AB 25th percentile | 1.76 | [1.58;1.97] |
| | AB 50th percentile | 1.84 | [1.66;2.04] |
| | AB 75thpercentile | 1.93 | [1.65;2.27] |
| $AUC_{IAsp,0\text{-}1h}$ | AB 25th percentile | 1.25 | [1.17;1.34] |
| | AB 50th percentile | 1.30 | [1.21;1.39] |
| | AB 75th percentile | 1.36 | [1.22;1.51] |
| $AUC_{IAsp,0\text{-}t}$ | AB 25th percentile | 1.01 | [0.95;1.06] |
| | AB 50th percentile | 1.02 | [0.97;1.08] |
| | AB 75th percentile | 1.05 | [0.96;1.13] |
| $C_{max,IAsp}$ | AB 25th percentile | 1.02 | [0.96;1.08] |
| | AB 50th percentile | 1.05 | [0.99;1.11] |
| | AB 75th percentile[a] | 1.09 | [1.00;1.19] |

[a]p=0.04. AB percentiles are based on the distribution in trial 3852.
**Number of profiles:** Faster aspart = 113, NovoRapid® = 113.
**Note:** NovoRapid® is known as NovoLog® in the U.S.

[1]Log-transformed endpoint was analyzed in a linear mixed model with treatment and period(trial) as fixed factors, log(body weight) and log(1+ab/13*) as covariates with treatment dependent slopes and subject(trial) as random effect

Endpoints adjusted to 0.2 unit/kg dose

t is the last observation time

(Source: Summary of clinical pharmacology studies, page 107; Appendix 5.2, page 39)

In the Phase 1 studies, a trend for increase in dose-adjusted total insulin aspart exposure with an increase in the level of total anti-insulin aspart antibodies was observed following administration of Fiasp and NovoLog as presented in Figure 21.

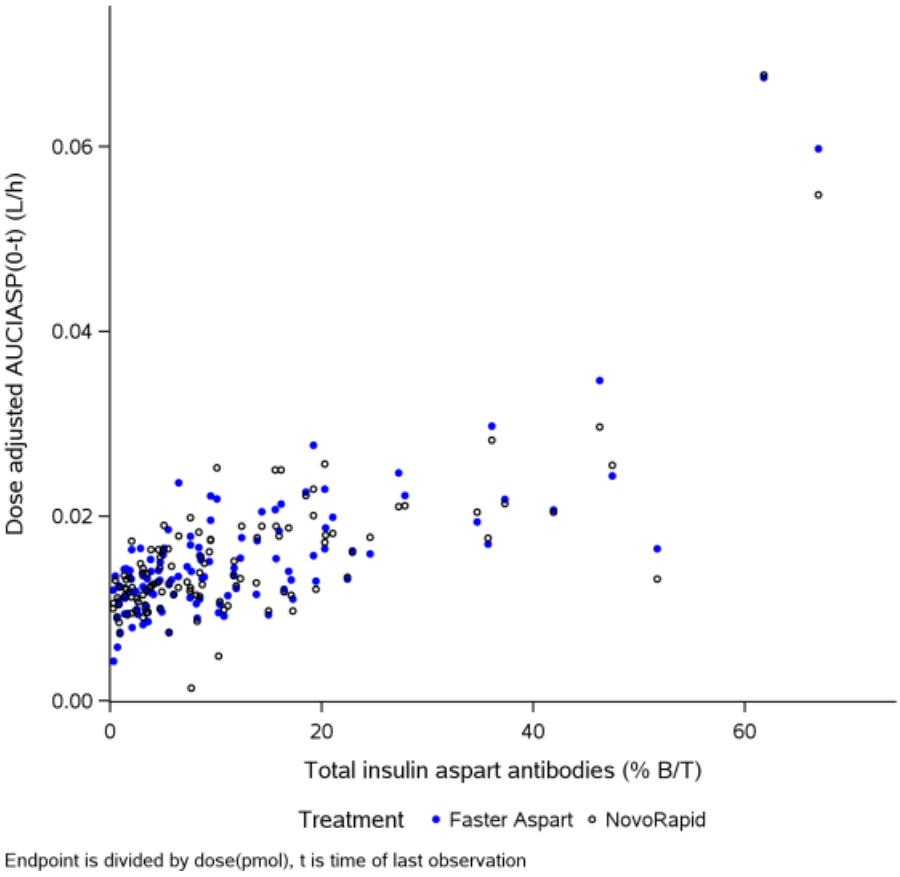



**Figure 21: Dose-adjusted total insulin aspart exposure versus total anti-insulin aspart antibodies following administration of Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog in patients with T1DM in the pooled analysis (adjusted to a dose of 0.2 unit/kg, Studies NN1218-3978, -3922, -3891 (young adult patients))**

(Source: Summary of clinical pharmacology studies, page 109)

**Pharmacodynamics**

The effect of age, BMI, gender, and anti-insulin aspart antibodies on the PD of insulin aspart following administration of Fiasp was assessed in a cross-trial analysis of data from Phase 1 studies (Studies NN1218-3978, NN1218-3891 (young adult patients), and NN1218-3887).

**Age**

Pharmacodynamic data from Study NN1218-3891 was used to assess the effect of age on the PD of insulin aspart following administration of a single dose of 0.2 unit/kg of Fiasp (not cross-trial analysis). Young adult patients (18-35 years) and geriatric patients (≥65 years) with T1DM was enrolled in the study.

As presented in Table 12, the total glucose lowering effect was comparable between the young adult patients and geriatric patients (estimated treatment ratio (geriatric/young adult) of 0.93 $[0.73; 1.17]_{95\%CI}$). The maximum glucose lowering effect was 15% lower in geriatric patients

when compared to young adult patients (estimated treatment ratio (geriatric/young) of 0.85 [0.66; 1.10]$_{95\%CI}$). The Applicant reports that this difference was not statistically significant. The Applicant concludes that the total and maximum glucose lowering effect of insulin aspart following administration of Fiasp was similar for young adult and geriatric patients.

**Table 12: Statistical analysis for total and maximum glucose lowering effect for Fiasp (indicated as faster aspart in the Applicant's table below) in young adult and geriatric patients**

| | N | Estimate | 95% CI |
|---|---|---|---|
| Primary endpoint: | | | |
| AUCGIR(0-12h) (mg/kg) | | | |
| LSMeans | | | |
| Faster Aspart : Geriatric | 21 | 1136.68 | |
| Faster Aspart : Younger | 22 | 1227.45 | |
| Age group/Treatment ratio | | | |
| Faster Aspart : Geriatric/Younger | | 0.93 | [0.73;1.17] |
| Secondary endpoint: | | | |
| GIRmax (mg/(kg*min)) | | | |
| LSMeans | | | |
| Faster Aspart : Geriatric | 21 | 5.55 | |
| Faster Aspart : Younger | 22 | 6.53 | |
| Age group/Treatment ratio | | | |
| Faster Aspart : Geriatric/Younger | | 0.85 | [0.66;1.10] |

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and residual variance depends on age group.

(Source: Study NN1218-3891, Clinical study report, page 86)

The Reviewer notes that for study NN1218-3891, 44 patients were planned to be randomized in the study of which 40 were to complete the study (20 young adult and 20 geriatric patients). However, a total of 23 patients were replaced due to technical issues with the ClampArt that may have affected the GIR data (identified during the blinded review of data). The PK of Fiasp in these replaced patients were only characterized using free insulin aspart concentrations, and therefore the PK of Fiasp based on insulin aspart concentrations (total insulin aspart) is missing.

The statistical analysis above (Table 12) was performed with 21 and 22 patients in the geriatric and young adult groups, respectively, however it is unclear to the Reviewer what proportion of these patients had PK characterized using insulin aspart concentrations (total insulin aspart). Therefore, the findings should be interpreted with this in mind. However, similar to historical findings (for other insulin products), the results from the present study shows similar glucose lowering effect for Fiasp in different age groups (young adult versus geriatric patients).

**Body mass index**

The effect of BMI on PD of Fiasp and NovoLog was assessed in a cross-trial analysis (Studies NN1218-3978, NN1218-3887, NN1218-3891 (younger adult patients) at the 0.2 unit/kg dose level).

As shown in Figure 22, a larger early glucose lowering effect was observed for Fiasp when compared to NovoLog within the first 2 hr post-dose across the BMI category. Total and maximum glucose lowering effect was comparable between the 2 treatments in all BMI categories.

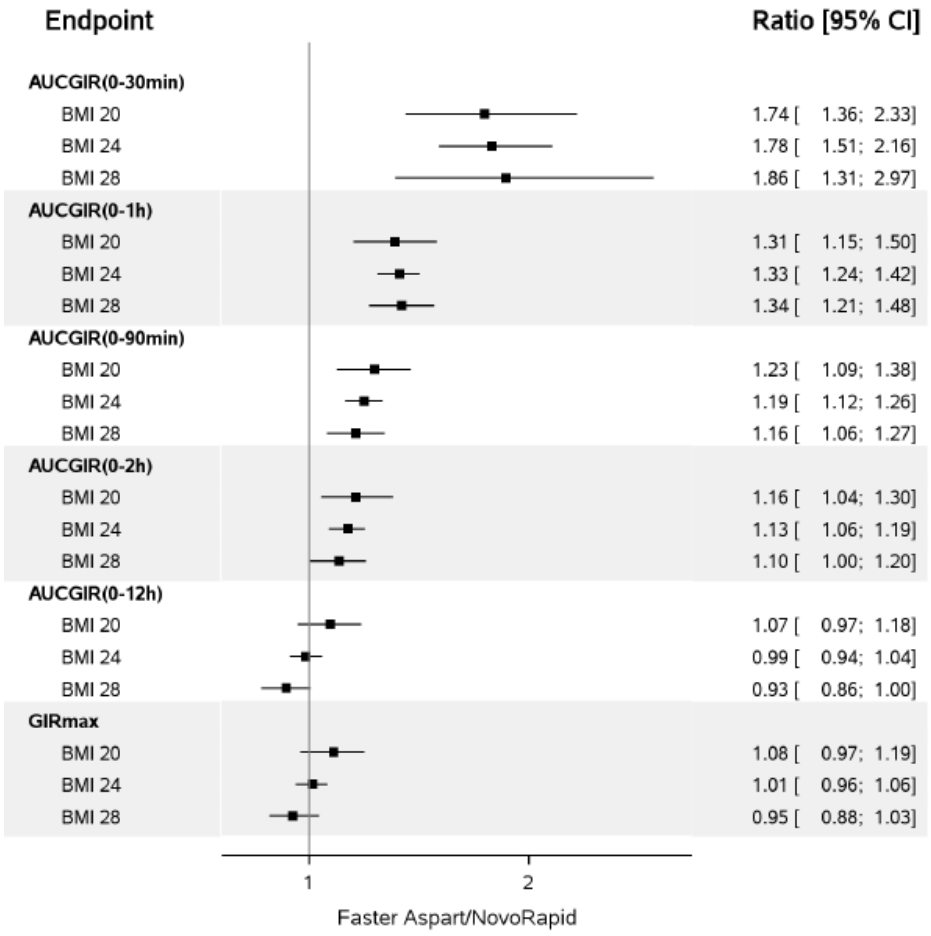



**Figure 22: Mean treatment ratios and 95%CI[1] for glucose lowering effect ($AUC_{GIR}$, $GIR_{max}$) by BMI category in patients with T1DM in the pooled analysis (Studies NN1218-3978, NN1218-3887, NN1218-3891 (younger adult patients))**

[1]Endpoints analyzed using a linear mixed model with period(trial), treatment*dose, treatment*BMI as fixed effects and subject as a random effect and dose-dependent residual variance (for $AUC_{GIR,0\text{-}30min}$). Endpoints was log-transformed and analyzed using a linear mixed model with treatment, period(trial), treatment*log(BMI) and treatment*dose-factor as fixed effects and subject as a random effect

(Source: Summary of clinical pharmacology studies, page 118; Appendix 5.2, page 51, 93-94)

Following administration of Fiasp, BMI had an effect on the PD of insulin aspart. As shown in Table 13, total glucose lowering effect ($AUC_{0\text{-}12hr}$) and maximum GIR decreased with increasing BMI category. The Applicant reports that this is in accordance to the well-known higher insulin resistance with increasing BMI.

**Table 13: BMI ratios and 95%CI[1] for glucose lowering effect ($AUC_{GIR}$, $GIR_{max}$) for Fiasp (indicated as faster aspart in the Applicant's table below) in patients with T1DM in the pooled analysis (Studies NN1218-3978, NN1218-3887, NN1218-3891 (younger adult patients))**

| | BMI ratio [95% CI] | | | |
|---|---|---|---|---|
| **Endpoint** | Faster aspart | | NovoRapid® | |
| **$AUC_{GIR,\ 0\text{-}30\ min}$** | | | | |
| BMI 20/BMI 24 | 1.24 | [1.10;1.38] | 1.28 | [1.03;1.53] |
| BMI 20/BMI 28 | 1.64 | [1.23;2.22] | 1.76 | [1.05;3.22] |
| BMI 24/BMI28 | 1.32 | [1.11;1.61] | 1.38 | [1.03;2.11] |
| **$AUC_{GIR,\ 0\text{-}1\ hour}$** | | | | |
| BMI 20/BMI 24 | 1.47 | [1.30;1.67] | 1.49 | [1.31;1.69] |
| BMI 20/BMI 28 | 2.04 | [1.61;2.58] | 2.09 | [1.65;2.64] |
| BMI 24/BMI28 | 1.39 | [1.25;1.54] | 1.40 | [1.26;1.56] |
| **$AUC_{GIR,\ 0\text{-}12\ hour}$** | | | | |
| BMI 20/BMI 24 | 1.14 | [1.04;1.25] | 1.05 | [0.96;1.16] |
| BMI 20/BMI 28 | 1.27 | [1.07;1.50] | 1.10 | [0.93;1.31] |
| BMI 24/BMI28 | 1.11 | [1.03;1.21] | 1.05 | [0.97;1.13] |
| **$GIR_{max}$** | | | | |
| BMI 20/BMI 24 | 1.32 | [1.19;1.46] | 1.23 | [1.12;1.36] |
| BMI 20/BMI 28 | 1.67 | [1.39;2.00] | 1.48 | [1.23;1.77] |
| BMI 24/BMI28 | 1.26 | [1.16;1.37] | 1.19 | [1.10;1.30] |

**Number of profiles:** Faster aspart = 253, NovoRapid® = 248. **Note:** NovoRapid® is known as NovoLog® in the U.S.

[1]Endpoints was log-transformed and analyzed using a linear mixed model with treatment, period(trial), treatment*log(BMI), and treatment*dose-factor as fixed effects and subject as a random effect (for $AUCGIR_{0\text{-}1hr}$, $AUCGIR_{0\text{-}12hr}$, $GIR_{max}$ endpoints)

(Source: Summary of clinical pharmacology studies, page 119; Appendix 5.2, page 93-94)

## Gender

The effect of gender (male, female) on the glucose lowering effect of Fiasp was assessed in a cross-trial analysis (at the 0.2 unit/kg dose level). Following administration of Fiasp, the total glucose lowering effect was 13% lower in females when compared to in males (estimated treatment ratio (female/male) of 0.87 $[0.76; 0.99]_{95\%CI}$) (Table 14). The maximum glucose lowering effect was 12% lower in females when compared to in males (estimated treatment ratio (female/male) of 0.88 $[0.75; 1.02]_{95\%CI}$). The Applicant concludes that the glucose lowering effect overall appeared to be similar between genders.

**Table 14: Gender ratios and 95%CI[1] for glucose lowering effect ($AUC_{GIR}$, $GIR_{max}$) for Fiasp (indicated as faster aspart in the Applicant's table below) in patients with T1DM in the pooled analysis (Studies NN1218-3978, NN1218-3887, NN1218-3891 (younger adult patients)**

| Endpoint | | Number of profiles | | Sex ratio (95 % CI) |
|---|---|---|---|---|
| | | Female | Male | Female/Male |
| $AUC_{GIR,0\text{-}30\ min}$ | Faster aspart | 61 | 192 | 1.08 [0.95;1.18] |
| | NovoRapid® | 49 | 199 | 0.79 [0.65;1.01] |
| $AUC_{GIR,0\text{-}1\ hr}$ | Faster aspart | 61 | 192 | 0.92 [0.76;1.12] |
| | NovoRapid® | 49 | 198 | 0.84 [0.69;1.02] |
| $AUC_{GIR,0\text{-}90\ min}$ | Faster aspart | 61 | 192 | 0.89 [0.74;1.09] |
| | NovoRapid® | 49 | 199 | 0.82 [0.67;1.00] |
| $AUC_{GIR,0\text{-}2\ hr}$ | Faster aspart | 61 | 192 | 0.89 [0.74;1.08] |
| | NovoRapid® | 49 | 199 | 0.81 [0.67;0.98] |
| $AUC_{GIR,0\text{-}12\ hr}$ | Faster aspart | 61 | 192 | 0.87 [0.76;0.99] |
| | NovoRapid® | 49 | 199 | 0.89 [0.78;1.02] |
| $GIR_{max}$ | Faster aspart | 61 | 192 | 0.88 [0.75;1.02] |
| | NovoRapid® | 49 | 199 | 0.85 [0.73;0.99] |

**Note:** NovoRapid® is known as NovoLog® in the U.S.

[1]Endpoints were log-transformed and analyzed in a linear mixed model with period(trial), treatment*dose, treatment*sex, bodyweight as fixed effects and subject as a random effect. Sex ratios adjusted for bodyweight (75kg)

(Source: Summary of clinical pharmacology studies, page 122; Appendix 5.2, page 93-94)

### Anti-insulin aspart antibodies

As shown in Table 15, a greater early glucose lowering effect (first hour post-dose) was observed for Fiasp when compared to NovoLog across all quartiles of total anti-insulin aspart antibodies. Total and maximum glucose lowering effect was overall similar for Fiasp and NovoLog across the total anti-insulin aspart antibody quartiles.

**Table 15: Mean treatment ratio and 95%CI[1] for glucose lowering effect ($AUC_{GIR}$, $GIR_{max}$) versus total anti-insulin aspart antibodies percentile in patients with T1DM in the pooled analysis (Studies NN1218-3978, NN1218-3887, NN1218-3891 (younger adult patients))**

| Endpoint | | Treatment ratio (95 % CI) Faster aspart/NovoRapid® | |
|---|---|---|---|
| $AUC_{GIR,0\text{-}1h}$ | AB 25th percentile | 1.30 | [1.21;1.40] |
| | AB 50th percentile | 1.33 | [1.24;1.42] |
| | AB 75thpercentile | 1.36 | [1.25;1.47] |
| $AUC_{GIR,0\text{-}12h}$ | AB 25th percentile | 0.97 | [0.92;1.03] |
| | AB 50th percentile | 0.99 | [0.94;1.04] |
| | AB 75th percentile | 1.00 | [0.94;1.07] |
| $GIR_{max}$ | AB 25th percentile | 0.98 | [0.93;1.04] |
| | AB 50th percentile | 1.01 | [0.96;1.06] |
| | AB 75th percentile | 1.04 | [0.98;1.10] |

**Number of profiles:** Faster aspart = 253, NovoRapid® = 248. **Abbreviation**: AB= antibody

[1]Log-transformed endpoint was analyzed in a linear mixed model with treatment, dose level and period(trial) as fixed factors, log(bodyweight) and log(1+ab/13) as covariates with treatment dependent slopes and subject(trial) as random effect

Fiasp indicated as faster aspart in the Applicant's table above

(Source: Summary of clinical pharmacology studies, page 123; Appendix 5.2, page 59)

Total glucose lowering effect versus total anti-insulin aspart antibodies for Fiasp and NovoLog is presented in Figure 23 and antibody ratios ($50^{th}/25^{th}$ percentile; $75^{th}/25^{th}$ percentile) for total and maximum glucose lowering effect for Fiasp and NovoLog are presented in Table 16. For Fiasp, total glucose lowering effect did not appear to be affected by the level of total anti-insulin aspart antibodies. The Applicant reports that maximum glucose lowering effect was slightly lower for the high total anti-insulin aspart antibody percentiles compared to the 25th percentile.

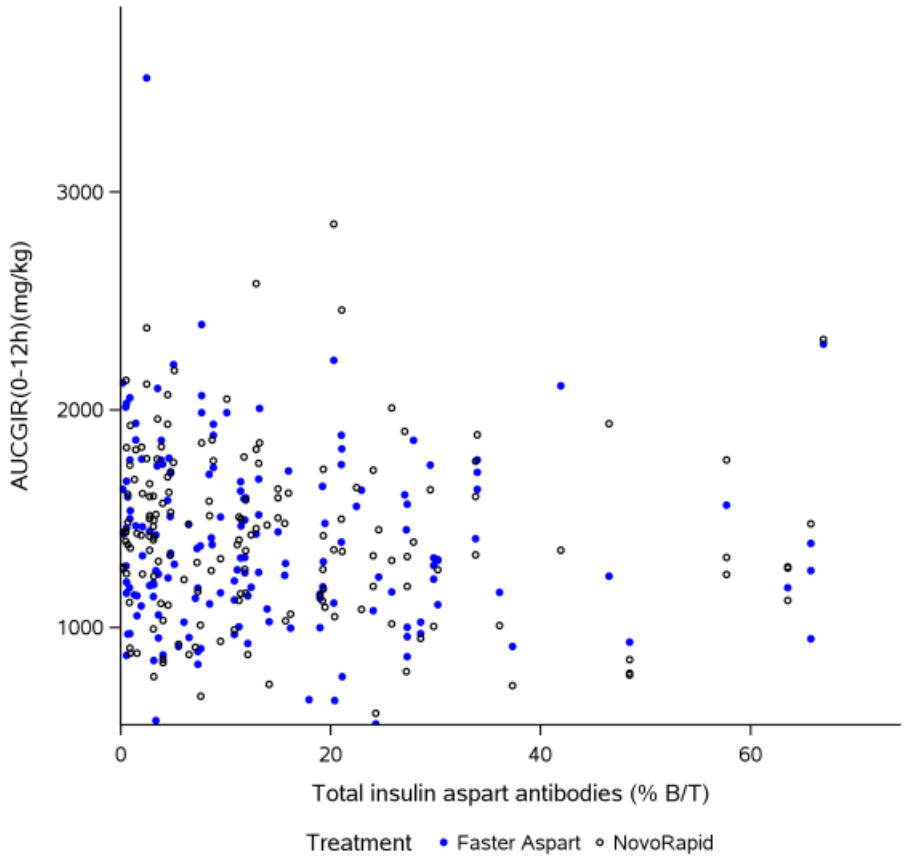



**Figure 23: Total glucose lowering effect versus total anti-insulin aspart antibodies for Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog in patients with T1DM in the pooled analysis (Studies NN1218-3978, NN1218-3887, NN1218-3891 (younger adult patients))**

(Source: Summary of clinical pharmacology studies, page 124)

**Table 16: Anti-insulin aspart antibody differences and 95%CI[1] for glucose lowering effect ($AUC_{GIR,0-12hr}$, $GIR_{max}$) versus total anti-insulin aspart antibody percentiles in patients with T1DM in the pooled analysis (Studies NN1218-3978, NN1218-3887, NN1218-3891 (younger adult patients))**

| Endpoint | | Total anti-insulin aspart antibody AB ratio (95 % CI) 50th/25th percentile | | Total anti-insulin aspart antibody AB ratio (95 % CI) 75th/25th percentile | |
|---|---|---|---|---|---|
| $AUC_{GIR,0-12h}$ | Faster aspart | 0.99 | [0.96;1.03] | 0.99 | [0.92;1.06] |
| | NovoRapid®/NovoLog® | 0.98 | [0.95;1.01] | 0.96 | [0.89;1.03] |
| $GIR_{max}$ | Faster aspart | 0.98 | [0.94;1.02] | 0.96 | [0.89;1.04] |
| | NovoRapid®/NovoLog® | 0.96 | [0.92;0.99] | 0.91 | [0.84;0.98] |

**Number of profiles:** Faster aspart = 253, NovoRapid® = 248. **Note:** NovoRapid® is known as NovoLog® in the U.S.
Abbreviation: AB=antibody.

