Office of Clinical Pharmacology Review

NDA Number	208751/S-10, S-11
Link to EDR	\\CDSESUB1\evsprod\NDA208751\208751.enx
Submission Date	2/21/2019 (S-010) & 2/25/2019 (S-011)
Submission Type	NDA 505(b)(1); Standard
Brand Name	FIASP®
Generic Name	Insulin Aspart
Dosage Form and Regimen	Solution for injection
Route of Administration	Subcutaneous injection and continuous subcutaneous insulin infusion
Proposed Indication	To improve glycemic control in children with diabetes mellitus
Applicant	Novo Nordisk Inc.
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Executive Summary

The applicant, Novo Nordisk Inc., has submitted a prior approval efficacy supplement (Supplement 10 &11) under NDA 208751 for Fiasp (insulin aspart injection), to support use of Fiasp subcutaneous injections (S-10) and the continuous subcutaneous insulin infusion (CSII) (S-11) in pediatric patients with diabetes mellitus.

Fiasp was approved to improve glycemic control in adults with diabetes mellitus on September 29, 2017 for subcutaneous (SC) and intravenous (IV) use. Fiasp was recently approved on October 21, 2019 for CSII use in adults (S-8). Fiasp was 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). Following PMR was included in the approval letter:

1. 3253-1 Conduct a 26-week, randomized, controlled efficacy and safety study comparing Fiasp (insulin aspart) administered at mealtime and Fiasp (insulin aspart) administered postmeal to NovoLog administered at mealtime, in combination with insulin degludec, in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive).

The clinical development program for pediatric use for Fiasp is comprised of three pharmacokinetic (PK)/ pharmacodynamic (PD) studies (3888, 4371 and 4265) and one confirmatory efficacy and safety study (study 4101).

1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the information submitted under NDA 208751, Supplement 10 & 11 and has the following recommendations:

- The clinical pharmacology data submitted under Supplement 10 is acceptable to support the approval of this supplement.
- The clinical pharmacology data submitted to support Supplement 11 is acceptable. However, the final approvability of this supplement is deferred to the assessments by Clinical and CDRH review disciplines.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The following data were included in this submission to support the pediatric indication (S-10) for SC injection:

- **NN1218-4101**: Efficacy and Safety of Fiasp compared to NovoLog® both in Combination with Insulin Degludec in Children and Adolescents with T1DM
- **NN1218-3888**: A study investigating the Pharmacokinetic Properties of Fiasp in Children, Adolescents and Adults with T1DM
- **NN1218-4371**: A study comparing the Pharmacokinetic Properties of Fiasp between Children, Adolescents and Adults with T1DM (same study design as study 3888 except the insulin aspart concentration was measured by total ELISA assay)
- **NN1218-4265**: A study Investigating the Pharmacokinetic and Pharmacodynamic Properties of Fiasp in Subjects with T2DM

In addition, prior approval efficacy supplement (S-11) is submitted to support CSII use in Insulin pump for Fiasp in pediatric patients with diabetes mellitus. In accordance with agreed initial pediatric study plan (iPSP) (dated 08/28/2015 in DARRTS), Novo Nordisk proposes to extrapolate efficacy results from the adult pump study in T1DM to pediatric T1DM based on the following:

- Efficacy data from the completed Phase 3b pump efficacy and safety study in adult subjects with T1DM (NN1218-3854). This study was submitted under Supplement 08 (NDA 208751).
- The completed single dose pump PK/PD study in adult subjects with T1DM (NN1218-4349). This study was also submitted under Supplement 08 (NDA 208751).
- Efficacy data from the completed subcutaneous pediatric efficacy and safety study in subjects with T1DM (NN1218-4101). This study is submitted in the current submission.

Novo Nordisk has also proposed to leverage the safety and dosing information from studies NN1218-3854 and 4101 to support the CSII use of Fiasp with pediatric patients. Furthermore, study NN1218-3852 (long-term efficacy) is used to provide reference data for supporting dosing recommendations.

Studies 4371 and 3888 were important PK/PD studies to support pediatric development (S-10) as SC injection. While studies 4371 and 3888 had similar design, study 3888 measured only free serum insulin aspart concentrations whereas repeat study 4371 measured both free and total serum insulin aspart. During the original NDA submission, the free serum insulin aspart assay was deemed to be unreliable (Refer to the review in DARRTS by Dr. Shalini Wickramaratne Senarath Yapa dated 09/06/2017; hereafter OCP review dated 09/06/2017), hence only total serum insulin aspart concentration were relied for PK conclusions from study 4371, as was done for the original NDA resubmission. Therefore, this review is focused on the PK/PD results from study 4371 and only PD results from study 3888.