[1]Log transformed endpoints analyzed in a linear mixed model with treatment, dose level and period(trial) as fixed effects, log(bodyweight) and log(1+ab/13) as covariates with treatment dependent slopes and subject(trial) as random effect

(Source: Summary of clinical pharmacology studies, page 125; Appendix 5.2, page 59)

### 3.2.7 What is the effect of extrinsic factors on the pharmacokinetics of insulin aspart following administration of Fiasp?

The effect of SC administration of Fiasp at different injection sites (abdomen, deltoid region, and thigh) on the PK of insulin aspart was assessed in healthy subjects in Study NN218-3949 (refer to Appendix 5.1 for description of the study).

Mean serum concentration-time profile of insulin aspart following administration of Fiasp via SC injection in the abdomen, deltoid (upper arm), and thigh in healthy subjects is presented in Figure 24. Of note, insulin aspart serum concentrations were below the LLOQ after 8 hr post-dose, however $AUC_{0-12hr}$ was estimated since this was a pre-specified PK endpoint.

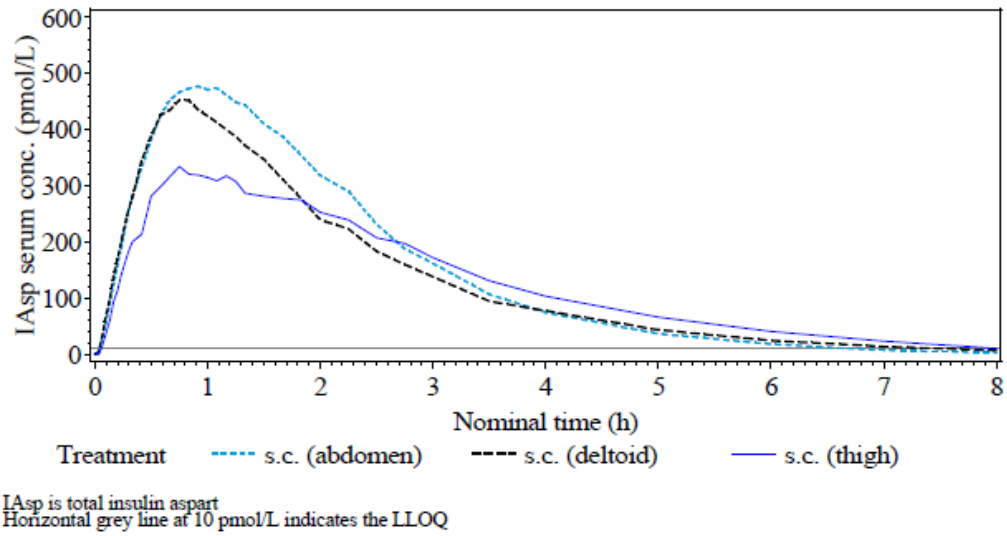



**Figure 24: Mean serum concentration-time profile stratified by SC injection sites following administration of 0.2 unit/kg Fiasp in healthy subjects**

(Source: Study NN1218-3949, Clinical study report_addendum, page 13)

Total exposure of insulin aspart ($AUC_{0\text{-}12\ hr,}$ primary PK endpoint) following SC administration of Fiasp in the abdomen, deltoid, and thigh was within the same range: estimated treatment ratio of 0.90 $[0.83; 0.98]_{95\%CI}$ for deltoid/abdomen, 0.89 $[0.82; 0.95]_{95\%\ CI}$ for thigh/abdomen and 0.98 $[0.90; 1.07]_{95\%CI}$ for thigh/deltoid.

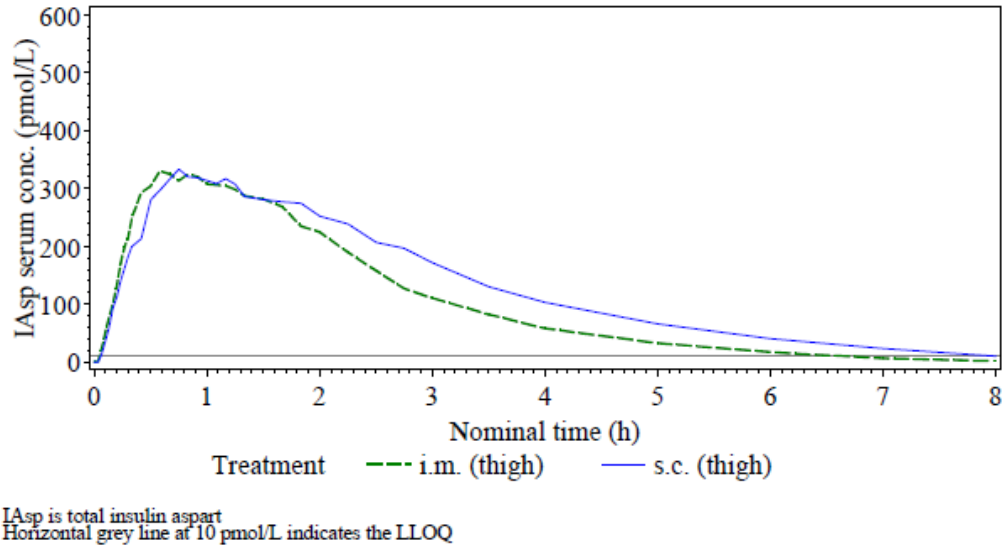
Comparable maximum concentrations of insulin aspart was observed following SC administration of Fiasp in the deltoid and abdomen (estimated treatment ratio (deltoid/abdomen) of 0.95 $[0.79; 1.15]_{95\%CI}$, p=0.608). Statistically significant lower $C_{max}$ was observed following SC administration in the thigh when compared to abdomen (estimated treatment ratio (thigh/abdomen) of 0.71 $[0.58; 0.87]_{95\%CI}$, p=0.001) and deltoid (estimated treatment ratio (thigh/deltoid) of 0.74 $[0.61; 0.91]_{95\%CI}$, p=0.004). Time to maximum concentrations of insulin aspart was overall comparable for the 3 different SC injection sites (range (medium): 50 to 62.5 min)).

The absolute bioavailability (BA) of insulin aspart following SC administration of 0.2 unit/kg Fiasp in the abdomen, deltoid, and thigh was 85%, 76%, and 75%, respectively (estimated treatment ratio of 0.85 $[0.75; 0.96]_{95\%CI}$ for abdomen/IV, 0.76 $[0.67; 0.87]_{95\%CI}$ for deltoid/IV, and 0.75 $[0.66; 0.85]_{95\%CI}$ for thigh/IV).

Following IV administration of 0.02 unit/kg Fiasp in healthy subjects, the geometric mean clearance, volume of distribution, elimination half-life was 0.90 (L/hr)/kg, 0.15 L/kg, and 7.16 min, respectively.

*SC versus IM injection (thigh)*

The PK of Fiasp following SC administration when compared to intramuscular (IM) administration in the thigh was also investigated in Study NN1218-3949. Since lean patients may unintentionally inject via the IM route instead of the SC route, the PK of Fiasp administered via the IM route was assessed. Mean serum concentration-time profile of insulin aspart following administration of Fiasp via SC and IM route (thigh) in healthy subjects is presented in Figure 25. Of note, insulin aspart serum concentrations were below the LLOQ after 8 hr post-dose, however $AUC_{0\text{-}12hr}$ was estimated since this was a pre-specified PK endpoint.




IAsp is total insulin aspart
Horizontal grey line at 10 pmol/L indicates the LLOQ

**Figure 25: Mean serum concentration-time profile following administration of 0.2 unit/kg Fiasp via the SC (thigh) and IM (thigh) route in healthy subjects**

(Source: Study NN1218-3949, Clinical study report_addendum, page 18)

The total exposure of insulin aspart ($AUC_{0\text{-}12\ hr}$) following IM administration (thigh) of Fiasp was statistically significantly lower when compared to administration via the SC route (thigh) (estimated treatment ratio (IM/SC) of 0.77 $[0.68; 0.89]_{95\%CI}$, $p<0.001$). Maximum concentration of insulin aspart were comparable following administration of Fiasp via the IM and SC route (estimated treatment ratio (IM/SC) of 1.01 $[0.82; 1.25]_{95\%CI}$). Time to maximum concentrations of insulin aspart was shorter following IM injection (45 min) compared to SC injection (62.5 min) in the thigh.

The absolute bioavailability of insulin aspart following IM administration of 0.2 unit/kg Fiasp in the thigh was 58% (estimated treatment ratio (IM-thigh/IV) of 0.58 $[0.50; 0.68]_{95\%CI}$).

### 3.2.8 Summary of Bioanalytical Method Validation

#### 3.2.8.1 Is the bioanalytical method for quantification of insulin aspart in human serum appropriately validated?

The Applicant has developed and validated a bioanalytical method for quantification of total insulin aspart (referred to as insulin aspart) in human serum. Concentration of insulin aspart in human serum was quantified using a validated specific sandwich enzyme-linked immunosorbent assay (ELISA). The bioanalytical method was validated for quantification of insulin aspart in human serum over a concentration range of 10 – 400 pM. Calibration curve fitting was done by non-linear regression using the 4 parameter logistic function with $1/Y^2$ weighting. In brief, the analytical method was as follows:

> A monoclonal specific antibody for insulin aspart (HUI-018) is coated onto a microplate used as capture antibody. Subsequent to removing excess capture antibody, the microplate wells are blocked by using blocking buffer. Standards, QC samples and unknown samples in human serum are added to the appropriate wells of the coated microplate. This is followed by the addition of a biotinylated antibody specific for insulin aspart (X14-6 F34 –Biotin). During an overnight incubation period, insulin aspart in the samples is captured by the immobilized capture antibody and in parallel binds the biotinylated antibody. Unbound materials are removed subsequently by a wash step followed by the addition of a horseradish peroxidase avidin D (HRP) conjugate. The avidin D HRP conjugate binds to the biotin on the bound antibody. Following an incubation period and a wash step, tetramethylbenzidine (TMB) solution is added to the wells, creating a colorimetric signal that is proportional to the amount of insulin aspart bound in the plate. Colour development is stopped using 2N sulfuric acid and the intensity of the colour (optical density (OD)) is measured at 450 nm - 620 nm using a plate reader.

(Source: Validation of an enzyme-linked immunosorbent assay (ELISA) method for the determination of insulin aspart in human serum, Study number: AA81208, page 12-13)

The ELISA method was validated (full validation, cross-site validation, and partial validation) as described below.

> The ELISA used for analysing trial samples for insulin aspart in human serum was originally developed and validated at Novo Nordisk A/S (M 5.3.1.4, Study 970046) as part of the development of NovoRapid®/NovoLog®. A full validation of the assay was performed at (b) (4) (b) (4) (M 5.3.1.4, Study AA81208). After a change in ownership, (b) (4) (b) (4) Therefore, the assay was validated at (b) (4) M 5.3.1.4, Study ZZ32463-01) and a cross-site validation between (b) (4) was performed (M 5.3.1.4, Study ZZ29614). All sample analysis in the clinical program for faster aspart was performed at (b) (4) Minor partial validations have been performed in order to cover an automated version of the assay (M 5.3.1.4, Study ZZ36951 and ZZ41765), optimisation of plate coating (M 5.3.1.4, Study ZZ33712 and ZZ36951), extended stability (M 5.3.1.4, Study CA20958), specificity (cross-reactivity and interference) (M 5.3.1.4, Study CA21882) and parallelism (M 5.3.1.4, Study CA21883).

(Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods, page 8)

The ELISA method was found to be sensitive, precise, accurate, and selective for quantification of insulin aspart in human serum. The Applicant reports that assessment for recovery was not performed since no sample processing or extraction step was utilized when analyzing human serum samples in the ELISA method. The method was validated in accordance to appropriate regulatory guidances. A summary of the validation assessments for the ELISA method for each validation study is provided below.

*Study Number AA81208*

| | | | |
|---|---|---|---|
| Analyte | | Insulin Aspart | |
| Matrix | | Human Serum | |
| SOP Number | | IA-S-4383-01, IA-S-4383-02, IA-S-4383-03, IA-S-4383-04, and IA-S-4383-05 | |
| Assay Method | | Enzyme-Linked Immunosorbent Assay (ELISA) | |
| Assay Volume Required per Assay | | 2 x 25µL | |
| Validated Range | | 10.0 – 400 pM | |
| Regression Type | | Four-Parameter Logistic (4-PL) Weighted $1/Y^2$ | |
| LLOQ Validation Samples | | Precision (%) | Accuracy (%) |
| Inter-batch | | 1.2 | -3.0 |
| Intra-batch | | 3.8 | N/AP |
| ULOQ Validation Samples | | Precision (%) | Accuracy (%) |
| Inter-batch | | 8.0 | -1.3 |
| Intra-batch | | 4.1 | N/AP |
| Quality Control Samples | | Precision (%) | Accuracy (%) |
| Inter-batch | Low | 2.5 | -3.3 |
| | Medium | 2.6 | 3.5 |
| | High | 5.5 | 0.0 |
| Intra-batch | Low | 3.8 | N/AP |
| | Medium | 4.0 | N/AP |
| | High | 5.1 | N/AP |
| Dilution Integrity | | 500-fold (inferred up to 2000-fold) | |
| Short-Term Stability | | 25 hours and 06 minutes at ambient temperature | |
| Freeze and Thaw Stability | | 5 cycles at -20°C | |
| | | 5 cycles at -80°C | |

| | |
|---|---|
| Long-Term Stability | 44 days at -20°C<br>92 days at -20°C<br>128 days at -20°C<br>155 days at -20°C<br><br>29 days at -80°C<br>77 days at -80°C<br>113 days at -80°C<br>140 days at -80°C |
| Stock Solution Stability | 111 days in human serum at -20°C |

- Reported precision and accuracy for QC levels (LLOQ, low, medium, high, ULOQ) for intra-batch and inter-batch runs in the above table is based on ANOVA analysis summary
- The intra-batch and inter-batch precision and accuracy for LLOQ, low, medium, high, and ULOQ QC levels are as follows:
  - QC Intra-batch (n=6 runs) precision range (%CV): 0.3% to 8.8%
  - QC Intra-batch (n=6 runs) accuracy range (%bias): -9.5% to 12.8%
  - QC Inter-batch precision range (%CV): 3.9% to 8.5%
  - QC Inter-batch accuracy range (%bias): -3.3% to 3.5%
- Dilution integrity: QC samples with concentrations greater than the ULOQ were diluted into the range of the calibration curve
- Hemolysis ≤4%: No effect on the quantification of insulin aspart
- Turbidity: No effect on the quantification of insulin aspart
- Selectivity (10 lots) in human serum and T1DM human serum: No significant matrix effect on the selectivity was observed in human serum and T1DM human serum.
- Selectivity (10 lots) in T2DM human serum and Japanese T1DM human serum: A significant matrix effect on the selectivity was observed in T2DM human serum and Japanese T1DM human serum.

N/AP: not applicable

(Source: Validation of an enzyme-linked immunosorbent assay (ELISA) method for the determination of insulin aspart in human serum, Study number: AA81208, page 10-11)

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| Information Requested | Data |
|---|---|
| **Validation Summary** | (b) (4) Validation Study ZZ32463-01 |
| **Analyte** | Insulin Aspart |
| **Method Description** | Direct analysis using enzyme linked immunosorbent assay (ELISA) |
| **Limit of Quantitation (pM)** | 10.0 pM |
| **Limit of Quantitation Japanese Type I Diabetes Mellitus Populations (pM)** | 20.0 pM |
| **Standard Curve Concentrations (pM)** | 10.0, 20.0, 40.0, 80.0, 120, 180, 220, 310, and 400 pM |
| **QC Concentrations (pM)** | LLOQ QC, 30.0, 170, 300, and ULOQ QC pM |
| **QC Intra-Batch Precision Range (% CV)** | 0.4 to 14.2% |
| **QC Intra-Batch Accuracy Range (% Bias)** | -24.8 to 9.3% |
| **QC Inter-Batch Precision Range (% CV)** | 3.8 to 11.0% |
| **QC Inter-Batch Accuracy Range (% Bias)** | -7.1 to 3.0% |
| **Bench-Top Stability (Hrs)** | Short-Term Stability: 25 hours, 6 minutes at ambient temperature |
| **Stock Stability (Days)** | Long-Term Stability for Stock Solutions (Stock): 111 days between 4000 and 20,000 pM in human serum at -20°C[1] |
| **Freeze-Thaw Stability (Cycles)** | 5 freeze (-20°C)-thaw (ambient temperature) cycles<br>5 freeze (-80°C)-thaw (ambient temperature) cycles |
| **Long-Term Storage Stability (Days)** | Long-Term Stability: 155 days at -20°C and 140 days at -80°C |
| **Dilution Integrity** | up to 5000 pM, diluted up to 40-fold |
| **Selectivity** | None of the 10 lots tested had detectable levels of insulin aspart |

[1] Stock solution was also subjected to 2 freeze (-20°C) and thaw (ambient temperature) and 4 hours, 31 minutes (cumulative) short term stability at ambient temperature.

| Additional Information | | | |
|---|---|---|---|
| Matrix | | Human Serum | |
| Bioanalytical Method (BAM) SOP Number | | BAM SOP ZZ32463-01 | |
| Test System | | Molecular Devices SpectraMax® 340PC$^{384}$ colorimetric plate reader | |
| Assay Volume Required | | 0.0250 mL | |
| Regression Type | | 4PL, 1/Y | |
| Quality Control Samples | | Precision (% CV) | Accuracy (% Bias) |
| Inter-Batch | LLOQ | 11.0 | -7.1 |
| | Low | 4.3 | 3.0 |
| | Medium | 3.8 | -3.5 |
| | High | 4.6 | -2.7 |
| | ULOQ | 5.0 | -0.8 |
| Intra-Batch (Batch 7)<br>Aliquot Method: Manual<br>Extraction Method: Manual | LLOQ | 1.5 | 2.0 |
| | Low | 1.3 | 3.0 |
| | Medium | 1.4 | 0.6 |
| | High | 1.0 | 1.3 |
| | ULOQ | 1.4 | -2.0 |
| Intra-Batch (Batch 5)<br>Aliquot Method: Manual<br>Extraction Method: Manual | LLOQ | 0.9 | -2.8 |
| | Low | 1.0 | -0.3 |
| | Medium | 0.4 | -3.5 |
| | High | 3.3 | -4.7 |
| | ULOQ | 2.0 | -2.5 |
| Intra-Batch (Batch 6)<br>Aliquot Method: Manual<br>Extraction Method: Manual | LLOQ | 4.8 | -14.4 |
| | Low | 1.3 | -2.0 |
| | Medium | 1.5 | -6.5 |
| | High | 3.3 | -5.0 |
| | ULOQ | 2.4 | -2.5 |
| Intra-Batch (Batch 8)<br>Aliquot Method: Manual<br>Extraction Method: Manual | LLOQ | 3.9 | -9.2 |
| | Low | 1.2 | -1.7 |
| | Medium | 2.3 | -7.6 |
| | High | 3.1 | -6.7 |
| | ULOQ | 1.5 | -5.3 |
| Intra-Batch (Batch 9)<br>Aliquot Method: Manual<br>Extraction Method: Manual | LLOQ | 3.6 | 1.0 |
| | Low | 1.0 | 4.3 |
| | Medium | 0.7 | 0.6 |
| | High | 2.1 | 4.0 |
| | ULOQ | 3.0 | 3.8 |
| Intra-Batch (Batch 10)*<br>Aliquot Method: Manual<br>Extraction Method: Manual | LLOQ | 14.2 | -24.8 |
| | Low | 2.9 | 9.3 |
| | Medium | 1.3 | -7.6 |
| | High | 2.6 | -1.7 |
| | ULOQ | 0.9 | 8.3 |

| | | | |
|---|---|---|---|
| **Intra-Batch (Batch 13)**<br>**Aliquot Method: Manual**<br>**Extraction Method: Manual** | **LLOQ**<br>**Low**<br>**Medium**<br>**High**<br>**ULOQ** | 4.8<br>2.2<br>3.6<br>5.3<br>2.7 | -1.8<br>7.3<br>-2.4<br>-5.0<br>-4.8 |
| **Matrix Effect** | | No significant matrix effect was observed in 19 of the 20 human serum lots that were fortified at the concentration of the LLOQ (10.0 pM) and at the concentration of the high QC (300 pM) sample | |
| **Hemolyzed Sample Integrity** | | Hemolysis below or equal to 4% has no effect on the accurate measurement of the analyte | |
| **Turbid Sample Integrity** | | No significant interference for insulin aspart was observed in any of the 3 turbid human serum lots that were fortified at the concentration of the low QC (30.0 pM) and at the concentration of the high QC (300 pM) sample | |
| **Long-Term Stability for Stock Solutions (Substock)** | | 23 days at 10.0 pM in citrate buffer in a polypropylene container at -20°C | |
| **Short-Term Stability for Stock Solutions (Substock)** | | 6 hours at 10,000 pM in citrate buffer in a polypropylene container at ambient temperature under white light<br>6 hours at 10.0 pM in citrate buffer in a polypropylene container at ambient temperature under white light | |
| **Stability of Analyte During Sample Collections and Handling** | | up to 120 minutes in human whole blood in polypropylene tubes at ambient temperature under white light | |
| **Batch Size** | | 1, 96 well plate | |
| **Coated and Blocked Plate Stability** | | 8 days | |

* = Batch fails intra-day PA, but passes batch acceptance criteria

- Dilution integrity: QC samples with concentrations greater than the ULOQ were diluted into the range of the calibration curve
- Matrix effect in Japanese T1DM human serum (10 lots): Accurate quantification of insulin aspart (10, 20, 300 pM) in Japanese T1DM human serum was demonstrated. In an initial run, acceptance criteria was not met at the LLOQ level (10 pM), however in a subsequent run acceptance criteria was met at the LLOQ level. Based on this evaluation the Applicant reports that the accuracy of quantification of insulin aspart down to 10 pM in Japanese T1DM human serum has been demonstrated.

- 1/Y 4PL regression model was used rather than $1/Y^2$ 4PL. The Applicant reports that this deviation has no impact in that the validation meets all acceptance criteria and any future batch assayed using this method will use the 1/Y regression model
- QC Intra-batch accuracy range of -24.8% is for the LLOQ level

(Source: Validation of an enzyme-linked immunosorbent assay (ELISA) method for the determination of insulin aspart in human serum, Study number: ZZ32463-01, page 10-12)

*Study Number ZZ29614 Cross-Site Validation*

| | | |
|---|---|---|
| Analyte | Insulin Aspart | |
| Matrix | Human Serum | |
| SOP Number | IA-S-4383-04 (SM3-309A to be issued) | |
| Assay Method | Enzyme-Linked Immunosorbent Assay (ELISA) | |
| Assay Volume Required per Assay | 50 µL | |
| Validated Range | 10.0 – 400 pM | |
| Regression Type | Four-Parameter Logistic (4-PL) Weighted $1/Y^2$ | |
| | | |
| LLOQ QC | Precision (% CV) | Accuracy (% Bias) |
| Inter-run | 4.7 | -4.6 |
| Intra-run | 5.0 | N/AP |
| Inter-site variation | 8.6 | N/AP |
| | | |
| Low QC | Precision (% CV) | Accuracy (% Bias) |
| Inter-run | 2.4 | -1.0 |
| Intra-run | 1.7 | N/AP |
| Inter-site variation | 0.1 | N/AP |
| | | |
| Medium QC | Precision (% CV) | Accuracy (% Bias) |
| Inter-run | 2.6 | -0.1 |
| Intra-run | 2.4 | N/AP |
| Inter-site variation | 5.1 | N/AP |
| | | |
| High QC | Precision (% CV) | Accuracy (% Bias) |
| Inter-run | 1.2 | -1.8 |
| Intra-run | 2.8 | N/AP |
| Inter-site variation | 7.4 | N/AP |
| | | |
| ULOQ QC | Precision (% CV) | Accuracy (% Bias) |
| Inter-run | 3.4 | -1.4 |
| Intra-run | 1.2 | N/AP |
| Inter-site variation | 9.8 | N/AP |
| | | |
| Dilution Integrity | 1000-fold | |
| | | |
| Hook Effect | No hook effect was observed until 40000 pM | |
| | | |
| Plate Stability | 22 days | |

- Reported precision and accuracy for QC levels (LLOQ, low, medium, high, ULOQ) for intra-batch and inter-batch runs in the above table is based on ANOVA analysis summary (n= 3 validation runs)
- Dilution integrity: QC sample with concentrations greater than the ULOQ were diluted into the range of the calibration curve
- Selectivity in human serum (6 lots): No significant matrix effect on the selectivity was observed in human serum
- Selectivity in T2DM human serum (10 lots): Selectivity was demonstrated in T2DM human serum

N/AP: not applicable

(Source: Cross-site validation of an ELISA method for the determination of insulin aspart in human serum, Study number: ZZ29614, page 11)

*Study Number ZZ33712: Partial validation for a simplified plate coating procedure without stabilizer and prolonged storage of coated and blocked plates*

| *Validation Parameter* | | *Description/Validated Value* | | |
|---|---|---|---|---|
| Analyte | | Insulin Aspart | | |
| Matrix | | Human Serum | | |
| Method SOP Number | | SOP SM3-309 | | |
| Assay Method | | ELISA | | |
| Sample Volume Required per Assay | | 50 µL (for duplicate determination) | | |
| Regression Type | | 4 parameter logistic curve fitting (weighting factor $1/y^2$) | | |
| Analytical Range | | 10 - 400 pM | | |
| Precision and Accuracy for Quality Control samples (ANOVA) | | *Inter-run %Bias* | *Inter-run precision (%CV)* | *Intra-run precision (%CV)* |
| 4 valid P&A runs | LLOQ QC (10 pM) | 0.5 | 1.7 | 6.8 |
| | Low QC (30 pM) | 0.1 | 2.5 | 2.3 |
| | Medium QC (170 pM) | 1.5 | 0.0 | 3.7 |
| | High QC (300 pM) | -1.7 | 2.6 | 2.3 |
| | ULOQ QC (400 pM) | -1.8 | 0.9 | 3.3 |
| Alternative coating & blocking procedure | | Coating at 24°C (19-23 hours) and blocking at 24°C for 65±5 min | | |
| Plate Homogeneity & stability | | criteria met (details see text), coated & blocked plates stable for up to 14 days at 5°C | | |

- Reported precision and accuracy for QC levels (LLOQ, low, medium, high, ULOQ) for intra-run (plates stored: Day 0, 2, 8, 14) and inter-run in the above table is based on ANOVA analysis summary (n= 4 runs)
- The intra-batch (plates stored: Day 0, 2, 8, 14) and inter-batch precision and accuracy for LLOQ, low, medium, high, and ULOQ QC levels are as follows:
  - QC Intra-batch (n=4 runs) precision range (%CV): 0.9% to 13.1%
  - QC Intra-batch (n=4 runs) accuracy range (%bias): -4.9% to 4.8%
  - QC Inter-batch precision range (%CV): 3.2% to 7.0%
  - QC Inter-batch accuracy range (%bias): -1.8% to 1.5%

(Source: Partial validation of an existing ELISA method for the determination of insulin aspart in human serum – simplification of plate coating, Study number: ZZ33712, page 10)

*Study Number ZZ36951[1]: Partial validation for qualification of specific automation steps done by pipetting robot (Genesis RSP 200, Tecan) and extension of coating procedure*

| *Parameter* | *(total) Insulin Aspart* |
|---|---|
| Matrix | Human Serum |
| Method SOP Number | SOP SM3-309 |
| Sample Volume | 2x25 µL (duplicate determination) |
| Regression Type | 4 parameter logistic curve fitting (weighting factor $1/y^2$) |
| Analytical Range | 10 - 400 pM |
| **Automation** | |
| Automated step | Sample dilution,<br>Sample transfer,<br>addition of detection antibody |
| Dilution | Dilution factor 3 and 5<br>(for maximum diluted concentration refer to study ZZ29614) |
| Precision and accuracy at 5 QC levels, including sensitivity | Acceptance criteria met |
| Precipitation control | Not applicable |
| Selectivity | 10 Individual blanks, criteria met |
| Cross-contamination | Adjacent blank/high samples processed, criteria met |
| Minimum required sample volume at Tecan | 100µL |
| **Plate coating, blocking, drying** | |
| Concentration of coating reagent | 4 µg/mL of HUI-018 (2, 4, 10 µg/mL were tested OK) |
| Coating at 5°C | Possible between overnight at least 19 hours and 7 days at 5°C |
| Blocking | using ready-to-use commercial solution 'StabilCoat' |
| Drying | 19-21 hours at 24°C (or use fresh after blocking without drying) |

- Dilution integrity: Dilution factor of 3 and 5 was performed at QC level of 300 pM

[1]Validation summary for (b) (4) has not been included in the above table by the Reviewer

(Source: Summarized Partial validation of ELISA assays for the determination of (b) (4) total insulin aspart: qualification of specific automation steps done by pipetting robot (Genesis RSP 200, Tecan) and extension of coating procedure (at 4°C), Study number: ZZ36951, page 11)

*Summary of Validation Parameters including Study Number ZZ41765 (Partial validation to qualify specific automation steps done by pipetting robot (Hamilton STAR))*

| | | |
|---|---|---|
| Analyte/ Matrix | Insulin aspart in human serum | |
| Method SOP | SM3-309, SM3-349 (including automation) | |
| Assay method | Enzyme-Linked Immunosorbent Assay (ELISA) | |
| Sample volume | 2 x 25 µL human serum | |
| Method history | | |
| Original validation | (at (b) (4) | AA81208 |
| Cross validation | Assay transfer | ZZ29614 |
| Partial validation | Coating and blocking procedure | ZZ33712 |
| Partial validation | Partly automation (Tecan), coating/blocking | ZZ36951 |
| Partial validation | Partly automation (Hamilton), stabilities | ZZ41765 |
| Validation parameters | | |
| Calibration curve | 10 - 400 pM, 4-parameter logistic, weighting 1/response$^2$ | all studies |
| Precision and accuracy | Tested at 5 concentration levels, 10, 30, 170, 300, 400 pM criteria met | all studies |
| Dilution, hook effect | Dilution up to 1000-fold, no hook effect, tested at 40 nM | ZZ29614 |
| Selectivity | Criteria met, tested with multiple donors | AA81208, ZZ29614, ZZ36951 |
| | including diabetes type I donors, haemolysed sera ≤ 4% blood content, turbid sera (referred to as lipaemic), criteria met | AA81208 |
| Robustness | Detection reagent (peroxidases cross-over tested) for mutual use in free and total insulin aspart assay,<br>Incubation time frame with biotinylated detection reagent extended (16-23 hours) | ZZ41765 |
| Automation (Tecan)<br>(Hamilton) | Criteria met (precision & accuracy, selectivity, cross contamination, dilution, minimum required volume | ZZ36951<br>ZZ41765 |
| Coated plate stability | Under coating solution 19 hours – 7 days at 5°C<br>Dried plate: 19 days at 5°C<br>Coating reagent applicable at 2-10 µg/mL (default: 4 µg/mL) | ZZ36951 |
| Stabilities in human serum | | |
| Short-term stability | 25 h at RT | AA81208 |
| Freeze/thaw stability | 5 cycles at -20°C, 5 cycles at -80°C | |
| Long-term stability -20°C | 713 days (within range), 255 days (up to 2nM)<br>111 days at -20°C (up to 20nM) | ZZ41765<br>AA81208 |
| Long-term stability -80°C | 140 days at -80°C (within range) | AA81208 |

- Minimum required volume: Volume of 50 µL and 120 µL in sample tube (2×25 µL required to take up) was tested. The lower volume was not consistently processable, the higher volume was processed as expected. The Applicant reports that samples with limited volume will be identified and can be processed manually.
- Dilution integrity: Dilution factor of 5 was performed at QC level of 300 pM

(Source: Partial validation to qualify specific automation steps done by pipetting robot (Hamilton STAR) in ELISA assays for the determination of (b) (4) total insulin aspart in human serum, Study number: ZZ41765, page 11)

*Study Number CA20958: Partial validation to extend stability*

| | |
|---|---|
| Analyte/ Matrix | Insulin aspart in human serum |
| Method SOP | SM3-349 (including automation) |
| Assay method | Enzyme-Linked Immunosorbent Assay (ELISA) |
| Sample volume | 2 x 25 µL human serum (for duplicate determination) |
| Analytical Range | 10 – 400 pM |
| Regression Type | Four-parametric logistic, with weighting $1/y^2$ |

Validation parameters

| | |
|---|---|
| Long term stability of QC (low and high level) samples | 1521 days at -20°C |
| Short term stability of QC (low and high level) samples | 32 hours at RT |
| Freeze/thaw stability of QC (low and high level) samples | 10 cycles at -20°C |
| Automated dilution step | Acceptance criteria met for variable dilutions of insulin aspart in human serum samples using automation |

- Dilution integrity: Dilution factor of 3 and 10 was performed at QC level of 300 pM

(Source: Partial validation of an existing ELISA method for the quantitative determination of total insulin aspart in human serum – Extension of long term and freeze/thaw stability, Study number: CA20958, page 11)

*Summary of Validation Parameters including Study Number CA21882[1] (Partial validation for cross reactivity) and CA21883[2] (Partial validation for parallelism)*

| | | |
|---|---|---|
| Analyte/ Matrix | Insulin aspart in human serum | |
| Method SOP | SM3-349 | |
| Assay method | Enzyme-Linked Immunosorbent Assay (ELISA) | |
| Sample volume | 2 x 25 µL human serum | |
| Method history | | Celerion study ID |
| Original validation | (at (b) (4) | AA81208 |
| Cross validation | Assay transfer | ZZ29614 |
| Partial validation | Coating and blocking procedure | ZZ33712 |
| Partial validation | Partly automation (Tecan), coating/blocking | ZZ36951 |
| Partial validation | Partly automation (Hamilton), stabilities | ZZ41765 |
| Partial validation | Long-term stability | CA20958 |
| Partial validation | Parallelism | CA21883 |
| Validation parameters | | |
| Calibration curve | 10 - 400 pM, 4-parameter logistic, weighting 1/response$^2$ | all studies |
| Precision and accuracy | Tested at 5 concentration levels, 10, 30, 170, 300, 400 pM criteria met | all studies |
| Dilution, hook effect | Dilution up to 1000-fold, no hook effect, tested at 40 nM | ZZ29614 |
| Selectivity | Criteria met, tested with multiple donors | AA81208, ZZ29614, ZZ36951 |
| | including diabetes type I donors, haemolysed sera ≤ 4% blood content, turbid sera (referred to as lipaemic), criteria met | AA81208 |
| Robustness | Detection reagent (peroxidases cross-over tested) for mutual use in free and total insulin aspart assay,<br>Incubation time frame with biotinylated detection reagent extended (16-23 hours) | ZZ41765 |
| Automation (Tecan)<br>(Hamilton) | Criteria met (precision & accuracy, selectivity, cross contamination, dilution, minimum required volume | ZZ36951<br>ZZ41765 |
| Coated plate stability | Under coating solution 19 hours – 7 days at 5°C<br>Dried plate: 19 days at 5°C<br>Coating reagent applicable at 2-10 µg/mL (default: 4 µg/mL) | ZZ36951 |
| Cross reactivity | No impact on insulin aspart quantification with (max. concentration in brackets) insulin human (500 pM), insulin degludec (10000 pM), insulin detemir (5000 pM), insulin glargine (300 pM), insulin lispro (1000 pM), proinsulin (500 pM), C-peptide (500 pM) | CA21882 |
| Parallelism | Met the criteria, tested with n=6 samples from individual subjects (type I diabetes) | CA21883 |
| Stabilities in human serum | | |
| Short-term stability | 32 h at RT | CA20958 |
| Freeze/thaw stability | 10 cycles at -20°C,<br>5 cycles at -80°C | CA20958<br>AA81208 |
| Long-term stability -20°C | 1521 days<br>255 days (up to 2nM)<br>111 days (up to 20nM) | CA20958<br>ZZ41765<br>AA81208 |
| Long-term stability -80°C | 140 days at -80°C (within range) | AA81208 |

(Source: Partial validation of an existing ELISA method for the quantitative determination of total insulin aspart in human serum – cross reactivity, Study number: CA21882, page 10; Partial validation of an existing ELISA method for the quantitative determination of total insulin aspart in human serum – parallelism, Study number: CA21883, page 10)

### 3.2.8.2 What is the performance of the bioanalytical method in individual studies?

The performance details of the bioanalytical method with the corresponding individual studies where the method was utilized is presented in Table 17.

**Table 17: Inter-run accuracy and precision of insulin aspart in individual studies**

| Study Number | Calibration Range, Matrix | Inter-Assay | Accuracy (%Theoretical or *%Bias*), Range | Precision (CV%), Range |
|---|---|---|---|---|
| **NN1218-3978 Phase 1** | 10-400 pM Human serum | QC (low, mid, high, diluted) | 92.2% to 99.5% | 2.2% to 13.5% |
| | | Calibration standards | 98.5% to 101.3% | 1.0% to 3.6% |
| **NN1218-3922 Phase 1** | 10-400 pM Human serum | QC (low, mid, high, diluted) | 94.6% to 100.7% | 2.2% to 7.4% |
| | | Calibration standards | *-1.3% to 1.3%* | 0.6% to 2.9% |
| **NN1218-3949 Phase 1** | 10-400 pM Human serum | QC (low, mid, high, diluted) | 98.9% to 102.3% | 4.6% to 7.4% |
| | | Calibration standards | *-2.3% to 1.9%* | 0.6% to 3.5% |
| **NN1218-3891 Phase 1** | 10-400 pM Human serum | QC (low, mid, high, diluted) | 100.8% to 104.9% | 4.2% to 6.1% |
| | | Calibration standards | 99.5% to 100.6% | 1.0% to 2.8% |
| **NN1218-3918 Phase 1** | 10-400 pM Human serum | QC (low, mid, high, diluted) | 102.0% to 102.4% | 3.6% to 5.8% |
| | | Calibration standards | 99.13% to 102.0% | 1.0% to 2.5% |
| **NN1218-3852 Phase 3a** | 10-400 pM Human serum | QC (low, mid, high, diluted) | 99.5% to 112.9% | 3.2% to 12.2% |
| | | Calibration standards | 99.5% to 101.0% | 1.5% to 2.2% |

Dilution QC samples were diluted by the same factor as that used for the dilution of the clinical samples. In all studies, the dilution QC sample concentration was 300 pM (within the calibration range) and a 5- and/or 10-fold dilution was performed (dilution factor of 5 and/or 10) (in some studies, dilution QC sample concentration of 2000 pM (with appropriate dilution factor) was also incorporated). During validation of the bioanalytical method, dilution up to 1000-fold was confirmed (validated) (refer to Section 3.2.8.1). Additionally, during partial validation of the bioanalytical method, dilution QC sample of 300 pM was also utilized (refer to Section 3.2.8.1).

(Source: Study NN1218-3978, Bioanalytical report (report no. AAA98569), page 398, 406; Study NN1218-3922, Bioanalytical report (report no. ACA17541-03), page 28, 34, 38; Study NN1218-3949, Bioanalytical report (report no. ACA20953), page 31, 43, 51; Study NN1218-3891, Bioanalytical report (report no. AAA96510), page 281, 286; Study NN1218-3918, Bioanalytical report (report no. AAA96542), page 182, 187, 192; Study NN1218-3852, Interim bioanalytical report (report no. ACA10654), page 226, 236, 243)

Reproducibility of the bioanalytical method was evaluated by performing incurred sample reanalysis for the above mentioned studies. All incurred sample reanalysis assessments were within the acceptance criteria (67% of the re-analyzed samples within 30% of the original value) and therefore the bioanalytical method is considered reproducible.

## 4. Labeling Recommendations

The following are the preliminary labeling recommendations relevant to clinical pharmacology for NDA 208751. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font is used to show text to be included.

### HIGHLIGHTS OF PRESCRIBING INFORMATION

### DRUG INTERACTIONS

- *Drugs that Increase Hypoglycemia Risk or Increase or Decrease Blood Glucose Lowering Effect:* [redacted] (b) (4) Adjustment of [redacted] (b) (4) TRADENAME dosage may be needed; closely monitor blood glucose (7).
- *Drugs that Blunt Hypoglycemia Signs and Symptoms* [redacted] (b) (4) *(e.g., beta-blockers, clonidine, guanethidine, and reserpine)*: Increased frequency of glucose monitoring may be required [redacted] (b) (4) (7).

### 7 DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with TRADENAME.

**Table 3. Clinically Significant Drug Interactions with TRADENAME**

| | |
|---|---|
| **Drugs That May Increase the Risk of Hypoglycemia** | |
| *Drugs:* | Antidiabetic agents [redacted] (b) (4), ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics. |
| *Intervention:* | Dose reductions of TRADENAME and increased frequency of glucose monitoring may be required when TRADENAME is co-administered with these drugs. |
| **Drugs That May Decrease the Blood Glucose Lowering Effect of TRADENAME** | |
| *Drugs:* | Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones. |
| *Intervention:* | Dose increases of TRADENAME and increased frequency of glucose monitoring may be required when TRADENAME is co-administered with these drugs. |
| **Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TRADENAME** | |
| *Drugs:* | Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. |
| *Intervention:* | Dose adjustment of TRADENAME and increased frequency of |

| | |
|---|---|
| | glucose monitoring may be required when TRADENAME is co-administered with these drugs. |
| **Drugs That May Blunt Signs and Symptoms of Hypoglycemia** | |
| *Drugs:* | Beta-blockers, clonidine, guanethidine, and reserpine. |
| *Intervention:* | Increased frequency of glucose monitoring may be required when TRADENAME is co-administered with these drugs. |

## 12 CLINICAL PHARMACOLOGY

### 12.2 Pharmacodynamics

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The day-to-day variability within-patients in glucose-lowering-effect (b) (4) of TRADENAME (b) (4) was ~18% for total glucose lowering ($AUC_{GIR,\ 0\text{-}12h}$ (b) (4) and ~19% for maximum glucose lowering effect ($GIR_{max}$; (b) (4)).

### 12.3 Pharmacokinetics

Absorption

(b) (4)

(b) (4)

(b) (4)

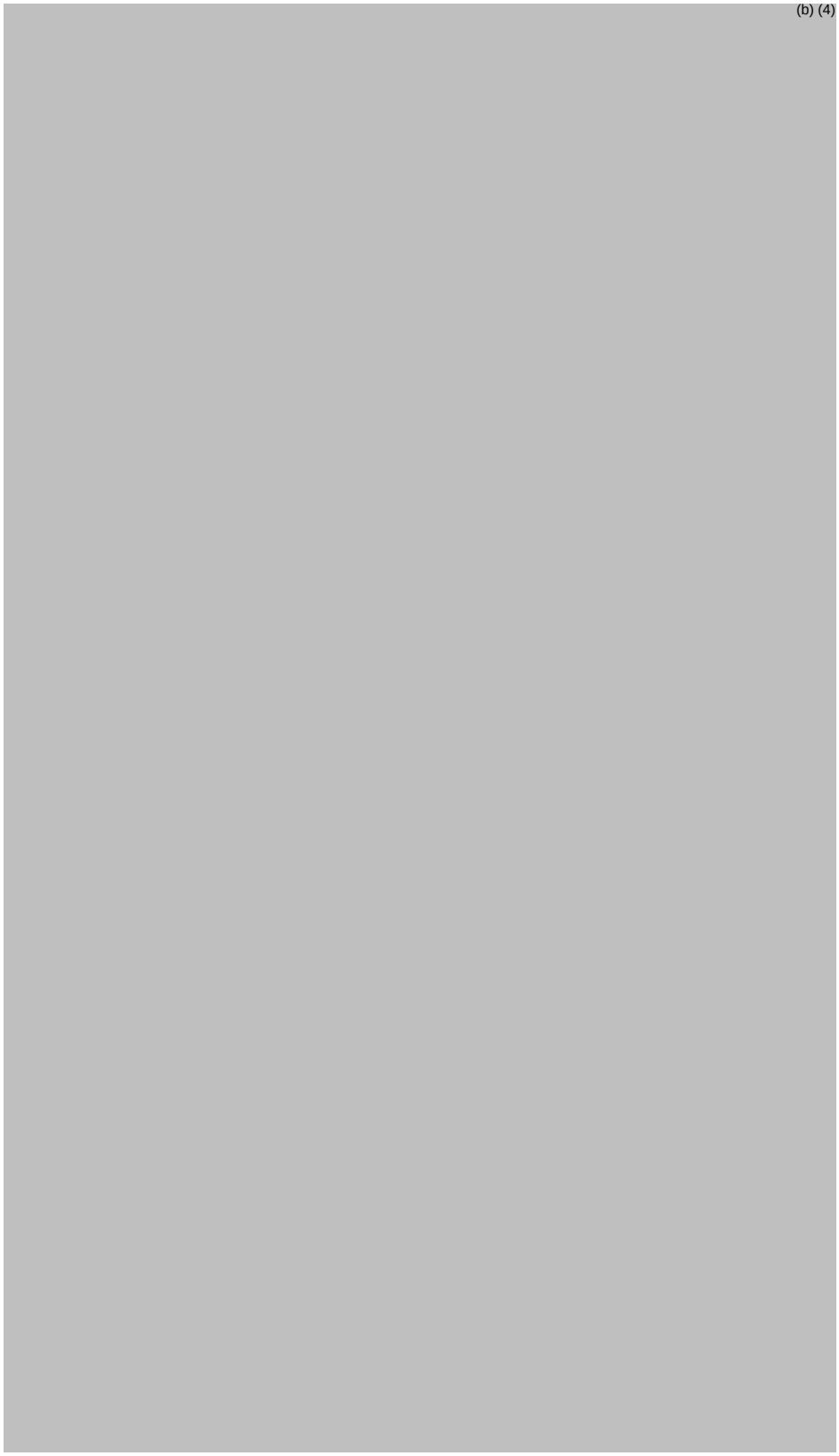



**Figure 2. Mean Insulin Aspart Serum Concentration Profile (top) and Mean Glucose Infusion Rate Profile (bottom) in Adult Subjects with Type 1 Diabetes following a single 0.2 unit~~U~~/kg (b) (4) -dose ((b) (4) subcutaneous) of TRADENAME**

Pharmacokinetic results in adult patients with type 1 diabetes showed that insulin aspart appeared in the circulation ~ 2.5 minutes after administration of TRADENAME. (b) (4)

Ttime to maximum concentration was achieved ~ 63 minutes after administration of TRADENAME (b) (4)

(b) (4)

(b) (4)

–Total insulin exposure and maximum insulin concentration increases proportionally with increasing subcutaneous dose of TRADENAME within the therapeutic dose range.