Study 4371 and 3888 were randomized, single-center, double-blind, single-dose, two-period cross-over studies investigating the PK properties of Fiasp and NovoLog® in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with T1DM. In addition, PD properties were investigated using a meal test setting. In studies 4371 and 3888 (pediatric and adult subjects with T1DM), a SC dose of 0.2 Unit/kg body weight was used for both Fiasp and NovoLog®.

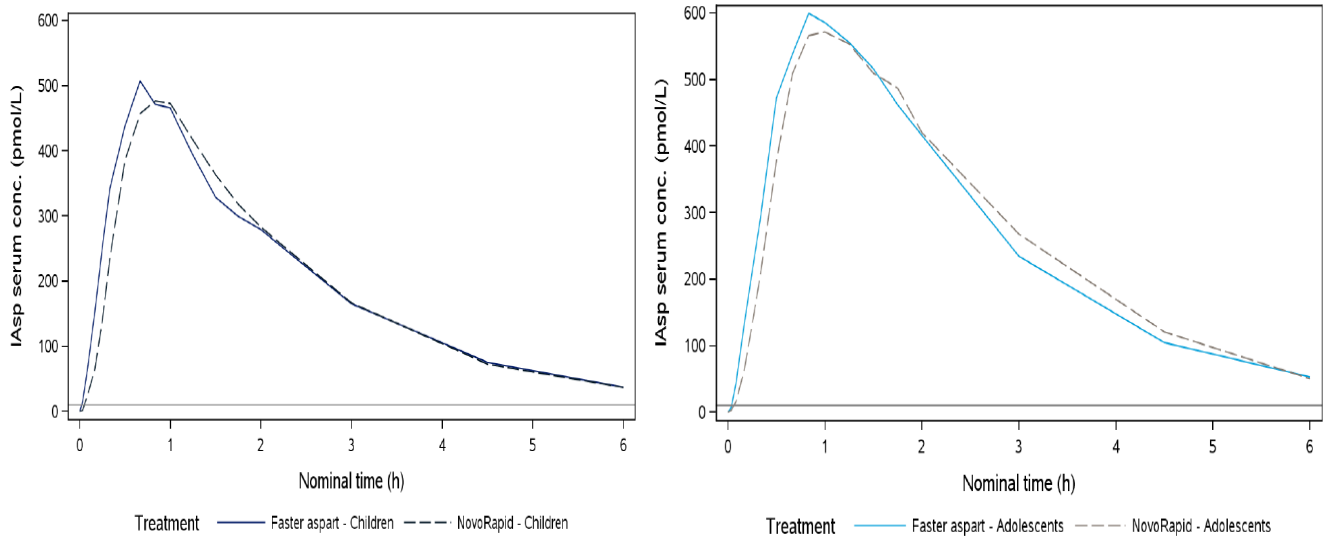
The mean profiles for total serum insulin aspart concentration after SC administration of Fiasp in children and adolescents were slightly shifted to the left compared to NovoLog, indicating a faster absorption and greater early insulin exposure with Fiasp (Figure 1). In children, estimates of mean onset of appearance were 2.4 minutes with Fiasp and 5.4 minutes with NovoLog®. The estimates of mean time to 50% $C_{max,IAsp}$ were 20.8 minutes with Fiasp and 27.1 minutes with NovoLog® in children. In adolescents, estimates of mean onset of appearance were 3.2 minutes with Fiasp and 5.0 minutes with NovoLog®. Estimates of mean time to 50% $C_{max,IAsp}$ were 21.9 minutes with Fiasp and 28.1 minutes with NovoLog® in adolescents. Both children and adolescents showed statistically significantly greater early total insulin aspart exposure (assessed using endpoints $AUC_{IAsp,0–15min}$, $AUC_{IAsp,0–30min}$) with Fiasp than NovoLog.

The duration of exposure for total insulin aspart (measured as time to late 50% $C_{max,IAsp}$) was comparable between Fiasp and NovoLog in children but in adolescents 12.3 minutes shorter for Fiasp than for NovoLog. In children and adolescents, the total exposure of insulin aspart ($AUC_{IAsp,0–12h}$) and the maximum insulin aspart concentration ($C_{max,IAsp}$) were comparable for Fiasp and NovoLog® .