Distribution

Insulin aspart has a low binding affinity to plasma proteins (<10%), similar to that seen with regular human insulin.

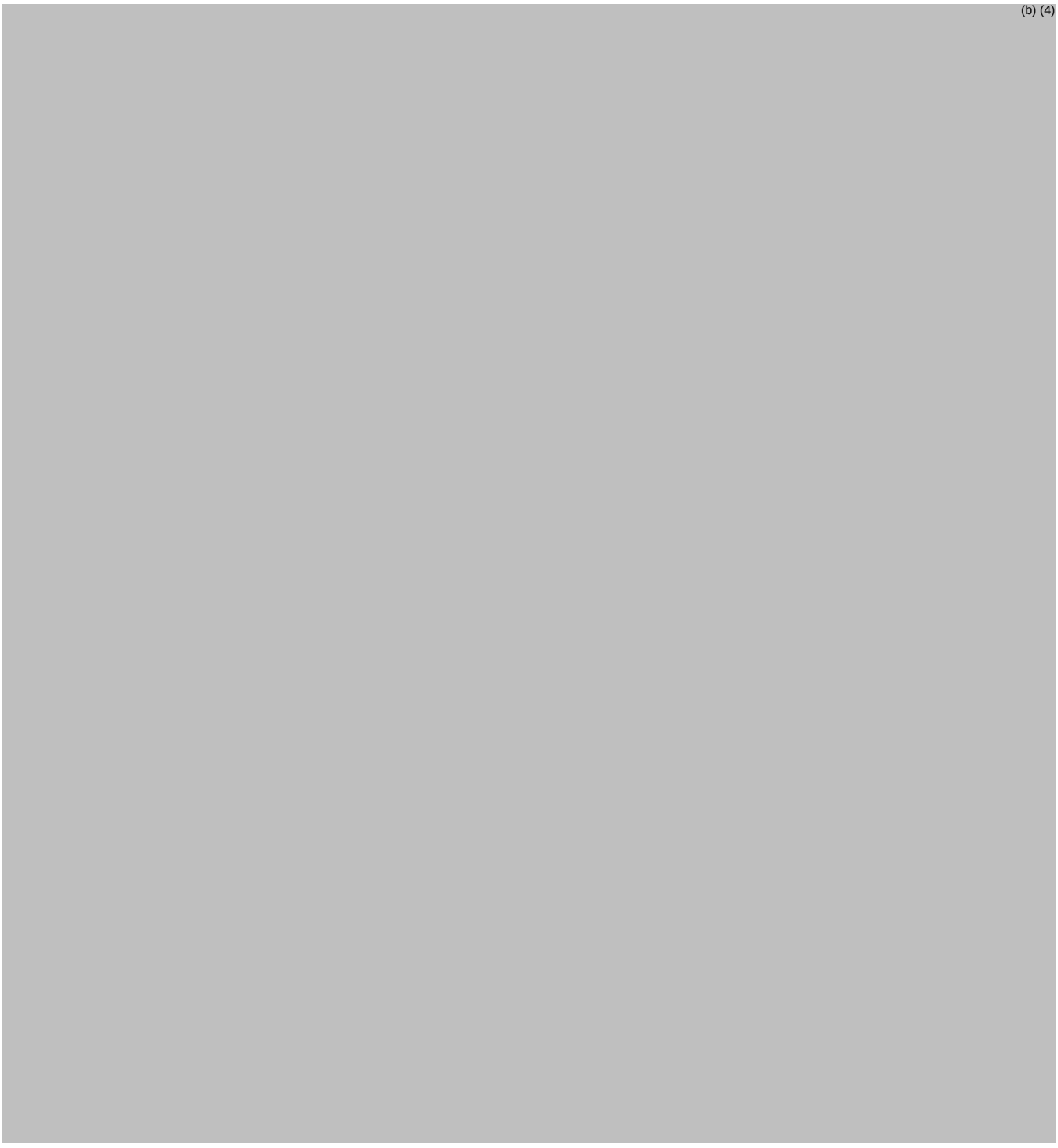
Elimination

The terminal Hhalf-life after subcutaneous administration of TRADENAME is (b) (4)

(b) (4)

**Specific Populations**

(b) (4)




*Age, Gender, BMI, Racial or Ethnic Groups*

Age, gender, BMI, and racial or ethnic groups did not meaningfully affect the pharmacokinetics and pharmacodynamics of TRADENAME.

*Pregnant* (b) (4) *Women*

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of TRADENAME has not been studied *[see Use in Specific Populations (8.1)]*.

*Patients with Renal and Hepatic Impairment*

Renal and hepatic impairment is not known to impact the pharmacokinetics of insulin aspart.

(b) (4)

## 5. Appendix

### 5.1 Key Highlights of Clinical Pharmacology Studies Cited in the Review

| Study Number | Description |
|---|---|
| **Study NN1218-3978 (Phase 1 study, Euglycemic clamp study)** | A randomized, double-blind, single dose, 3-period, crossover study in patients with T1DM (18-64 years; n=52 randomized). Patients were randomized to receive a single SC dose of Fiasp, an exploratory formulation of insulin aspart (FIA(R)), and NovoLog in a euglycemic clamp setting. A single dose of 0.2 unit/kg was administered via the SC injection (lower abdominal wall above the inguinal area). The euglycemic clamp was conducted for 12 hrs post-dose. It should be noted that since Fiasp is the to-be-marketed formulation, results for the exploratory formulation (FIA(R)) has not been reported in the Clinical Pharmacology review. Blood samples for assessment of PK of insulin aspart was collected for 12 hrs following SC dosing. |
| **Study NN1218-3891 (Phase 1 study, Euglycemic clamp study)** | A randomized, single-center, double-blind, single dose, 2-period, crossover study in young adult patients (18-35 years; n=37 randomized) and in geriatric patients (≥65 years; n=30 randomized) with T1DM. Patients were randomized to receive a single SC dose of 0.2 unit/kg (lower abdominal wall above the inguinal area) of Fiasp and NovoLog in a euglycemic clamp setting. The euglycemic clamp was conducted for 12 hrs post-dose. Blood samples for assessment of PK of insulin aspart was collected for 12 hrs following SC dosing. |
| **Study NN1218-3887 (Phase 1 study, Euglycemic clamp study)** | A randomized, single-center, double-blind, single dose, 8-period, crossover study in patients with T1DM (18-64 years, n=46 randomized). Patients were randomized to a treatment sequence in which they received single doses at 3 matched dose levels (0.1, 0.2, 0.4 unit/kg) of Fiasp and NovoLog and 2 additional single doses of 0.2 unit/kg of either Fiasp or NovoLog via SC injection (lower abdominal wall above the inguinal area) in a euglycemic clamp setting. The euglycemic clamp was conducted for 12 hrs post-dose. |
| **Study NN1218-3922 (Phase 1 study, Meal challenge study)** | A randomized, single-center, double-blind, single dose, 2-period, crossover study in patients with T1DM (18-64 years, n=42 randomized). Patients were randomized to receive an individualized single SC dose of Fiasp and NovoLog in a meal challenge setting. The meal test was conducted to assess the postprandial glucose metabolism following dosing of Fiasp and NovoLog using a triple-tracer approach. Patients were administered an individualized dose based on the patient's customary insulin:carbohydrate ratio (actual dose range from 0.06 to 0.28 unit/kg); the same dose was administered for each patient at both dosing visits. Fiasp and NovoLog was administered immediately before intake of a standardized mixed meal (10 kcal/kg, |

| | |
|---|---|
| | individualized meal size) including Jell-O containing 75 g carbohydrate labelled with [1-$^{13}$C] glucose. The meal was to be consumed by the patient within 15 min. The duration of the meal test was for 6 hrs after dosing; during this period patients refrained from eating and water was not allowed in the initial 2 hr after dosing. Blood samples for assessment of PK of insulin aspart was collected for 8 hrs following SC dosing. |
| **Study NN1218-3889 (Phase 1 study, Meal challenge study)** | A randomized, single-center, double-blind, single dose, crossover study in patients with T1DM (n=36 randomized). Patients were randomized to receive a single dose of 0.2 unit/kg of Fiasp and NovoLog via SC injection (lower abdominal wall above the inguinal area) immediately before a standardized meal. Immediately after dose administration a standardized liquid meal (BOOST Nestle/Novartis Medical Nutrition, 20 fl. oz., 600 kcal, macronutrient distribution: 67% carbohydrates, 17% protein, 16% fat) was to be consumed by patients. The consumption of the meal was to be as quick as possible, within 8 min after dosing. The duration of the meal test was for 6 hrs after dosing; during this period patients refrained from eating and water was not allowed in the initial 2 hr after dosing. |
| **Study NN1218-3921 (Phase 1 study, Meal challenge study)** | A randomized, single-center, open-label, single dose, 2-period, crossover study in patients with T1DM (n=33 randomized). Patients were randomized to receive a single dose of 0.2 unit/kg of Fiasp and NovoLog via SC injection (lower abdominal wall above the inguinal area). Fiasp was administered 20 min after the start of intake of a standardized meal (post-meal) and NovoLog was administered immediately before a standardized meal (pre-meal). The standardized liquid meal (BOOST Nestle/Novartis Medical Nutrition, 20 fl. oz., 600 kcal, macronutrient distribution: 67% carbohydrates, 17% protein, 16% fat) was to be consumed by patients as quick as possible, within 8 min. The duration of the meal test was 6 hrs following intake of a standardized meal; during this period patients refrained from eating and water was not allowed in the initial 2 hr after the start of intake of the standardized meal. |
| **Study NN1218-3852 (Phase 3a study)** | A 26+26 week, multicenter, multinational, active control, treat-to-target, parallel group study in patients with T1DM (n= 1143 randomized). Following a 8 week run-in period (meal time bolus insulin (NovoLog), optimization of basal insulin treatment (insulin detemir, Levemir®)) patients were randomized to receive either pre-meal NovoLog + insulin detemir (double-blind), pre-meal Fiasp + insulin detemir (double-blind), or post-meal Fiasp + insulin detemir (open-label) via SC injection for 26 weeks. Fiasp and NovoLog were administered 0-2 min before a meal (pre-meal dosing) and Fiasp was administered 20 min after the start of a meal (post-meal dosing). During the randomization period, optimization of the bolus insulin regimen was permitted, however the basal insulin regimen (once- or twice-daily dosing) could not be |

| | |
|---|---|
| | changed.<br><br>A standardized meal test (carbohydrate-rich liquid meal (80g); consumed quickly as possible and within 12 min) was performed at baseline (before randomization at the randomization visit) and at week 26 of the study. A bolus insulin dose of 0.1 unit/kg was administered to all patients. At the baseline meal test, all patients received 0.1 unit/kg of NovoLog 0-2 min before the meal and at week 26 patients were administered 0.1 unit/kg of either NovoLog or Fiasp 0-2 min before the meal or Fiasp 20 min after the start of the meal (based on the treatment arm). Blood samples for quantification of plasma glucose were collected for 4 hr (1, 2, 3, 4 hr) from the start of the meal and for quantification of insulin aspart at 1 hr and 2 hr from the start of the meal. The results from the initial 26 weeks of the study (primary analysis of efficacy and safety) are reported in the Clinical Pharmacology review. |
| **Study NN1218-3853 (Phase 3a study)** | A 26 week, multicenter, multinational, randomized, double-blind, active controlled, treat-to-target, parallel group study in patients with T2DM (n=689 randomized). Following a 8 week run-in period (insulin glargine (Lantus®) + metformin; optimization of basal insulin titration) patients were randomized to receive either pre-meal Fiasp + insulin glargine + metformin or pre-meal NovoLog + insulin glargine + metformin via SC injection for 26 weeks (bolus dose titration). At randomization, all patients received 4 units of bolus insulin (Fiasp or NovoLog) 0-2 min before a meal, thereafter the bolus insulin was titrated to the pre-prandial glycemic target of 4 – 6 mmol/L in a treat-to-target manner.<br><br>A standardized meal test (liquid meal (80g of carbohydrates); consumed quickly as possible and within 12 min) was performed at baseline (before randomization) and at week 26 of the study. At week 26 meal test, patients were administered a bolus insulin dose that was calculated by dividing carbohydrate content of the meal by I:Carb ratio (which was 500 divided by the total daily dose of both basal and bolus insulin) of either NovoLog or Fiasp 0-2 min before the meal. Blood samples for quantification of plasma glucose were collected for 4 hr (1, 2, 3, 4 hr) from the start of the meal. |
| **NN1218-3949**<br><br>**(Phase 1 study, Euglycemic clamp study)** | A randomized, single center, single-dose, open-label, 5-period, crossover study in healthy subjects (n=22 randomized) comparing the rate and extent of systemic absorption of insulin aspart following SC administration of Fiasp in the abdomen, deltoid region and thigh under euglycemic clamp setting. The PK of insulin aspart following administration of Fiasp via the intramuscular route (IM, thigh) and IV route (to assess absolute bioavailability) was also assessed under euglycemic clamp setting. The PK of Fiasp via the IM route was assessed since lean patients may unintentionally inject via this route instead of the SC route. Single dose of 0.2 unit/kg Fiasp was administered via the SC |

| | |
|---|---|
| | route (abdomen, deltoid, thigh), IM route (thigh), and a single dose of 0.02 unit/kg was dosed via the IV route (injected over 1 min duration). The euglycemic clamp was conducted for 12 hrs after SC and IM dosing and for 8 hrs after IV dosing. Blood samples for assessment of PK of insulin aspart were collected for 12 hrs and 8 hrs after SC/IM and IV dosing, respectively. |

(Source: Clinical study report NN1215-3978, -3891, -3887, -3922, -3889, -3921, -3852, -3853, 3949)

## 5.2 Definition of Pharmacokinetic and Pharmacodynamic Endpoints

| Endpoint | Description |
|---|---|
| **Pharmacokinetic** | |
| **Onset of appearance** | First time point after dose administration when insulin aspart serum concentrations reaches 10 pmol/L (LLOQ) assessed using imputed insulin aspart concentrations from the compartmental PK model |
| **Time to 50% $C_{max}$** | First time point where insulin aspart serum concentrations equals 50% of $C_{max}$ using linear interpolation between observed insulin aspart concentrations. In order for time to 50% $C_{max}$ and $t_{max}$ to be a valid measure of differences in onset of insulin exposure and initial absorption rate between the 2 insulins, $C_{max}$ for the 2 insulins must be comparable |
| **$AUC_{0-s}$** | s=15, 30, 60, 90, 120 min. Estimated using linear trapezoidal method imputing data from the compartmental PK model prior to the first measurement above LLOQ |
| **Time to late 50% $C_{max}$** | Last time point where insulin aspart serum concentration equal 50% $C_{max}$ based on linear interpolation between observed insulin aspart concentrations |
| **$AUC_{2hr-t}$** | Area under the insulin aspart serum concentration-time profile from 2 hr to time of last planned measurement of insulin aspart concentration (t), was calculated as the difference $AUC_{0-t} - AUC_{0-2hr}$ |
| **Pharmacodynamic** | |
| **Onset of action** | Time from trial product administration until blood glucose concentration has decreased at least 5 mg/dL (0.3 mmol/L) from baseline |
| **Duration of action[1]** | Time from trial product administration until blood glucose concentration is consistently above 8.3 mmol/L during the glucose clamp |
| **Duration of action[2]** | Time from trial product administration until smooth GIR (in the tail) is consistently below 0.1 mg/kg(*min) for at least 30 min |
| **Duration of action[3]** | Time from trial product administration until smooth GIR (in the tail) is consistently below 0.1 mg/kg(*min) for at least 30 min |

[1]Study NN1218-3978
[2]Study NN1218-3887
[3]Study NN1218-3891
(Source: Summary of clinical pharmacology studies, page 27-28; Study NN1218-3978, -3891, -3887, Clinical study report, page 60-61, 62, 62 and 74, respectively)

### 5.3 Pharmacokinetic-Pharmacodynamic and Exposure-Response Analysis

A population PK-PD model was developed and validated to evaluate the PK-PD and exposure-response relationship for insulin aspart following SC administration of Fiasp and NovoLog.

Reported below are the model development methods, validation, results and conclusions from the analysis conducted by the Applicant. The Reviewer is in agreement with the model development and validation conducted by the Applicant and conclusions drawn by the Applicant.

***Data Source***

*PK-PD model*

Pharmacokinetic data for Fiasp and NovoLog was obtained from the following studies:

- Study NN1218-3978 (euglycemic clamp study, 0.2 unit/kg)
- Study NN1218-3891 (euglycemic clamp study, 0.2 unit/kg)
- Study NN1218-3922 (meal challenge study, individualized dosing (actual dose range: 0.06 to 0.28 unit/kg)

The final PK data set consisted of data from 135 subjects; the demographic characteristics are presented in Table 1.

**Table 1: Demographic characteristics of subjects included in the PK data file**

| Category | Group | Trial ID | | | Total |
|---|---|---|---|---|---|
| | | NN1218-3891 | NN1218-3922 | NN1218-3978 | |
| All | N | 44 (32.6%) | 40 (29.6%) | 51 (37.8%) | 135 (100%) |
| Age group | Younger | 22 (50%) | 40 (100%) | 51 (100%) | 113 (83.7%) |
| | Geriatric | 22 (50%) | - | - | 22 (16.3%) |
| Population | T1DM | 44 (100%) | 40 (100%) | 51 (100%) | 135 (100%) |
| Sex | Male | 28 (63.6%) | 19 (47.5%) | 42 (82.4%) | 89 (65.9%) |
| | Female | 16 (36.4%) | 21 (52.5%) | 9 (17.6%) | 46 (34.1%) |
| Race | White | 43 (97.7%) | 39 (97.5%) | 51 (100%) | 133 (98.5%) |
| | Asian | - | 1 (2.5%) | - | 1 (0.7%) |
| | Other | 1 (2.3%) | - | - | 1 (0.7%) |
| Ethnicity | Not Hispanic or Latino | 44 (100%) | 40 (100%) | 51 (100%) | 135 (100%) |
| Age | Mean (SD) | 48 (20.8) | 42 (12.1) | 39.9 (11.6) | 43.2 (15.6) |
| | Range | [22-73] | [24.7-64.4] | [21-60] | [21-73] |
| Body weight | Mean (SD) | 75.7 (10.2) | 72.4 (10.8) | 76.4 (10) | 75 (10.4) |
| | Range | [50-97.4] | [52.7-100] | [53.3-96.9] | [50-100] |
| BMI | Mean (SD) | 24.5 (2.1) | 24.1 (2.3) | 24.3 (2.2) | 24.3 (2.2) |
| | Range | [19.3-28.4] | [19.7-28] | [18.9-28.7] | [18.9-28.7] |
| %B/T* | Mean (SD) | 9.2 (9.5) | 11.2 (14.8) | 12.9 (12.7) | 11.2 (12.5) |
| | Range | [0.3-35.7] | [0.3-61.8] | [0.5-66.9] | [0.3-66.9] |

*Degree of antibody binding

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 15)

Pharmacodynamic data for Fiasp and NovoLog was obtained from the following studies:

- Study NN1218-3978 (euglycemic clamp study)
- Study NN1218-3891 (euglycemic clamp study)

The final PD data set contained smoothed GIR values from 72 subjects; the demographic characteristics are presented in Table 2. The Applicant reports the following for the smoothed GIR value-time data "to avoid bias due to non-zero smoothed GIR in the initial phase after dosing, where raw GIR is zero due to clamp procedure, only data from 15 minutes after dosing and onwards was used. This was evaluated not to affect the conclusions".

**Table 2: Demographic characteristics of subjects included in the PD data file**

| Category | Group | Trial ID | | Total |
|---|---|---|---|---|
| | | NN1218-3891 | NN1218-3978 | |
| All | N | 21 (29.2%) | 51 (70.8%) | 72 (100%) |
| Age group | Younger | 7 (33.3%) | 51 (100%) | 58 (80.6%) |
| | Geriatric | 14 (66.7%) | - | 14 (19.4%) |
| Population | T1DM | 21 (100%) | 51 (100%) | 72 (100%) |
| Sex | Male | 16 (76.2%) | 42 (82.4%) | 58 (80.6%) |
| | Female | 5 (23.8%) | 9 (17.6%) | 14 (19.4%) |
| Race | White | 20 (95.2%) | 51 (100%) | 71 (98.6%) |
| | Other | 1 (4.8%) | - | 1 (1.4%) |
| Ethnicity | Not Hispanic or Latino | 21 (100%) | 51 (100%) | 72 (100%) |
| Age | Mean (SD) | 54.8 (20.6) | 39.9 (11.6) | 44.2 (16.1) |
| | Range | [23-73] | [21-60] | [21-73] |
| Body weight | Mean (SD) | 77.5 (10) | 76.4 (10) | 76.7 (10) |
| | Range | [60.2-97.4] | [53.3-96.9] | [53.3-97.4] |
| BMI | Mean (SD) | 24.6 (2.4) | 24.3 (2.2) | 24.3 (2.3) |
| | Range | [19.3-28.4] | [18.9-28.7] | [18.9-28.7] |
| %B/T* | Mean (SD) | 9.1 (9.7) | 12.9 (12.7) | 11.8 (12) |
| | Range | [0.5-35.6] | [0.5-66.9] | [0.5-66.9] |

*Degree of antibody binding

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 16)

*Exposure-response analysis*

Pharmacodynamic data ($AUC_{GIR,0\text{-}12hr}$) for Fiasp and NovoLog was obtained from the following study:

- Study NN1218-3887 (euglycemic clamp study, 0.1, 0.2, 0.4 unit/kg)

The final data set contained response data from 46 subjects; the demographic characteristics are presented in Table 3.

**Table 3: Demographic characteristics of subjects included in the exposure-response analysis**

| Category | Group | NN1218-3887 |
|---|---|---|
| All | N | 46 (100%) |
| Age group | Younger | 46 (100%) |
| Population | T1DM | 46 (100%) |
| Sex | M | 35 (76.1%) |
| | F | 11 (23.9%) |
| Race | White | 46 (100%) |
| Ethnicity | Not Hispanic or Latino | 46 (100%) |
| Age | Mean (SD) | 44 (10.4) |
| | Range | [20-61] |
| Body weight | Mean (SD) | 77.4 (10.8) |
| | Range | [52.6-95.3] |
| BMI | Mean (SD) | 24.6 (2.4) |
| | Range | [19.3-28.2] |
| %B/T* | Mean (SD) | 15.4 (17) |
| | Range | [0.2-65.7] |

* Degree of antibody binding

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 16)

***PK-PD modeling approach and exposure-response analysis***

*PK-PD modeling*

A one-compartment model with first-order absorption through 3 transit compartments and first-order elimination was used to describe the PK of insulin aspart following SC administration of Fiasp or NovoLog (Figure 1). An effect compartment model driven by concentration profiles predicted from the PK model, and a sigmoidal $E_{max}$-type relationship between the effect compartment concentration (X) and the GIR response was used to describe the PD of insulin aspart following SC administration of Fiasp or NovoLog (Figure 1). Effect compartment was initialized with a non-zero value ($X_0$) to account for the initial non-zero smoothed GIR values.

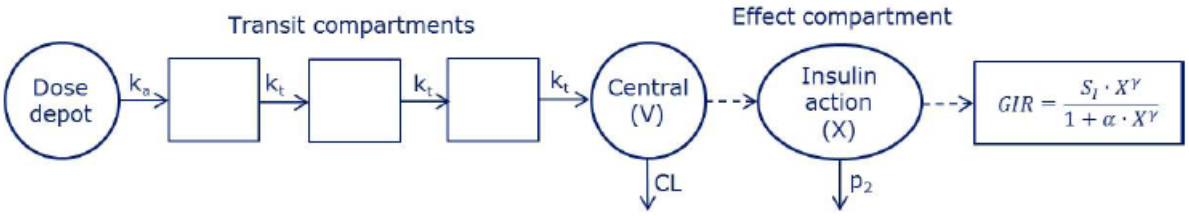



**Figure 1: PK-PD model of insulin aspart following SC administration of Fiasp or NovoLog**

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 6)

The PK and PD models were parameterized as follows:

| **PK Model: 5 Parameters** | **PD Model: 4 Parameters** |
|---|---|
| **F**: relative BA parameter, with a fixed typical value of 1 | $\mathbf{p_2}$: turn-over rate constant for the effect compartment |
| $\mathbf{k_a}$: absorption rate constant | $\mathbf{S_I}$: insulin sensitivity parameter |
| $\mathbf{k_t}$: transit rate constant | $\boldsymbol{\alpha}$: nonlinearity parameter |
| **CL/F**: clearance parameter | $\gamma$: a Hill coefficient |
| **V/F**: volume of distribution parameter | - |
| **Variability** | |
| **Between-subject variability:** on CL/F and V/F<br><br>**Between-occasion variability:** on F, $k_t$, $k_a$ | **Between-subject variability:** on $p_2$, $S_I$, $\alpha$ (with correlated $S_I$ and $\alpha$)<br><br>**Between-occasion variability:** on $p_2$ and $S_I$ |
| **Residual variability**: combined proportional and additive error model | **Residual variability**: additive error model |

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 6-7)

As presented in Table 4, covariate relationships were implemented on certain parameters in the combined PK-PD model. The Applicant reports that to confirm that the PK disposition properties and the concentration-effect relationship were identical for both treatments (Fiasp and NovoLog), treatment was only included as a covariate on the PK absorption parameters, F and $k_t$.

**Table 4: Covariate effects included in the combined PK-PD model for Fiasp and NovoLog**

| Parameter | Covariates | Categories |
|---|---|---|
| **F** | Treatment | Faster aspart, NovoRapid®/NovoLog® |
| **$k_t$** | Treatment | Faster aspart, NovoRapid®/NovoLog® |
| **$k_a$** | BMI | Continuous |
| **CL/F** | Age group | Geriatric (≥65 years), younger (18-64 years) |
| | Antibody binding (%B/T) | Continuous |
| | BMI | Continuous |
| | Body weight | Continuous |
| | Insulin dose | Continuous |
| | Sex | Male, female |
| **V/F** | Body weight | Continuous |
| **$S_I$** | Antibody binding (%B/T) | Continuous |
| | Age group | Geriatric (≥65 years), younger (18-64 years) |
| | BMI | Continuous |
| | Sex | Male, female |

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 17)

The PK and PD models were estimated sequentially. The PK model was estimated using the FOCE+I algorithm in NONMEM (version 7.3). Then the individual estimates of the PK model parameters were used as input for estimation of the PD model (using FOCE algorithm in NONMEM).

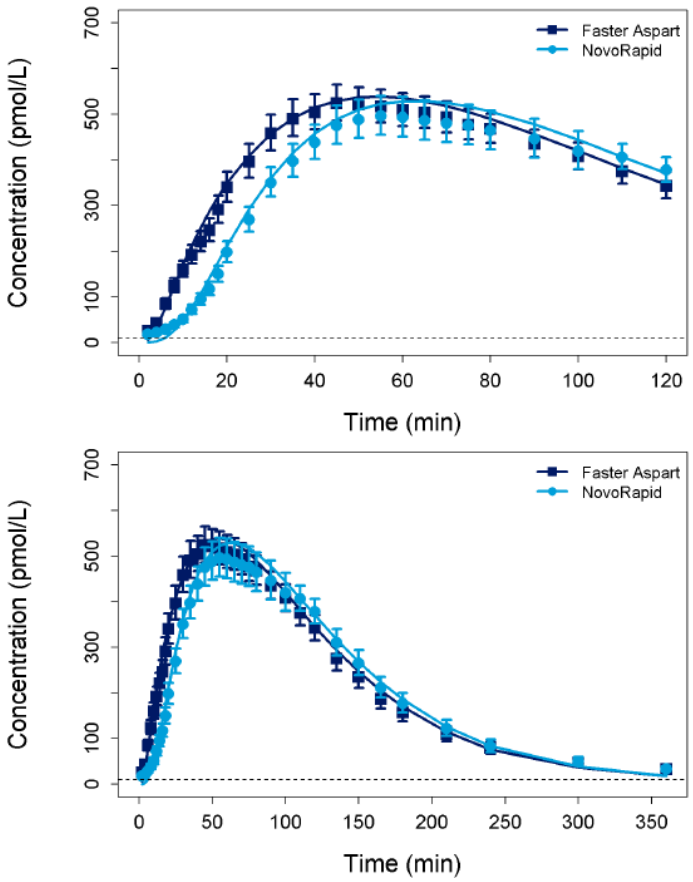
*Exposure-response analysis*

The analysis was performed by relating the overall glycemic response (observed $AUC_{GIR,0\text{-}12hr}$ from Study NN1218-3887) to the overall exposure of insulin aspart (predicted $AUC_{0\text{-}12hr}$ using the PK model) for Fiasp and NovoLog. Concentration-time profiles and exposure for insulin aspart ($AUC_{0\text{-}12hr}$) was predicted using the PK model based on actual dose levels and demographics of subjects in Study NN1218-3887.

***Results and Conclusions***

*PK model*

Observed and model-predicted insulin aspart concentration-time profiles for Fiasp and NovoLog following SC dosing are presented in Figure 2, showing that the PK model was able to describe the observed insulin aspart concentration-time profile for both treatments.




Top: 0-2 hours. Bottom: 0-6 hours. Data points are geometric means with 95% CI of observed concentration and lines are population predicted profiles. Data from the PK population (n=135).

**Figure 2: Observed and model-predicted insulin aspart concentration-time profiles for Fiasp (indicated as faster aspart in the Applicant's figures above) and NovoLog following SC administration**

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 8)

The Applicant reports that the different absorption properties for Fiasp and NovoLog were captured by difference values for the transit rate constant (Table 5). The absorption rate constant values were identical for both treatments. The disposition part of the PK model was treatment-independent by assumption, which in turn confirmed that the PK disposition properties were identical for both treatments. Parameter values from the estimation of the PK model are presented in Table 5. Overall, the shrinkage estimates for inter-individual and inter-occasion variability was low.

**Table 5: Parameter values obtained from estimation of the PK model**

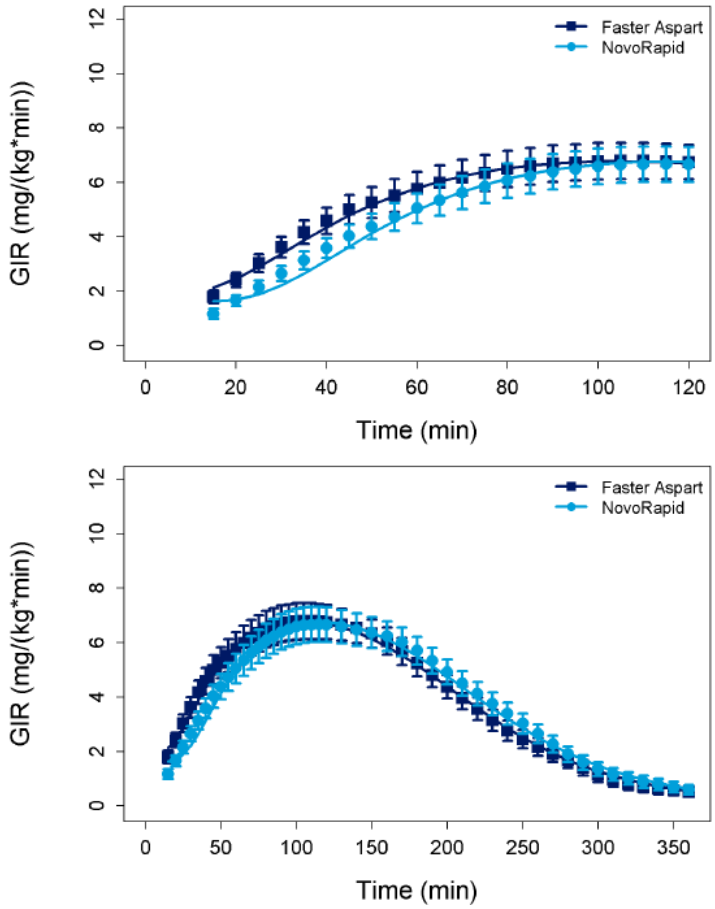
| Parameter | Parameter name* | Estimate | Unit | 95% CI | | RSE (% CV) | IIV (% CV) | Shrinkage (%) | IOV (% CV) | Shrinkage of IOV (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound | | | | | |
| Absorption rate constant | KA | 1.53 | $h^{-1}$ | NA | NA | NA | NA | NA | 47.8 | 10.5 |
| Transit rate constant | KT | 55.8 | $h^{-1}$ | NA | NA | NA | NA | NA | 67.7 | -3.60 |
| | KT.NovoRapid | 16.1 | $h^{-1}$ | NA | NA | NA | NA | NA | NA | NA |
| Clearance/F | CL | 67.8 | L/h | NA | NA | NA | 25.6 | 11.2 | NA | NA |
| Volume of distribution/F | V | 78.6 | L | NA | NA | NA | 39.4 | 10.1 | NA | NA |
| Relative bioavailability | BA | 1 | - | Fixed | Fixed | Fixed | NA | NA | 19.6 | 26.6 |
| | BA.NovoRapid | 0.99 | - | NA | NA | NA | NA | NA | NA | NA |
| Covariate relationships | BWonCL | 1 | - | Fixed | Fixed | Fixed | NA | NA | NA | NA |
| | BWonV | 1 | - | Fixed | Fixed | Fixed | NA | NA | NA | NA |
| | ABonCL | -0.183 | - | NA | NA | NA | NA | NA | NA | NA |
| | AGEGRPonCL | 0.905 | - | NA | NA | NA | NA | NA | NA | NA |
| | DOSEonCL | -0.198 | - | NA | NA | NA | NA | NA | NA | NA |
| | SEXonCL | 0.914 | - | NA | NA | NA | NA | NA | NA | NA |
| | BMIonKA | -1.18 | - | NA | NA | NA | NA | NA | NA | NA |
| Residual error components | Add. Error | 12.6 | pmol/L | NA | NA | NA | NA | 5.52 | NA | NA |
| | Prop. Error | 9.49 | % | NA | NA | NA | NA | 5.52 | NA | NA |

*Name used in model scripts

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 18)

*PD model*

Observed and model-predicted GIR profiles for Fiasp and NovoLog following SC dosing are presented in Figure 3, showing that the PD model was able to describe the observed GIR profiles for both treatments. The Applicant reports that the more rapid onset of action for Fiasp when compared to NovoLog was explained by the different absorption properties (accounted for in the PK model) since the PD model was treatment-independent by assumption and in turn confirming that the concentration-effect relationship was identical for both treatments.




Top: 0-2 hours. Bottom: 0-6 hours. Data points are means with 95% CI of observed smoothed GIR and lines are population predicted profiles. Data from the PD population (n=72).

**Figure 3: Observed and model-predicted GIR profiles for Fiasp (indicated as faster aspart in the Applicant's figures above) and NovoLog following SC administration**

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 9)

Parameter values from the estimation of the PD model are presented in Table 6. The largest RSE for the structural model was observed for α (24.1%) and $S_I$ (20.5%). Overall, the shrinkage estimates for inter-individual and inter-occasion variability was low. For the covariate effects, the largest RSE was observed for antibody binding on $S_I$ (41.5%) and BMI on $S_I$ (33.3%); this is due to the small sample size.

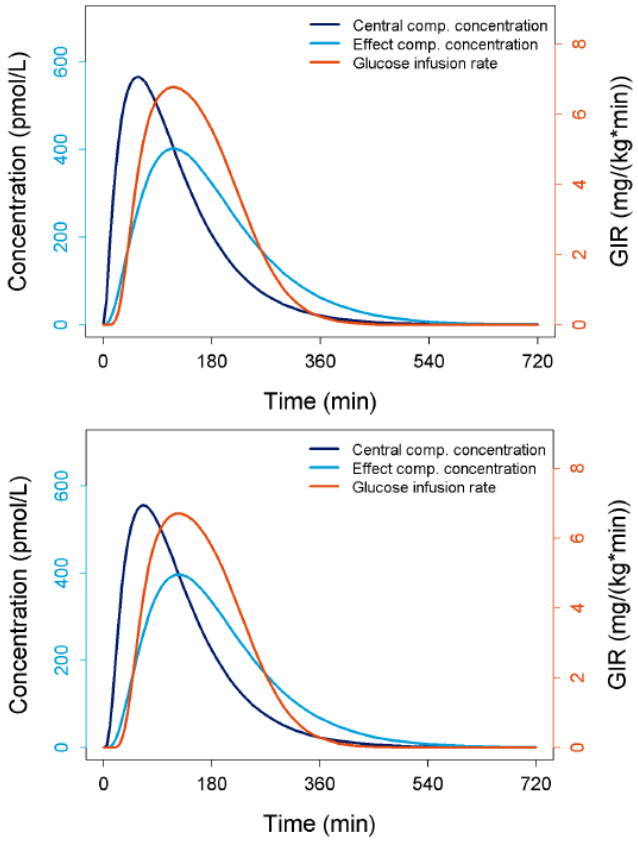
**Table 6: Parameter values obtained from estimation of the PD model**

| Parameter | Parameter name* | Estimate | Unit | 95% CI | | RSE (% CV) | IIV (% CV) | Shrinkage (%) | IOV (% CV) | Shrinkage of IOV (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit | | | | | |
| **Turnover rate constant** | **P2** | 0.996 | $h^{-1}$ | 0.88 | 1.11 | 5.93 | 31.9 | 19.5 | 30.4 | 17.6 |
| **Insulin sensitivity** | **SI** | 183 | mg/kg /min /nmol/L | 109 | 257 | 20.5 | 84.4 | 2.18 | 20.2 | 22.4 |
| **Initial effect compartment concentration** | **X0** | 0.175 | nmol/L | 0.156 | 0.195 | 5.56 | NA | NA | 45.3 | 8.0 |
| ***α*** | **ALFA** | 20.1 | L/nmol | 10.6 | 29.6 | 24.1 | 119 | 1.97 | NA | NA |
| **Hill coefficient** | **GAMMA** | 2.42 | - | 2.16 | 2.68 | 5.49 | NA | NA | NA | NA |
| **Covariate relationships** | **ABonSI** | -0.101 | - | -0.183 | -0.0188 | 41.5 | NA | NA | NA | NA |
| | **AGEGRPonSI** | 0.872 | - | 0.622 | 1.12 | 14.7 | NA | NA | NA | NA |
| | **BMIonSI** | -1.47 | - | -2.43 | -0.511 | 33.3 | NA | NA | NA | NA |
| | **SEXonSI** | 1.08 | - | 0.833 | 1.33 | 11.7 | NA | NA | NA | NA |
| **Residual error** | **Add. Error** | 0.449 | mg/kg /min | NA | NA | NA | NA | 2.62 | NA | NA |

*Name used in model scripts

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 20)

Simulated profiles for insulin aspart concentration in the central compartment, concentration in the effect compartment, and GIR for a 0.2 unit/kg dose for a typical subject using the combined PK-PD model are presented in Figure 4. An effect compartment was incorporated in the combined PK-PD model to describe the delay between the observed insulin aspart concentration-time data and the observed smoothed GIR data. The effect compartment provides a delay between the insulin aspart concentration in the central compartment and the effect compartment concentration.

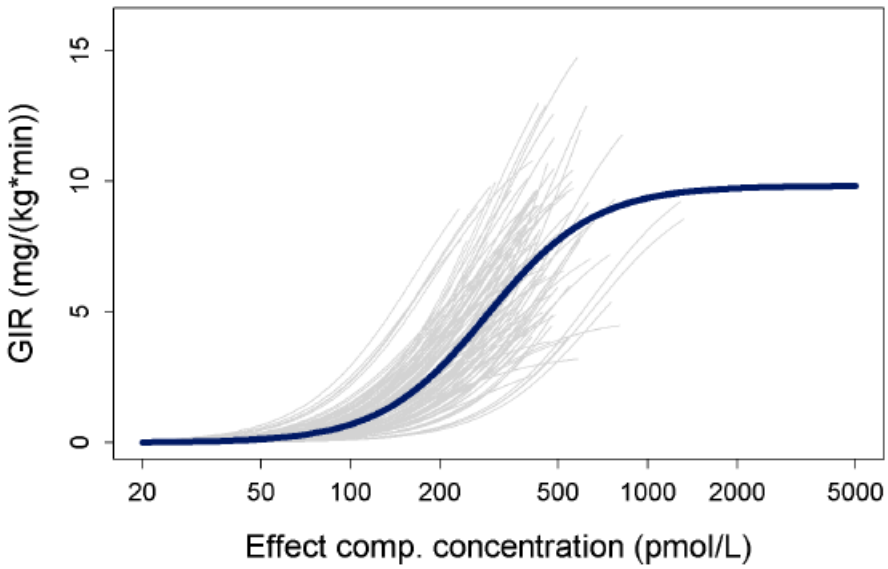



Top: Faster aspart. Bottom: NovoRapid®/NovoLog®. Left y-axis: Total insulin aspart concentration in the central compartment and concentration in the effect compartment. Right y-axis: GIR. Data are simulated profiles following a dose of 0.2 U/kg for a typical subject using the combined PK-PD model.

**Figure 4: Simulated profiles for insulin aspart concentration in the central compartment, concentration in the effect compartment, and GIR for a 0.2 unit/kg dose for a typical subject using the combined PK-PD model**

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 10)

The estimated $E_{max}$-type relationship between the effect compartment concentration and GIR after SC administration of Fiasp and NovoLog is presented in Figure 5. There was an increase in glucose lowering effect with increasing effect compartment concentrations, and therefore also with increasing insulin aspart concentrations. The Applicant reports that the relationship was identical for Fiasp and NovoLog in the model.



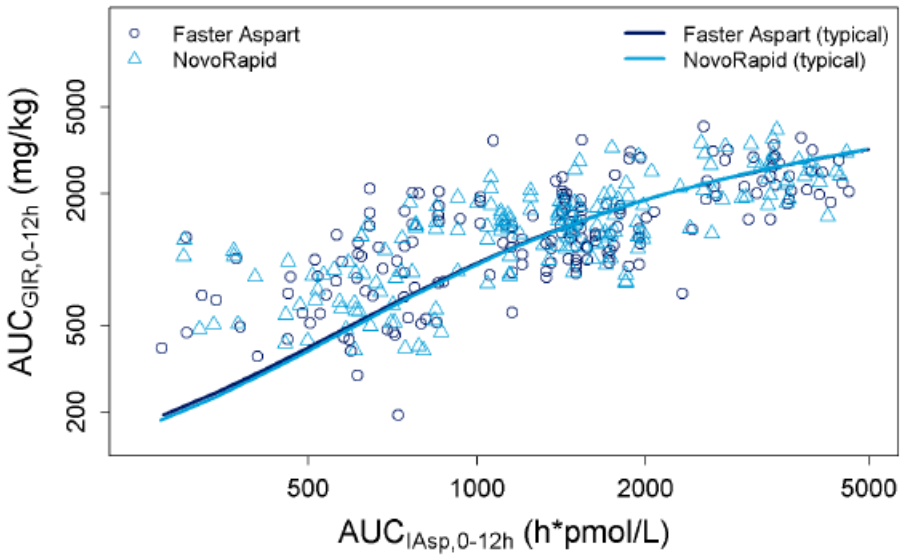

Profiles are model-derived values obtained from the PD model. Individual profiles are shown for the actual range of effect compartment concentrations spanned for each subject (n=72). The typical subject profile is shown for a wider range.

**Figure 5: Relationship between the effect compartment concentration and glucose lowering effect for a typical subject (thick line) and for individual subjects (thin lines) after SC administration of Fiasp and NovoLog**

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 11)

*Exposure-response relationship*

Exposure-response relationship for predicted total exposure ($AUC_{0\text{-}12hr}$) and observed total glucose lowering effect ($AUC_{GIR,0\text{-}12hr}$) for Fiasp and NovoLog is presented in Figure 6. For the individual data points, similar relationships were observed between observed $AUC_{GIR,0\text{-}12hr}$ and predicted $AUC_{0\text{-}12hr}$ across the dose range of 0.1 to 0.4 unit/kg for both treatments. The model-derived relationships (lines) between total glucose lowering effect and insulin aspart exposure were similar for Fiasp and NovoLog.



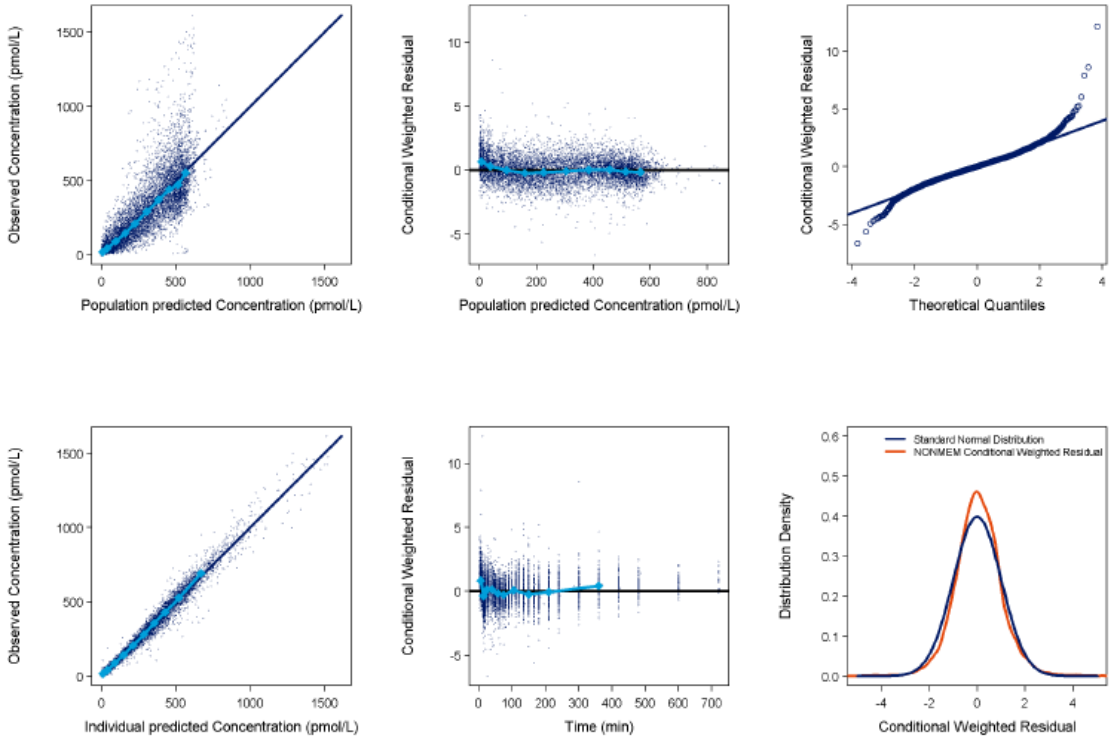

Data points are individual subject values from trial 3887 (n=46, 8-way cross-over) and the lines are typical subject relationships obtained from the combined PK-PD model.