For children and adolescents with T1DM in the clinical pharmacology studies 4371 and 3888, the PG profiles for the first 2 hours after meal test were lower for Fiasp compared to that for NovoLog®.

The results from study 4371 demonstrated that PK from SC injection in children and adolescents preserved the initial (0-30 minutes) absorption differences with the SC delivery of the Fiasp versus Novolog. These relative PK/PD differences between Fiasp and NovoLog, when administrated in pediatric T1DM patients were consistent with the observations after SC administration in adults in the original NDA submission (see OCP review dated 09/06/2017). When compared to the adult group within study 4371, the PK analysis indicated that AUC_{12h} and C_{max} was higher in pediatrics (~25-50%) compared to adults. This difference was due to the higher baseline mean total antibody level for children (30.3 %B/T) and adolescents (36.0 %B/T) than for adults (18.9 %B/T). After adjusting for antibody level AUC_{12h} and C_{max} were comparable for children and adolescents compared to adults. Additionally, other PK parameters like onset of appearance, time to 50% $C_{max,IAsp,}$ t_{max} and duration of exposure were also similar to adults.

Figure 1. Mean children PK (left) and mean adolescent PK (right) profiles of Fiasp and NovoLog in study 4371.



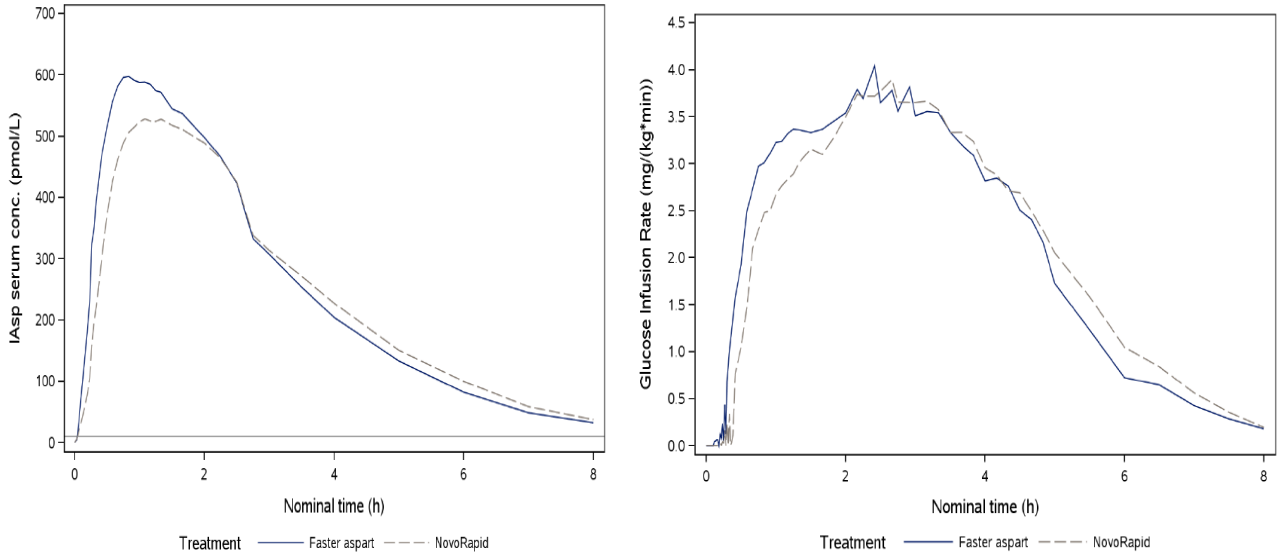
Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Pages 19 and 20

To support indication in pediatric T2DM patients the sponsor conducted study 4265 to evaluate the PK/PD in adult T2DM using a euglycemic clamp. This was a randomized, single-center, double-blind, single-dose, two-period, cross-over, active-comparator study investigating the PK and PD properties of Fiasp in a euglycemic clamp setting in subjects with T2DM. In adults with T2DM, Fiasp showed earlier onset of exposure, greater early and maximum exposure compared to NovoLog® with a comparable total insulin exposure (Figure 2). In adults with T2DM, the mean onset of appearance of insulin aspart was 3.1 minutes for Fiasp compared to 4.3 minutes for NovoLog®. The time to reach 50% C_{max} (time to 50% $C_{max,IAsp}$) of insulin aspart was 19.0 minutes for Fiasp compared to 26.7 minutes for NovoLog®.