**Figure 6: Relationship between predicted total exposure ($AUC_{0\text{-}12hr}$) and observed total glucose lowering effect ($AUC_{GIR,0\text{-}12hr}$) for Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog**

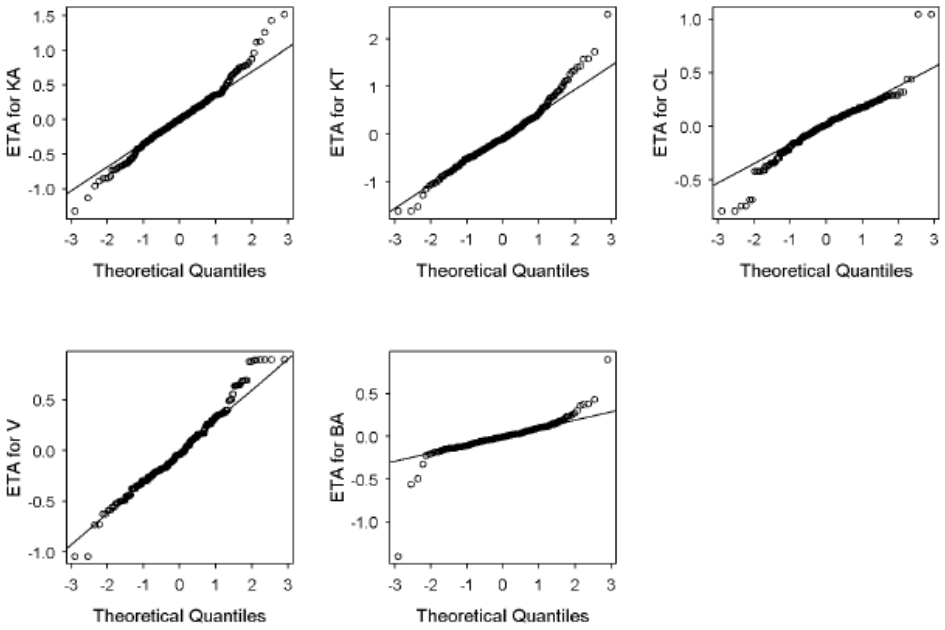
(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 12)

***Qualification of the PK and PD models***

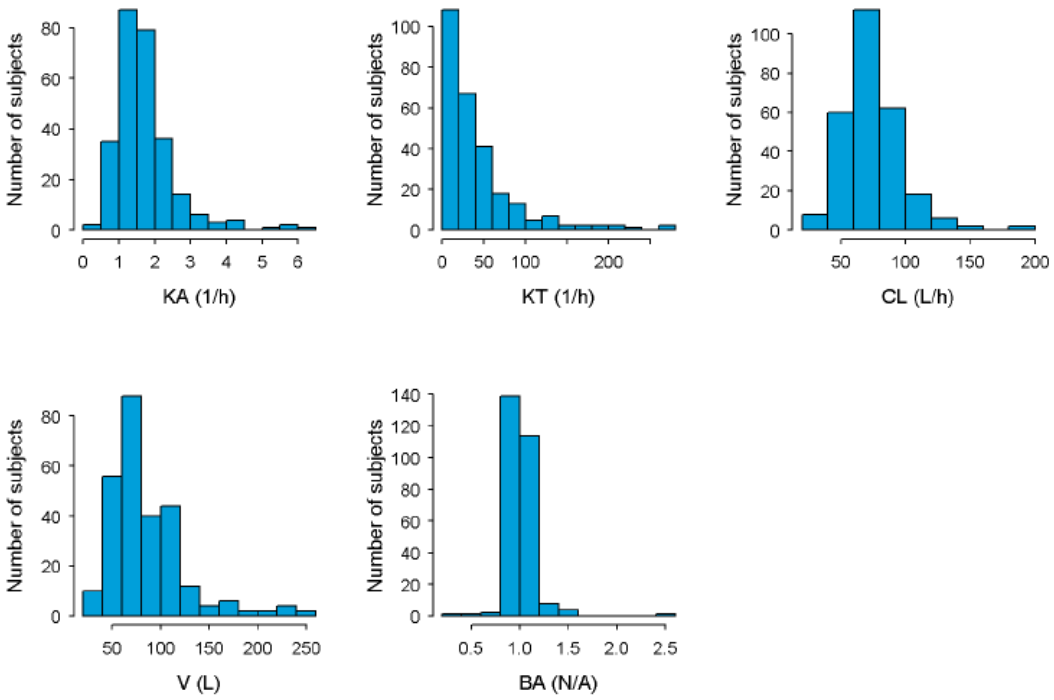
*PK model*



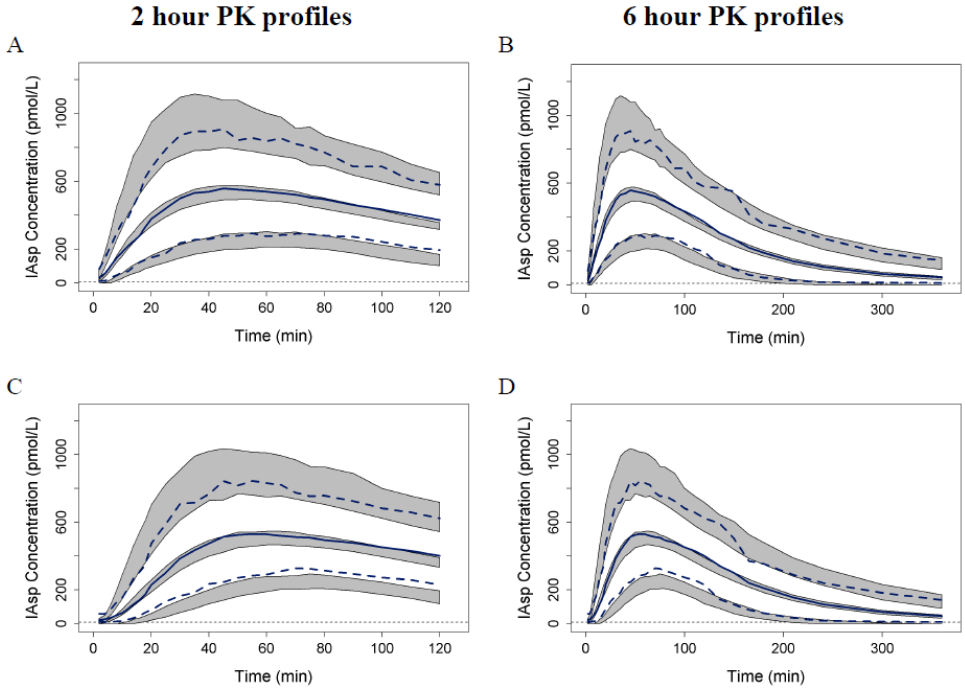

**Standard goodness of fit plots for the PK model.**




**QQ-plots of empirical Bayes estimates for the PK model.**




**Histograms of distributions of model parameter values for the PK model.**




**VPC of the PK model for faster aspart (A, B) and NovoRapid®/NovoLog® (C, D).**

Full and stippled lines represent medians and 95% ranges of observed insulin aspart concentrations. Shaded areas are 95% CIs for the medians and 95% ranges based on 200 simulations.

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 22-24)

The covariance step following model estimation with FOCE+I method was not successful, therefore uncertainties of model estimates were evaluated using bootstrap analysis (shown below).

**Parameter values and uncertainties obtained by bootstrap analysis of the PK model (200 bootstrap samples)**

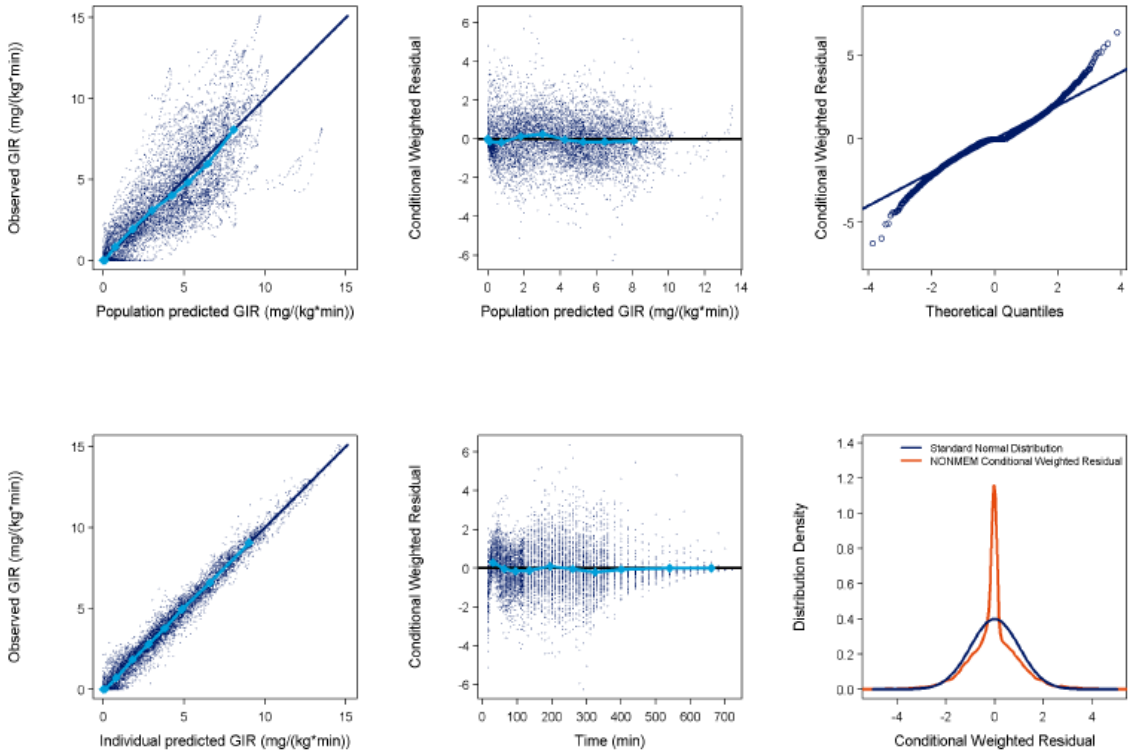
| Parameter | Parameter name* | Unit | Mean | Standard error | Median | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower limit | Upper limit |
| Absorption rate constant | KA | $h^{-1}$ | 1.51 | 0.101 | 1.52 | 1.28 | 1.71 |
| Transit rate constant | KT | $h^{-1}$ | 55.8 | 3.93 | 55.5 | 48.5 | 63.9 |
| | KT.NovoRapid | $h^{-1}$ | 16.1 | 0.751 | 16.1 | 14.8 | 17.7 |
| Clearance/F | CL | L/h | 67.8 | 3.08 | 67.8 | 61.8 | 74.4 |
| Volume of distribution/F | V | L | 76.9 | 5.43 | 77.2 | 66.5 | 86.5 |
| Relative bioavailability | BA | - | 1 | - | 1 | 1 | 1 |
| | BA.NovoRapid | - | 0.991 | 0.0248 | 0.991 | 0.936 | 1.04 |
| Covariate relationships | BWonCL | - | 1 | - | 1 | 1 | 1 |
| | BWonV | - | 1 | - | 1 | 1 | 1 |
| | ABonCL | - | -0.187 | 0.0326 | -0.184 | -0.252 | -0.118 |
| | AGEGRPonCL | - | 0.916 | 0.07 | 0.911 | 0.794 | 1.05 |
| | DOSEonCL | - | -0.209 | 0.0963 | -0.218 | -0.389 | -0.011 |
| | SEXonCL | - | 0.911 | 0.0487 | 0.911 | 0.812 | 1.01 |
| | BMIonKA | - | -1.22 | 0.459 | -1.17 | -1.99 | -0.182 |

*Name used in model scripts

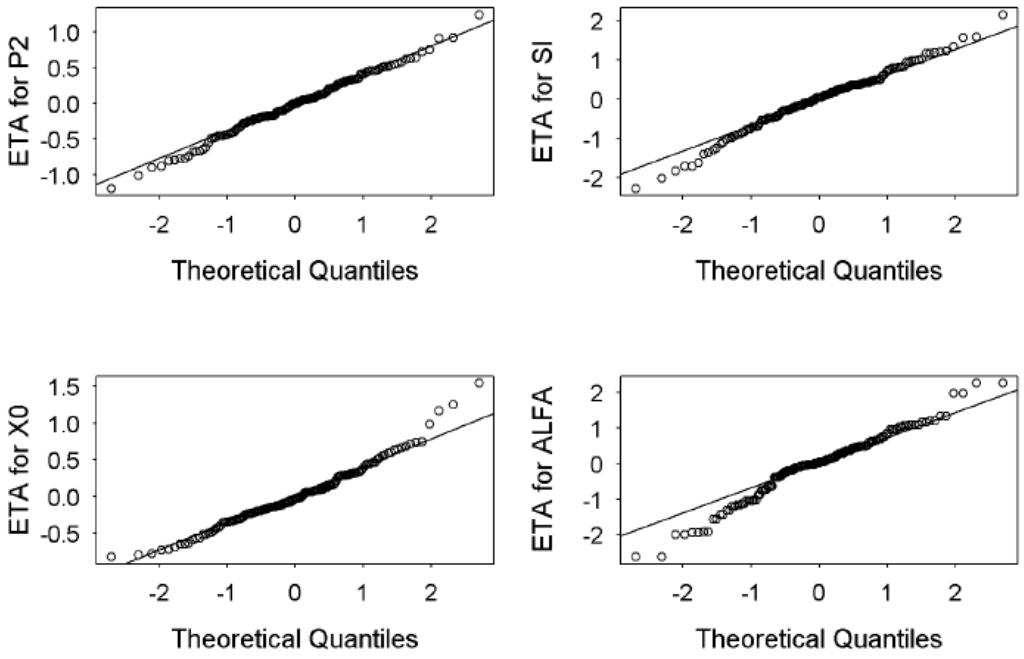
(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 19)

*PD model*

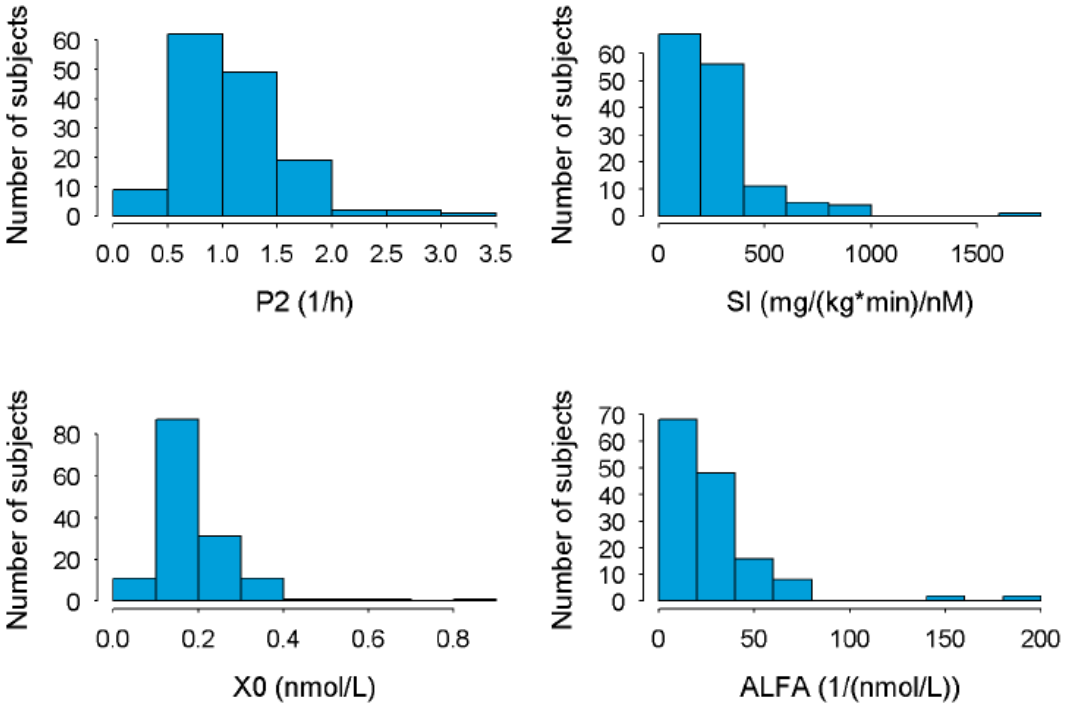
A deviation from normality for the conditional weighted residual (zero-inflation) was observed, which the Applicant reports is due to the many (close-to) zero smoothed GIR values in the late phase of each clamp.



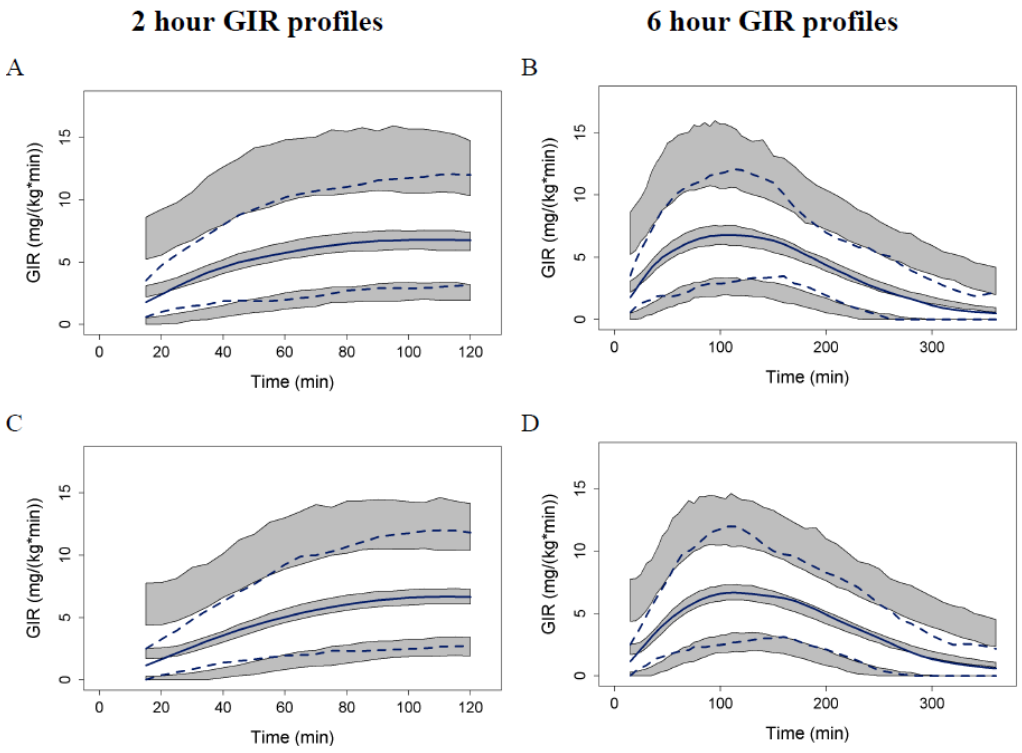

**Standard goodness of fit plots for the PD model.**




**QQ-plots of empirical Bayes estimates for the PD model.**




**Histograms of distributions of model parameter values for the PD model.**




**VPC of the PD model for faster aspart (A, B) and NovoRapid®/NovoLog® (C, D).**

Full and stippled lines represent medians and 95% ranges of observed smoothed GIR values. Shaded areas are 95% CIs for the medians and 95% ranges based on 200 simulations.

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 25-27)

**Parameter values and uncertainties obtained by bootstrap analysis of the PD model (200 bootstrap samples)**

| Parameter | Parameter name* | Unit | Mean | Standard error | Median | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower limit | Upper limit |
| Turnover rate constant | P2 | $h^{-1}$ | 0.995 | 0.0653 | 0.99 | 0.87 | 1.14 |
| Insulin sensitivity | SI | mg/kg /min /nmol/L | 192 | 48.2 | 187 | 111 | 303 |
| Initial effect compartment concentration | X0 | nmol/L | 0.174 | 0.00944 | 0.174 | 0.156 | 0.194 |
| α | ALFA | L/nmol | 21.6 | 6.61 | 20.8 | 12.3 | 34.6 |
| Hill coefficient | GAMMA | - | 2.43 | 0.15 | 2.42 | 2.18 | 2.73 |
| Covariate relationships | ABonSI | - | -0.1 | 0.0462 | -0.101 | -0.196 | -0.00642 |
| | AGEGRPonSI | - | 0.893 | 0.132 | 0.889 | 0.639 | 1.15 |
| | BMIonSI | - | -1.5 | 0.512 | -1.52 | -2.44 | -0.4 |
| | SEXonSI | - | 1.1 | 0.119 | 1.09 | 0.9 | 1.36 |

*Name used in model scripts

(Source: Summary of clinical pharmacology studies, Appendix 5.4, page 21)

### 5.4 Compartmental Pharmacokinetic Model

The Applicant utilized a transit compartment model to predict insulin aspart serum concentrations for the time period from Fiasp and NovoLog administration to the time of the first insulin aspart concentration that was above the LLOQ ($t_{first}$). Pharmacokinetic parameters such as onset of appearance and area under the curve, will therefore be estimated based on both model predicted insulin aspart concentrations and observed insulin aspart concentrations.

The transit compartment model is presented in Figure 1, where D, $T_i$, A, and C are drug amount in dose, -$i^{th}$ transit compartment, absorption compartment, and central compartment, respectively.

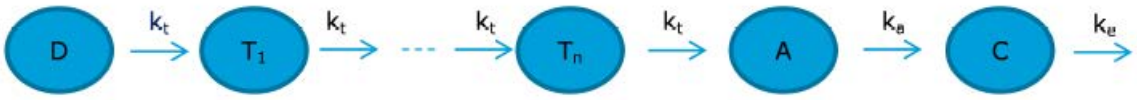



**Figure 1: Transit compartment model**
(Source: Study NN1218-3922, 16-1-09-statistical-methods, page 15)

The description of the model as reported by the Applicant is shown below.

The model will be fitted to individual IAsp concentration-time for each PK profile in turn, using proc nlmixed (without random effects) in SAS with IAsp concentration as response and actual time as covariate assuming an additive error on log scale. LLOQ is 10 pmol/L and the values below LLOQ are treated as censored (i.e. between 0 and 10 pmol/L). The model parameters are: Fractional transit rate ($k_t$), fractional absorption rate ($k_a$), fractional elimination rate ($k_e$), and apparent volume of distribution of the central compartment (V). All parameters are estimated on log scale and it is assumed that $k_a$ is greater than $k_e$ (ensured using the parameterisation $k_a=k_e+k_d$, $k_d>0$).

In case convergence is not reached or the standard error of log($k_d$) is not estimable or greater than 5, the model is re-run assuming $k_a=k_e$.

The model with n transit compartments is described in terms of differential equations below:

1) $\frac{dD}{dt} = -k_t \cdot D$

2) $\frac{dT_1}{dt} = k_t \cdot (D - T_1)$

3) $\frac{dT_i}{dt} = k_t \cdot (T_{i-1} - T_i), \quad i = 2, \dots, n$

4) $\frac{dA}{dt} = k_t \cdot T_n - k_a \cdot A$

5) $\frac{dC}{dt} = k_a \cdot A - k_e \cdot C$

with initial conditions: $D(0)=Dose$, $T_i(0)=0$, $A(0)=0$, $C(0)=0$.

The concentration of IAsp in the central compartment is given by c(t)=C(t)/V and the closed form solution is given below:

$k_a \neq k_e$:

$$c(t) = \frac{Dose \cdot k_a \cdot {k_t}^{n+1}}{V \cdot n! \cdot (k_a - k_e)} \left\{ \frac{e^{-k_e t}}{(k_t - k_e)^{n+1}} \gamma(n+1, (k_t - k_e)t) - \frac{e^{-k_a t}}{(k_t - k_a)^{n+1}} \gamma(n+1, (k_t - k_a)t) \right\}$$

$\boldsymbol{k_a = k_e}$:

$$c(t) = \frac{Dose \cdot k_a \cdot {k_t}^{n+1} \cdot e^{-k_a t}}{V \cdot n! \cdot (k_t - k_a)^{n+2}} \{t \cdot (k_t - k_a) \cdot \gamma(n+1, (k_t - k_a)t) - \gamma(n+2, (k_t - k_a)t)\}$$

where

$$\gamma(n+1, x) = n! \left(1 - e^{-x} \sum_{k=0}^{n} \frac{x^k}{k!}\right)$$

If the model does not i.m. profiles a new model must be considered.

(Source: Study NN1218-3922, 16-1-09-statistical-methods, page 15-16)

Insulin aspart exposure in the first 15 min after dose admsinitration ($AUC_{0\text{-}15\ min}$) which would be most influenced by predicted serum concentrations of insulin aspart was estimated as follows:

- *If time of first sample above LLOQ, $t_{first}$, is earlier than 15 min:* Area will be calculated as the sum of the AUC from 0 to $t_{first}$ ($AUC_{0\text{-}tfirst}$) and AUC from $t_{first}$ until 15 min ($AUC_{tfirst\text{-}15min}$). $AUC_{0\text{-}tfirst}$ will be calcualted using the fitted curve from the compartmental model. $AUC_{tfirst\text{-}15min}$ will be calculated using linear trapezodial based on observed concentrations and actual sampling times between $t_{first}$ and 15 min.
- *If $t_{first}$ is later than 15 min:* Area will be calculated using the fitted curve from the compartmental model from 0 to 15 min.

An analysis conducted by the Reviewer showed that in study NN1218-3978, the time of first sample above LLOQ in a majority of subjects in both the Fiasp and NovoLog treatment groups occurred within the first 5 min following dosing (Figure 2).

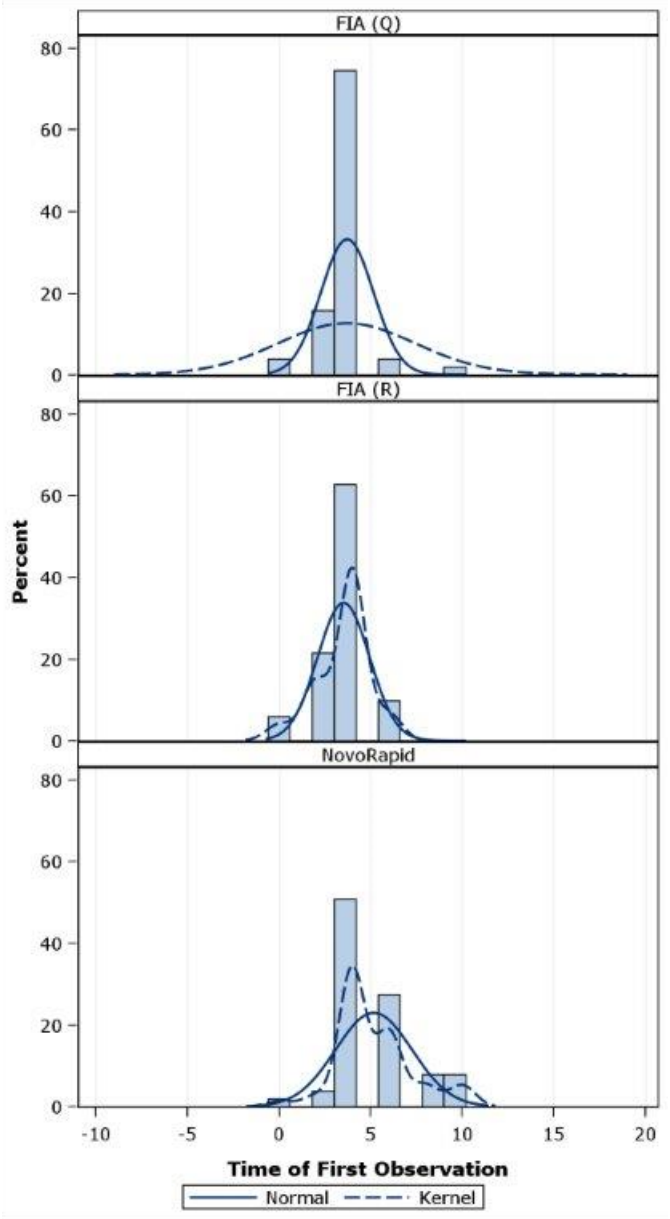



**Figure 2: Time of first observed insulin aspart concentration above LLOQ following administration of Fiasp (FIA(Q)), NovoLog, and an exploratory formulation (FIA(R)) in Study NN1218-3978**

(Source: Reviewer's analysis of data from Study NN1218-3978)

## 5.5 Euglycemic clamp studies: Blood glucose profiles

### Study NN1218-3978

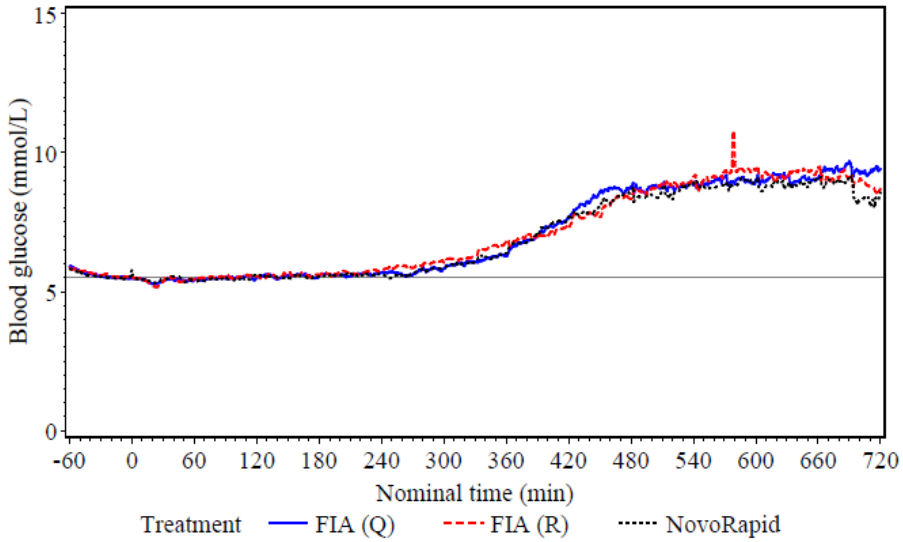



**Figure 1: Blood glucose profile for Fiasp (FIA(Q)), NovoLog, and exploratory formulation (FIA(R)) during the euglycemic clamp in patients with T1DM**

(Source: Study NN1218-3978, Clinical study report, page 111)

### Study NN1218-3891

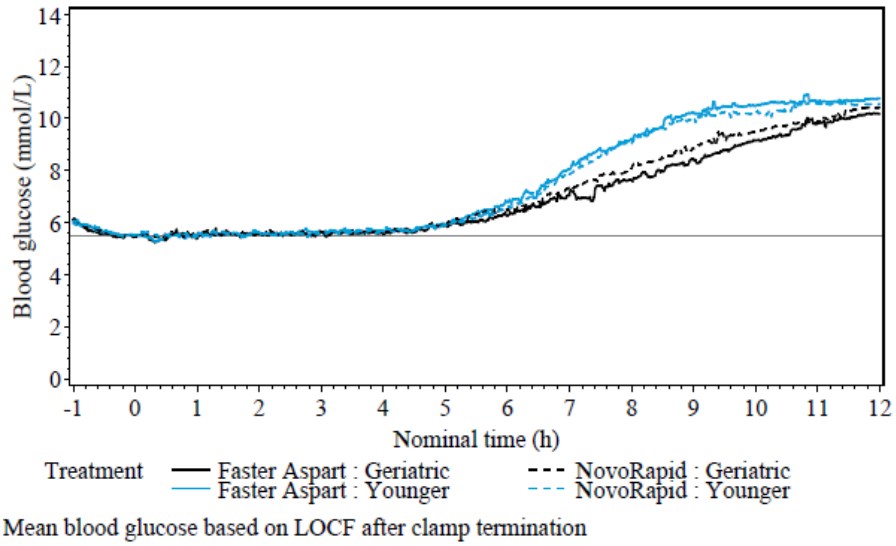



**Figure 2: Blood glucose profile for Fiasp (indicated as faster aspart in the Applicant's figure above and NovoLog during the euglycemic clamp in young adult patients with T1DM (also shows data for geriatric patients with T1DM)**

(Source: Study NN1218-3891, Clinical study report, page 155)

**Study NN1218-3887**

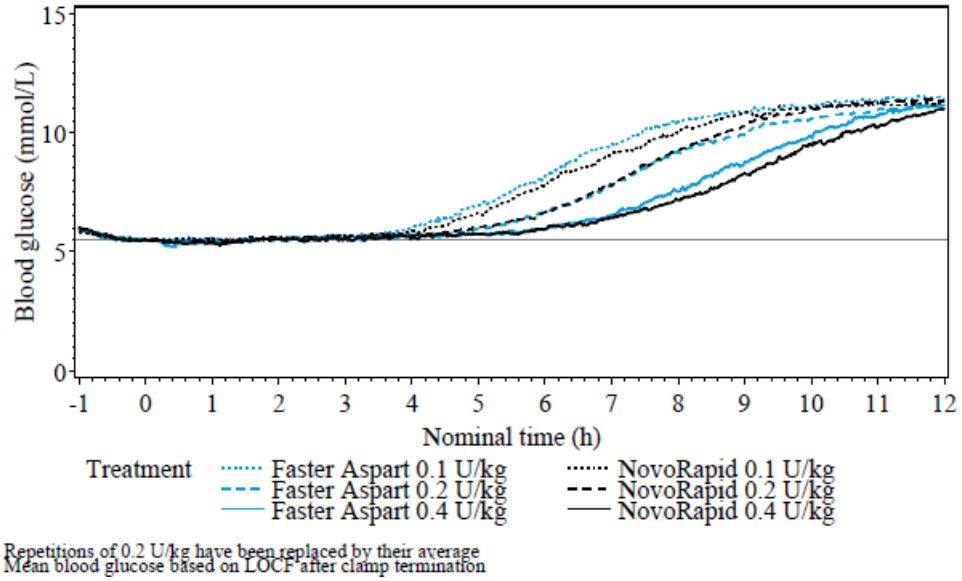



**Figure 3: Blood glucose profile for Fiasp (indicated as faster aspart in the Applicant's figure above) and NovoLog during the euglycemic clamp in patients with T1DM**

(Source: Study NN1218-3887, Clinical study report, page 159)

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/s/

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SHALINI WICKRAMARATNE SENARATH YAPA
09/06/2017

MANOJ KHURANA
09/06/2017

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA: 208751** | Submission Date(s): 12/08/2015 |
| **Brand Name** | TBD |
| **Generic Name** | NN1218 |
| **Clinical Pharmacology Reviewer** | Shalini Wickramaratne Senarath Yapa, Ph.D. |
| **Clinical Pharmacology Team Leader** | Manoj Khurana, Ph.D. |
| **OCP Division** | Clinical Pharmacology -2 |
| **OND Division** | Metabolic and Endocrine Products |
| **Sponsor** | Novo-Nordisk |
| **Submission Type; Code** | 505(b)(1); Standard |
| **Formulation; Strength(s)** | 10 mL vials, 3 mL FlexTouch; 100 Units of insulin aspart per mL (U-100) |
| **Proposed Indication** | To improve glycemic control in adults with diabetes mellitus |

## Executive Summary

NN1218 (insulin aspart) developed by Novo Nordisk Inc., is an insulin analog proposed to improve glycemic control in adults with diabetes mellitus. This is a 505 (b)(1) NDA submission.

NN1218 is developed as a mealtime insulin with the claim of 'greater early glucose-lowering effect' compared to the currently approved insulin aspart, NovoLog®. Compared to NovoLog®, NN1218 formulation has two additional excipients, nicotinamide and L-arginine hydrochloride. The sponsor claims that the addition of nicotinamide results in a '*faster initial absorption of insulin aspart following subcutaneous (SC) injection, leading to a greater early glucose-lowering effect compared to NovoLog®*'. The claimed changes to the time-action profile of NN1218 is reflected in the proposed label language under Dosage and Administration Section, which states that NN1218 can be administered at the start of a meal or postmeal (within 20 minutes after the start of a meal).

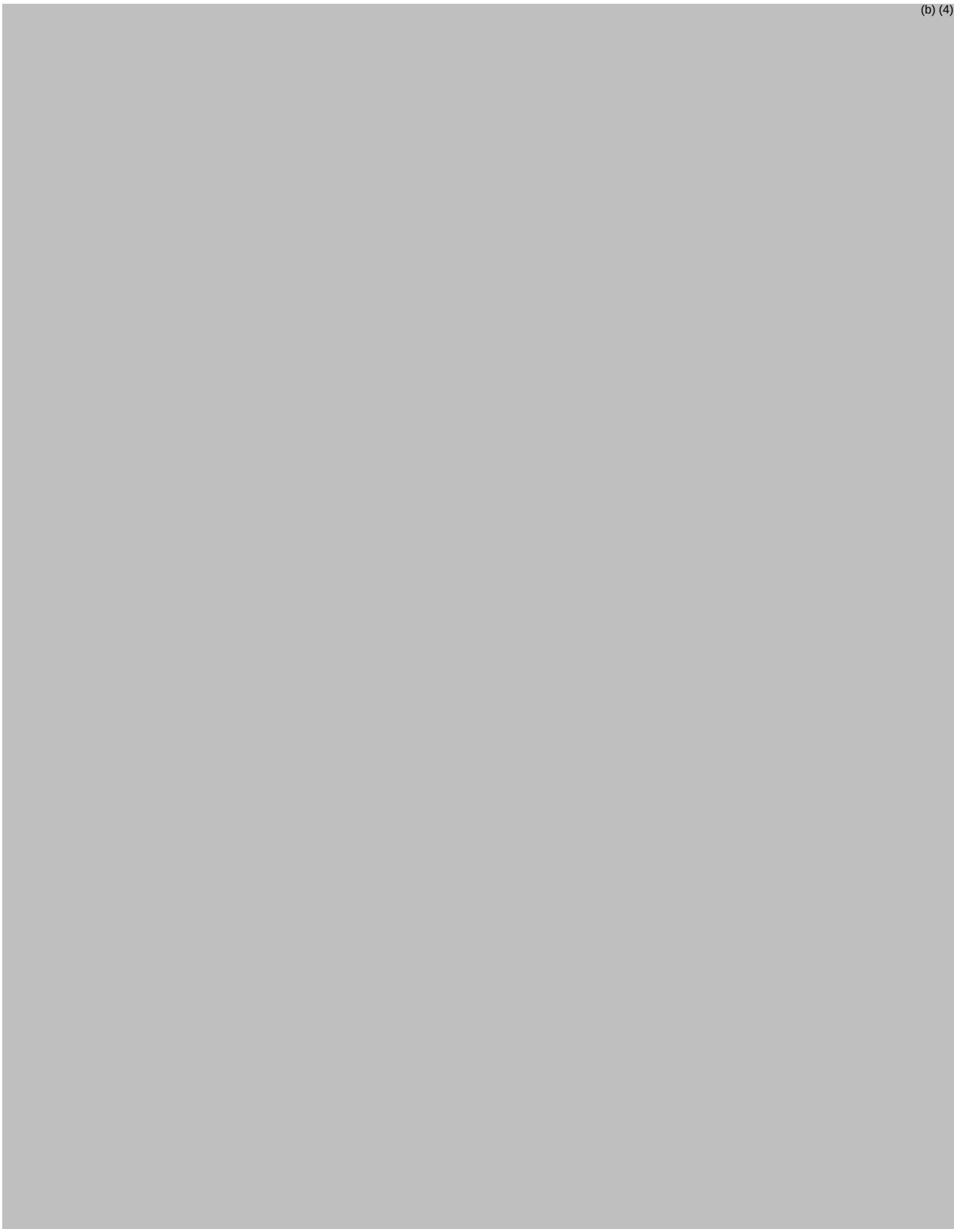
Sponsor relies on the results of the pharmacokinetic (PK) and pharmacodynamic (PD) data from the clinical pharmacology studies (euglycemic clamp studies and meal challenge studies) to claim that there is 'faster initial absorption of insulin leading to greater early insulin exposure following administration of NN1218 compared to NovoLog®'. This emphasizes the importance of understanding the PK and PD profile (collectively regarded as the time-action profile) of NN1218 compared to NovoLog®. As has been the case with any approved insulin product to date, from a regulatory and scientific perspective, the time-action profile of NN1218 (time to onset, peak action, and duration of action) is fundamental in guiding the safe and effective clinical use of this insulin product. The time-action profile provides information pertaining to the optimal time of administration of the insulin product in relation to a meal and enables optimization of the insulin therapy in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

## Recommendation

The office of clinical pharmacology (OCP) has reviewed the clinical pharmacology data submitted under NDA 208751 and found the data unacceptable to support the approval of the NDA pending adequate resolution of the deficiencies identified with the data. The following deficiency and the recommendations to address the deficiency should be communicated to the sponsor as appropriate:

Deficiency: The bioanalytical method used for (b) (4) is deemed unreliable due a number of issues mentioned below, which affect the reliability of the pharmacokinetic data for all clinical pharmacology studies generated using the bioanalytical methodology under question.

Issues:



(b) (4)

The review team's concerns were discussed with the senior leadership team of the OCP (Meeting date - 08/23/2016) and there was overall agreement that the bioanalytical method used to (b) (4) has significant deficiencies and fails to produce reliable pharmacokinetic data.

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 [1]. 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)

**Summary of Key Clinical Pharmacology Assessments**

The clinical pharmacology development program consisted of 10 trials, all in patients with T1DM, except in 1 trial (Figure 1). Two Phase 3 trials, trial NN1218-3852 (therapeutic confirmatory trial) and NN1218-3853 (not shown in Figure 1) were conducted in T1DM and T2DM patients, respectively. The Phase 3 trials characterized the postprandial glucose (PPG)

excursion of NN1218 following a standardized meal test. The sponsor reports that all trials were conducted with the to-be-marketed formulation of insulin aspart.

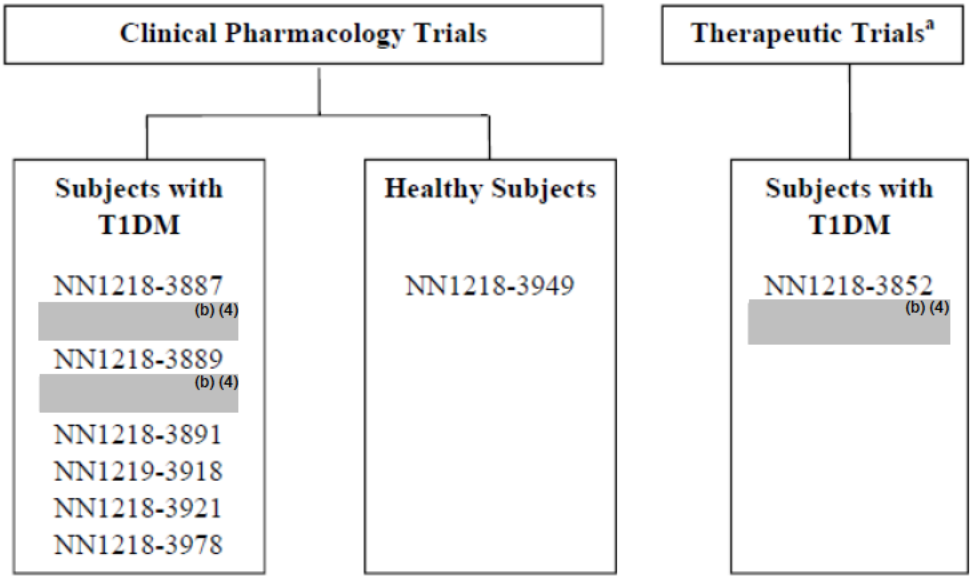



**Figure 1: Overview of clinical trials submitted to support the NDA for NN1218**
*(Source: Summary of clinical pharmacology studies, page16)*

Since we identified deficiencies in the bioanalytical method used to generate the clinical pharmacology data for this NDA, the clinical pharmacology data is deemed unacceptable at this stage. This memo focuses on the deficiencies identified during review of the submission and captures the clinical pharmacology recommendations to resolve the deficiencies.

(b) (4)

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

**Reference**

1. Food and Drug Administration, Guidance for Industry - Bioanalytical Method Validation, September 2013

2. NovoLog®, Prescribing information, Novo Nordisk, Inc., Label approved on 04/17/2015

(b) (4)

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/s/

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SHALINI WICKRAMARATNE SENARATH YAPA
09/08/2016

MANOJ KHURANA
09/08/2016

# CLINICAL PHARMACOLOGY FILING FORM

## Application Information

| | | | |
|---|---|---|---|
| **NDA/BLA Number** | 208751 | **SDN** | 1 |
| **Applicant** | Novo Nordisk Inc. | **Submission Date** | 12/08/2015 |
| **Generic Name** | Insulin aspart | **Brand Name** | Fiasp |
| **Drug Class** | Human insulin analog | | |
| **Indication** | Fiasp is a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus. | | |
| **Dosage Regimen** | Starting Dose:<br>(b) (4)<br>  <br>Converting from other insulins in patients with T1DM or T2DM:<br>▫ If converting from another mealtime insulin to Fiasp, the change can be done on a unit-to-unit basis.<br><br>Fiasp should be administered at the start of a meal or postmeal (within 20 min after starting a meal). | | |
| **Dosage Form** | Solution for injection | **Route of Administration** | Subcutaneous and Intravenous |
| **OCP Division** | DCP 2 | **OND Division** | DMEP |

| **OCP Review Team** | **Primary Reviewer(s)** | **Secondary Reviewer/ Team Leader** |
|---|---|---|
| **Division** | Shalini Wickramaratne Senarath Yapa, Ph.D. | Manoj Khurana, Ph.D. |
| **Pharmacometrics** | | |
| **Genomics** | | |

| | | | |
|---|---|---|---|
| **Review Classification** | ☑ Standard ☐ Priority ☐ Expedited | | |
| **Filing Date** | 02/06/2016 | **74-Day Letter Date** | 02/19/2016 |
| **Review Due Date** | 09/02/2016 | **PDUFA Goal Date** | 10/08/2016 |

## Application Fileability

**Is the Clinical Pharmacology section of the application fileable?**

☑ Yes

☐ No

If no list reason(s)

**Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?**

☑ Yes

☐ No

If yes list comment(s):

- For study NN1218-3852 specify the location of the data files or submit the relevant data files pertaining to the population pharmacokinetic modeling described in the study report (Section 9.7.6)
- Specify the location of the data files and output files pertaining to the population pharmacokinetic analysis conducted to determine the effect of age/body mass index on the insulin exposure of FIASP

**Is there a need for clinical trial(s) inspection?**

☐ Yes

☑ No

If yes explain: See comment in item 1 under 'criteria for refusal to file'.