The estimated time to late 50% $C_{max,IAsp}$ (duration of exposure) was 30 minutes shorter with Fiasp compared with NovoLog®. Exposure during the last part of the PK profile ($AUC_{IAsp,2-12h}$) of Fiasp was statistically significantly lower by 11% compared to NovoLog®. In adults with T2DM, the total insulin exposure (measured as $AUC_{IAsp,0-12h}$) was similar between Fiasp and NovoLog®, while the maximum insulin aspart concentration ($C_{max,IAsp}$) was 12% higher for Fiasp compared to NovoLog®, however these differences were not considered clinically meaningful. In adults with T2DM, the median terminal half-life was 80.6 minutes for Fiasp and 85.9 minutes for NovoLog®.

The mean GIR profiles for Fiasp were left-shifted compared to NovoLog®, indicating a greater early glucose-lowering effect with Fiasp compared to NovoLog®/ NovoLog® (Figure 2). Fiasp showed earlier onset of glucose-lowering effect, greater early glucose-lowering effect compared to NovoLog® while maintaining a comparable total and maximum glucose-lowering effect. Onset of action was 22.4 minutes for Fiasp compared to 31.3 minutes for NovoLog®. Time to 50% GIR_{max} was 39.3 minutes for Fiasp and 51.1 minutes for NovoLog. The $tGIR_{max}$ was 150.9 minutes for Fiasp compared to 155.7 minutes for NovoLog®. However, the estimated time to late 50% GIR_{max} was 14.4 minutes earlier with Fiasp compared to that with NovoLog®. In study 4265, the total glucose-lowering effect (measured as $AUC_{GIR,0-t}$) and the maximum observed GIR (GIR_{max}) for Fiasp was comparable to NovoLog®.

Figure 2. Mean PK (left) and mean GIR (right) profiles of Fiasp and NovoLog in study 4265.



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Pages 27 and 40

Efficacy and safety of Fiasp in pediatric population was assessed in study 4101. This was a 26-week, randomized, partly double-blind, multicenter, multinational, active controlled, treat-to-target, 3-armed parallel-group study with a 12-week run-in period. The study compared effect and safety of mealtime Fiasp versus mealtime NovoLog®, both in combination with insulin degludec once daily in a basal-bolus regimen, in subjects with T1DM aged 1 year to less than 18 years of age. Fiasp and NovoLog were titrated following the same recommendations.

Sponsor reported that the results of the hierarchical testing procedure showed that mealtime Fiasp was non-inferior to mealtime NovoLog®, both in combination with insulin degludec, in terms of change from baseline to 26 weeks after randomization in HbA1c (-0.17 % [-0.30; -0.03]95% CI). Non-inferiority of postmeal Fiasp versus mealtime NovoLog®, both in combination with insulin degludec, was confirmed in terms of change from baseline to 26 weeks after randomization in HbA1c (0.13 % [-0.01; 0.26]95% CI). Superiority of mealtime Fiasp versus mealtime NovoLog®, both in combination with insulin degludec, was confirmed in terms of change from baseline to 26 weeks after randomization in HbA1c.

The comparability in the PK/PD with respect to overall unit dose-response of Fiasp and NovoLog, corroborates with the observation of non-inferior glycemic control vis-à-vis comparable total insulin dose utilization from the 4101 study. The clinical relevance of the initial PK/PD differences between Fiasp and NovoLog as claimed by the sponsor is uncertain towards efficacy differences in the clinical use setting.

The acceptability of the efficacy claims and risk-benefit assessment from the study 4101 are further deferred to the reviews by Statistical and Clinical disciplines.

Overall, Clinical Pharmacology data submitted for supplement 10 and 11 of NDA 208751 is acceptable to support the use of Fiasp in pediatrics.

2. Question-Based Review

2.1. Background

Fast-acting insulin aspart, tradename Fiasp, for improvement of glycemic control in adults with diabetes mellitus was approved on September 29, 2017 under NDA 208751 for subcutaneous (SC) and intravenous (IV) use. Fiasp is currently not approved for CSII in pump systems in the US. Compared to NovoLog, Fiasp contains two additional excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride (an amino acid). (b) (4) Both Fiasp and NovoLog contain the same API (insulin aspart) and therefore, once systemically absorbed, no difference in biological action at the insulin receptor is anticipated.