## Clinical Pharmacology Package

| | | | |
|---|---|---|---|
| Tabular Listing of All Human Studies | ☑ Yes ☐ No | Clinical Pharmacology Summary | ☑ Yes ☐ No |
| Bioanalytical and Analytical Methods | ☑ Yes ☐ No | Labeling | ☑ Yes ☐ No |

**Clinical Pharmacology Studies**

| Study Type | | Count | Comment(s) |
|---|---|---|---|
| **In Vitro Studies** | | | |
| ☐ Metabolism Characterization | | | |
| ☐ Transporter Characterization | | | |
| ☐ Distribution | | | |
| ☐ Drug-Drug Interaction | | | |
| **In Vivo Studies** | | | |
| **Biopharmaceutics** | | | |
| ☐ Absolute Bioavailability | | | |
| ☐ Relative Bioavailability | | | |
| ☐ Bioequivalence | | | |
| ☐ Food Effect | | | |
| ☐ Other | | | |
| **Human Pharmacokinetics** | | | |
| Healthy Subjects | ☐ Single Dose | | |
| | ☐ Multiple Dose | | |
| Patients | ☑ Single Dose | 1 | (b) (4) (Module 5.3.3.3) |
| | ☐ Multiple Dose | | |
| ☐ Mass Balance Study | | | |
| ☐ Other (e.g. dose proportionality) | | | |
| **Intrinsic Factors** | | | |
| ☑ Race | | 1 | NN1218-3918 (Module 5.3.4.2) |
| ☐ Sex | | | |
| ☑ Geriatrics | | 1 | NN1218-3891 (Module 5.3.3.3) |
| (b) (4) | | | Module 5.3.3.3) |
| ☐ Hepatic Impairment | | | |
| ☐ Renal Impairment | | | |
| ☐ Genetics | | | |
| **Extrinsic Factors** | | | |
| ☐ Effects on Primary Drug | | | |

| | | |
|---|---|---|
| ☐ Effects of Primary Drug | | |
| **Pharmacodynamics** | | |
| ☐ Healthy Subjects | | |
| ☑ Patients | 1 | (b) (4) (Module 5.3.5.1) |
| **Pharmacokinetics/Pharmacodynamics** | | |
| ☑ Healthy Subjects | 1 | NN1218-3949 (Module 5.3.1.1) |
| ☑ Patients | 7 | NN1218-3978 (Module 5.3.4.2)<br>NN1218-3887 (Module 5.3.4.2)<br>(b) (4) (Module 5.3.4.2)<br>NN1218-3889 (Module 5.3.4.2)<br>NN1218-3921 (Module 5.3.4.2)<br>NN1218-3891 (Module 5.3.3.3)<br>NN1218-3852 (Module 5.3.5.1) |
| ☐ QT | | |
| **Pharmacometrics** | | |
| ☑ Population Pharmacokinetics | 1 | NN1218-3852 (Module 5.3.5.1); See comments to sponsor. |
| ☐ Exposure-Efficacy | | |
| ☐ Exposure-Safety | | |

| | | | | | |
|---|---|---|---|---|---|
| **Total Number of Studies** | **11** | **In Vitro** | | **In Vivo** | 11 |
| **Total Number of Studies to be Reviewed** | **11** | | | | 11 |

| Criteria for Refusal to File (RTF) | | |
|---|---|---|
| **RTF Parameter** | **Assessment** | **Comments** |
| **1.** Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | ☐Yes ☑ No ☐N/A | The sponsor reports that the formulation (faster-acting insulin aspart) intended for the market is identical to the formulation tested in the Phase 3a clinical program. The formulation used for the PK/PD clinical studies are also the faster-acting insulin aspart, FIA(Q), to be marketed formulation. |
| **2.** Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information) | ☐Yes ☑ No ☐N/A | Cross-reference NDA20986 for drug-drug interaction information (class labeling). |
| **3.** Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request? | ☑Yes ☐ No ☐N/A | Sponsor has submitted pharmacokinetic (PK) studies and PK/pharmacodynamic studies. |
| **4.** Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application? | ☐ Yes ☐No ☑N/A | |
| **5.** Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest? | ☑ Yes ☐No ☐N/A | |
| **6.** Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment? | ☑ Yes ☐No ☐N/A | |
| **7.** Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)? | ☐ Yes ☑No ☐N/A | Comments included in the 74-Day Letter asking sponsor to specify the location of the data/output files or submit the data/output files for the population PK analysis conducted for study NN1218-3852 and for a proposed label claim (refer to the Filing Memo). |
| **8.** Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)? | ☑ Yes ☐No ☐N/A | |
| **9.** Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and | ☑ Yes ☐ No ☐N/A | |

| | | |
|---|---|---|
| appendices? | | |
| **Complete Application**<br>**10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission? | ☑ Yes ☐No ☐N/A | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist** | | |
| **Data** | | |
| **1.** Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | ☐Yes ☑ No ☐N/A | The data has not been submitted in the standard SDTM format. However, pertinent information (raw plasma concentration vs. time data, PK data, PD data) can be imported from the provided SAS transport files. |
| **2.** If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | ☐Yes ☐No ☑ N/A | |
| **Studies and Analysis** | | |
| **3.** Is the appropriate pharmacokinetic information submitted? | ☑ Yes ☐No ☐N/A | |
| **4.** Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | ☑Yes ☐No ☐ N/A | The doses are Unit per body weight; therefore the doses have been individualized. |
| **5.** Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | ☑Yes ☐No ☐ N/A | |
| **6.** Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | ☑Yes ☐No ☐ N/A | Study NN1218-3891 (geriatric subjects with T1DM).<br>(b) (4) [redacted] |
| **7.** Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | ☑Yes ☐No ☐ N/A | The sponsor has requested partial waivers for conducting pediatric studies in patients below 1 year of age with T1DM and patients below 10 years of age with T2DM. The sponsor has requested deferrals for conducting pediatric studies in patients between 1 to 17 years of age with T1DM and patients between 10 to 18 years of age with T2DM.<br>(b) (4) [redacted] |
| **General** | | |
| **8.** Are the clinical pharmacology and | ☑ Yes ☐No ☐N/A | |

| | | |
|---|---|---|
| biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | | |
| **9.** Was the translation (of study reports or other study information) from another language needed and provided in this submission? | ☐Yes ☐No ☑ N/A | |

## Filing Memo

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ☑Yes ☐ No

Overview of the NDA 208751 submission:

- Refer to the attached presentation slides.

Number of Studies:

- Total of 11 studies will be the primary focus of this review.

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

- **For study NN1218-3852 specify the location of the data files or submit the relevant data files pertaining to the population pharmacokinetic modeling described in the study report (Section 9.7.6)**
- **Specify the location of the data files and output files pertaining to the population pharmacokinetic analysis conducted to determine the effect of age/body mass index on the insulin exposure of FIASP**

Shalini Wickramaratne Senarath Yapa 11th February 2016
Reviewing Clinical Pharmacologist

Manoj Khurana 11th February 2016
Team Leader

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# NDA 208751 Filing Meeting

## Insulin aspart injection (FIASP)

Sponsor: Novo Nordisk Inc.
Submitted: 9th December 2015

**OCP Review Team:**

**Clinical Pharmacology Reviewer:** **Shalini W.S. Yapa, Ph.D.**
**Clinical Pharmacology Team Leader:** **Manoj Khurana, Ph.D.**

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# Overview

- **Type of Submission:** Section 505(b)(1)
- **Proposed Indications:**
  - To improve glycemic control in adults with diabetes mellitus
- **Formulation:** FIASP (insulin aspart) 100 units/mL (U-100)
  - Addition of nicotinamide results in faster initial absorption of insulin aspart following SC injection, leading to a greater early glucose-lowering effect compared to NovoRapid®/NovoLog®
  - 10 mL vials, 3 mL FIASP FlexTouch®
- **Administration:**
  - SC injection, (b) (4) Intravenous infusion
- **Proposed dose range:**
  - FIASP should be injected at the start of a meal or post-meal (within 20 min after starting a meal)
  - Dosage of FIASP is individualized based on patient's metabolic needs, blood glucose monitoring results, and glycemic control goal

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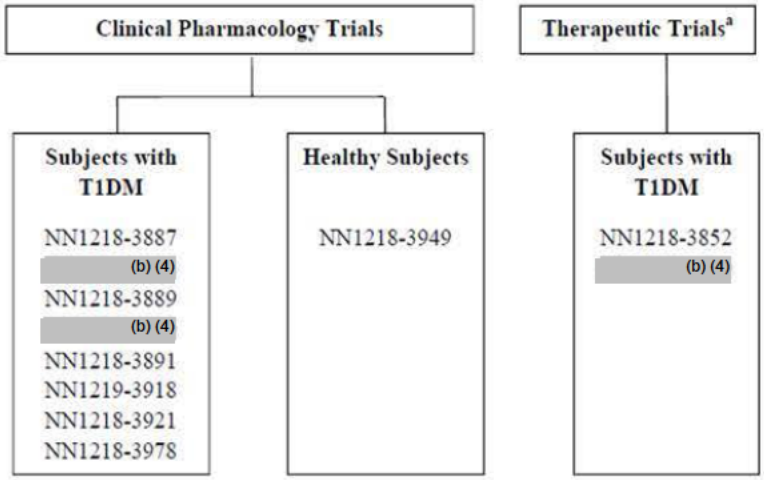
# FIASP Development Program




[a] Trial 3852 was a therapeutic confirmatory trial which included a meal test and population pharmacokinetic analyses
(b) (4)

Trials contributing to the PK and PD evaluation conducted with the final FIASP formulation, the to be marketed formulation.

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# Clinical Pharmacology Studies & Objectives

| Type | Trial | Subject No. | T1DM or Healthy | Objective |
|---|---|---|---|---|
| PK/PD | NN1218-**3978** | 52 | T1DM | Compare the early PD response of FIASP and NovoRapid® |
| PK/PD | NN1218-**3889** | 36 | T1DM | Compare the early PD response of FIASP and NovoRapid® admin immediately before a meal |
| (b) (4) | | | | |
| PK/PD | NN1218-**3887** | 46 | T1DM | PD dose-response relationship for 3 clinically relevant doses of FIASP |
| PK/PD | NN1218-**3921** | 33 | T1DM | Compare the total PD response of FIASP when admin 20 min after start of meal with NovoRapid® admin immediately before a meal |
| PK/PD | NN1218-**3949** | 21 | Healthy | Systemic extent of absorption of insulin aspart following SC injection in different regions of the body |
| PK/PD | NN1218-**3918** | 43 | T1DM | Compare early PK exposure of FIASP and NovoRapid® in Japanese subjects |
| (b) (4) | | | | |
| PK/PD | NN1218-**3891** | 67 | T1DM | Compare the PD response of FIASP between geriatric and younger adult subjects |

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# Review Questions

- What are the PK and PD characteristics of FIASP and how do they support sponsor's claim?
- What is the dose-PK/PD relationship of FIASP?
- What is the effect of injection site on FIASP PK/PD?
- What is the PK/PD characteristics of FIASP following both mealtime dosing and postmeal dosing?
- [redacted] (b) (4)
- What is the PK/PD of FIASP in [redacted] (b) (4) geriatric patient population?

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# Filing Conclusion, Consults and IRs

- Application is filable from the clinical pharmacology perspective
- No OSIS consult needed:
  - To be marketed formulation used in the PK/PD studies and Phase 3 studies
- Information Request:
  - For study NN1218-3852 specify the location of the data files or submit the relevant data files pertaining to the population PK modeling described in the study report (Section 9.7.6)
  - Specify the location of the data files and output files pertaining to the population PK analysis conducted to determine the effect of age/BMI on the insulin exposure of FIASP

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# Backup Slides



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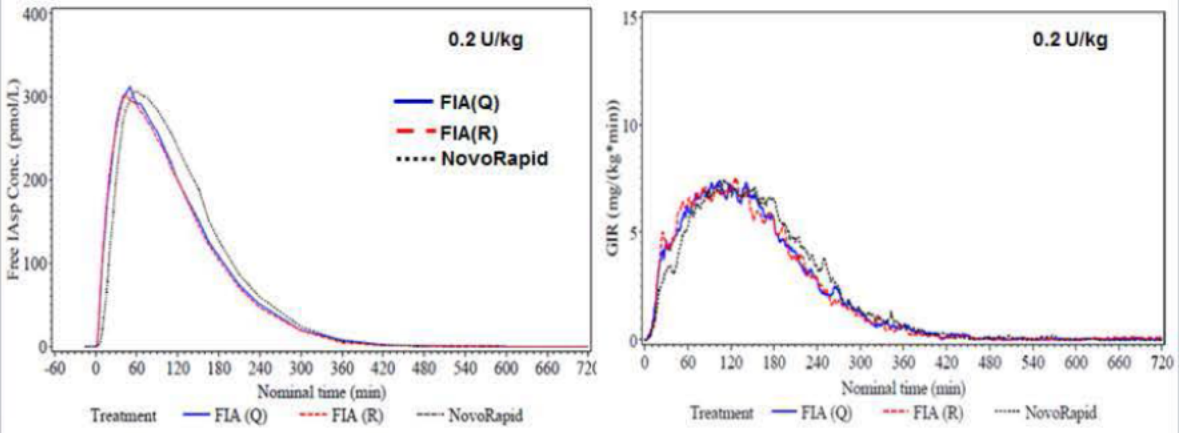
## FIASP claimed to have faster onset and early glucose-lowering effect as compared to NovoRapid®

- FIASP administered via SC injection results in a faster initial absorption of insulin (left shift in profile) compared to NovoRapid®/NovoLog®




**Review Question:** What are the PK and PD characteristics of FIASP and how do they support sponsor's claim? (SC injection, (b) (4) within-subject variability)

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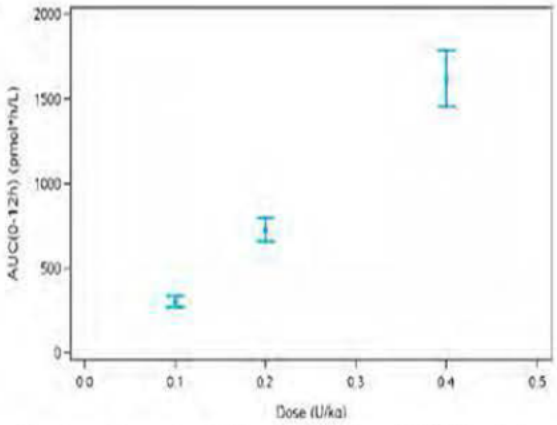
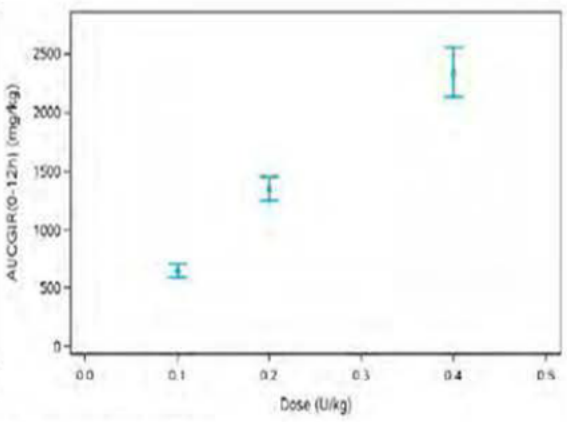
# Dose-response relationship for FIASP

- **Sponsor:** $AUC_{IAsp,0-12hr}$ and $C_{max}$ increases with increasing SC doses of FIASP. This increase was slightly greater than proportional
- **Sponsor:** $AUC_{GIR}$ and $GIR_{max}$ of FIASP increased linearly with increasing dose. For some subjects it exceeded the linear part of the s-shaped dose-response curve before the highest dose level (0.4 U/kg)

**$AUC_{0-12}$ vs. Dose**




**$AUC_{GIR}$ vs. Dose**




**Review Question:** What is the dose-PK/PD relationship of FIASP?



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(b) (4)

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(b) (4)



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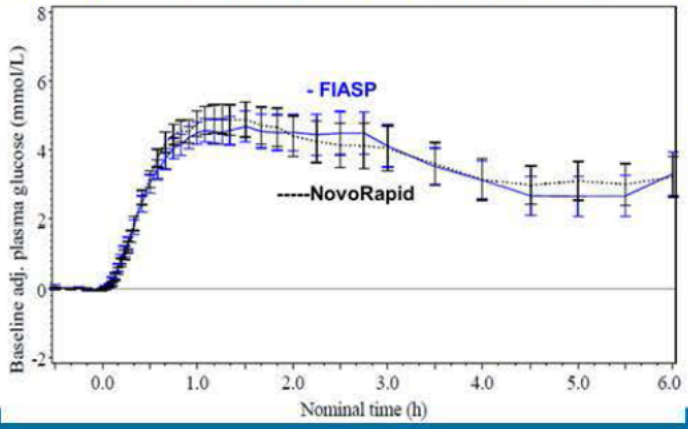
# Mealtime Dosing - Overlapping PPG profiles between FIASP and NovoRapid®

| Study | Design | Outcome |
|---|---|---|
| 3889 | Single SC dose (0.2 U/kg)<br>FIASP + NovoRapid®/NovoLog®<br>Administered immediately before a standardized meal | Plasma glucose parameters were not statistically significantly difference between FIASP and NovoRapid®/NovoLog® |

**Mean (SEM) baseline adjusted plasma glucose profiles for FIASP and NovoRapid® (0-6 hr)**




**Review Question:** What is the PK/PD characteristics of FIASP following mealtime dosing?

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# Mealtime Dosing

- 4 studies characterized the PD effect of FIASP® following mealtime dosing

| Study | Design | Outcome |
|---|---|---|
| 3889 | Single SC dose (0.2 U/kg)<br>FIASP + NovoRapid®/NovoLog®<br>Administered immediately before a standardized meal | Plasma glucose parameters were not statistically significantly difference between FIASP and NovoRapid®/NovoLog® |
| | | (b) (4) |
| 3852 | 26 weeks basal-bolus trial, SC dose (0.1 U/kg)<br>FIASP + NovoRapid®/NovoLog® Mealtime dosing (0-2 min before meal) | FIASP reduced the 2 hr PPG increment during the meal test, and superiority to NovoRapid®/NovoLog® was confirmed |
| | | (b) (4) |

**Review Question:** What is the PK/PD characteristics of FIASP following mealtime dosing?



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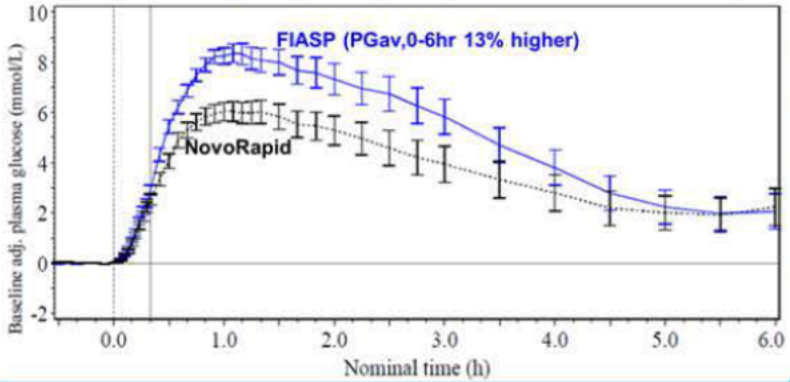
# Post-meal dosing - FIASP resulted in a smaller glucose-lowering effect than NovoRapid®

| Study | Design | Outcomes |
|---|---|---|
| 3921 | Single SC dose 0.2 U/kg<br>FIASP (postmeal (20 min) dosing)<br>NovoRapid®/NovoLog® (mealtime dosing) | FIASP resulted in a smaller glucose-lowering effect compared to NovoRapid®/NovoLog®<br><br>Does not reflect advantage of postmeal dosing in the clinical setting as meal nor dose was individualized |

**Mean (SEM) baseline adjusted plasma glucose profiles for FIASP and NovoRapid® (0-6 hr)**




**Review Question:** What is the PK/PD characteristics of FIASP following postmeal dosing and does it support the post-meal dosing claim in the label?

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# Postmeal Dosing

- 2 studies characterized the PD effect of FIASP® following postmeal dosing

| Study | Design | Outcomes |
|---|---|---|
| 3921 | Single SC dose 0.2 U/kg<br>FIASP (postmeal (20 min) dosing)<br>NovoRapid®/NovoLog® (mealtime dosing) | FIASP resulted in a smaller glucose-lowering effect ($PG_{av,0\text{-}6hr}$ 13% higher) compared to NovoRapid®/NovoLog®<br><br>Does not reflect advantage of postmeal dosing in the clinical setting as meal nor dose was individualized |
| 3852 | 26 weeks basal-bolus trial, SC dose (0.1 U/kg), clinical setting<br>FIASP (postmeal (20 min) dosing)<br>NovoRapid®/NovoLog® (mealtime dosing ) | The estimated treatment difference was statistically significant in favor of mealtime NovoRapid®/NovoLog® at 1 hr post-dose<br><br>No statistically significant treatment differences in PPG increments at 2,3 and 4 hr post dose<br><br>Postmeal FAISP effectively improved overall glycemic control, and non-inferiority to mealtime NovoRapid®/NovoLog® regarding lowering HbA1c |

**Review Question:** What is the PK/PD characteristics of FIASP following postmeal dosing and does it support the post-meal dosing claim in the label?

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# PK/PD of FIASP in (b) (4) Geriatric Patients

- **PK**
  - Statistically significant faster onset of exposure and greater early exposure for FIASP compared to NovoRapid®/NovoLog®
  - Comparable total exposure and maximum concentration between FIASP and NovoRapid®/NovoLog®
- **PD**

(b) (4)

  - In geriatric patients a greater early glucose-lowering effect was observed for FIASP when compared to NovoRapid®/NovoLog®

**Review Question:** What is the PK/PD of FIASP in the (b) (4) geriatric patient population?

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# PK/PD of FIASP in Japanese Patients

- **PK:**
  - Similar to White subjects with T1DM, greater early exposure was observed for FIASP compared to NovoRapid®/NovoLog®
  - Comparable overall total and maximum exposure were evident for FIASP and NovoRapid®/NovoLog®
- **PD:**
  - Greater early glucose-lowering effect for FIASP compared to NovoRapid®/NovoLog® was observed in Japanese subjects with T1DM, similar to that in White subjects with T1DM
  - Overall glucose-lowering effect was comparable between FIASP and NovoRapid® /NovoLog® in both populations

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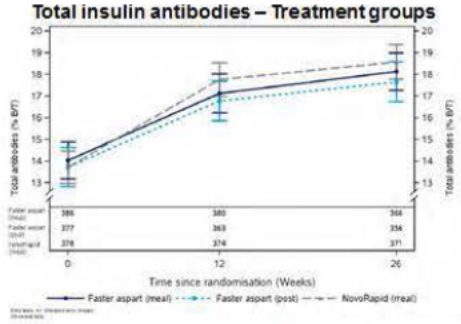
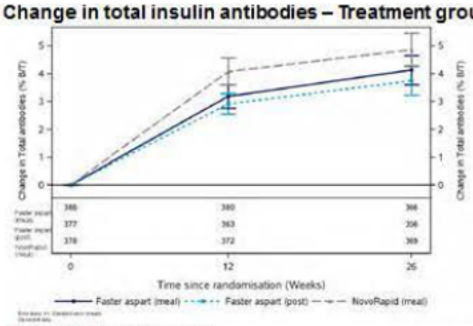
# Impact of Antibody on Insulin PK

- Population PK modeling was utilized to examine the impact of antibody concentrations on insulin PK

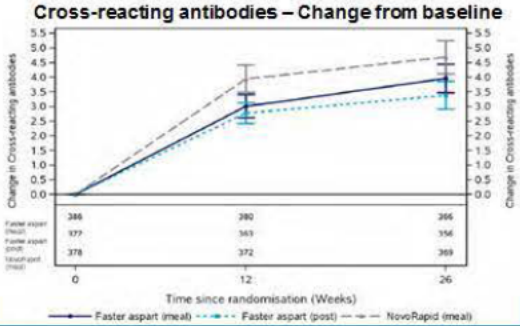
**Total insulin antibodies – Treatment groups**




**Change in total insulin antibodies – Treatment groups**




**Cross-reacting antibodies – Change from baseline**

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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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SHALINI WICKRAMARATNE SENARATH YAPA
02/11/2016

MANOJ KHURANA
02/11/2016