Based on the clinical pharmacology program conducted for the original NDA for Fiasp in adults (Refer to OCP review dated 09/06/2017), the following attributes about Fiasp were concluded:

PK properties:

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

PD properties

- 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
- 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)

- 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

2.1.1. What are the Clinical Pharmacology and Biopharmaceutics studies submitted in this NDA?

The clinical pharmacology program for pediatric SC injection consisted of the following:

Table 1. Summary of clinical pharmacology development program.

Study	Description
NN1218-3888	Pharmacokinetic Properties of Fiasp (free) in Children, Adolescents and Adults with T1DM
NN1218-4371	Pharmacokinetic Properties of Fiasp (total) between Children, Adolescents and Adults with T1DM
NN1218-4265	Pharmacokinetic and Pharmacodynamic Properties of Fiasp in Subjects with T2DM
NN1218-4101	Efficacy and Safety of Fiasp compared to NovoLog® both in Combination with Insulin Degludec in Children and Adolescents with T1DM

Source: Reviewer's summary of information submitted in Module 2.7.2. Summary of Clinical Pharmacology Studies

2.2. General Attributes

2.2.1. What was the formulation/device used in the clinical studies?

The formulation of the Fiasp drug product used in the clinical studies supporting this application is the same as the Fiasp drug product used in the clinical development program supporting the original NDA and is identical to the marketed Fiasp drug product. The investigational medicinal products (IMPs) used in study 4371 and 3888 are below:

- Fiasp, 100 U/mL, solution for injection, 3 mL PDS290 pen-injector, 0.2 Unit/kg body weight administered subcutaneously.
- Insulin aspart (NovoLog®), 100 U/mL, solution for injection, 3 mL PDS290 pen-injector, 0.2 Unit/kg body weight administered subcutaneously.

In study 4265 the investigational study product was Fiasp, 100 U/mL in 3 mL Penfill® (batch EP51006 and FP53116). The active comparator was NovoLog®, 100 U/mL in 3 mL Penfill® (batch EP51136 and GP51088). The dose level was 0.3 Unit/kg body weight and was administered SC (single dose) in the abdomen.

In study 4101 the investigational study product was Fiasp, 100 U/mL in 3 mL Penfill® (batch EW5F973, EW5F974 and FWN773). The active comparator was NovoLog®, 100 U/mL in 3 mL Penfill® (batch FWSR240).

2.3. General Clinical Pharmacology

2.3.1. Do the clinical pharmacology information submitted support the pediatric indication for use of Fiasp via multiple daily subcutaneous injection?

The sponsor seeks indication for SC injection in T1DM and T2DM pediatric population. Studies conducted for T1DM pediatric population are shown in Table 1. According to iPSP (dated 08/28/2015 in

DARRTS), it was agreed to extrapolate efficacy results from pediatric T1DM subjects to pediatric T2DM patients age 10 and above. The extrapolation was based on the following:

- A comparative PK/PD study using the euglycemic clamp procedure in adult T2DM to show that the PK and PD differences between Fiasp and NovoLog®, as noted in T1DM, are preserved in T2DM patients (Study 4265 in this submission).
- The efficacy results from a planned pediatric T1DM study, NN1218-4101

Note that the PK/PD study in T2DM was requested at the initial PSP stage (see DARRTS document dated 05/01/2015) and following concerns were listed in the iPSP:

- We acknowledge that trial NN1218-3824 in adults indicated similarity between T1DM and T2DM with regards to the differences in the pharmacokinetic profile of NN1218 and Novolog. However, the PD results in adult T2DM do not indicate if these PK differences translated to a meaningful difference in the PD profile of NN1218 to support the proposed pre-meal/post-meal use in adult T2DM patients.
- The study used a different formulation of NN1218 that differs in composition from the to-be-marketed formulation.

There are three important aspects of the Fiasp PK/PD data as it compares to NovoLog to support the SC use in pediatric T1DM and T2DM patients:

1. Do Fiasp PK/PD differences from Novolog observed in adults preserved in pediatric population?
2. Are Fiasp PK/PD properties observed in pediatric population comparable to adults?
3. Do Fiasp PK/PD differences from Novolog observed in T1DM adults preserved in T2DM population?

These three PK/PD aspects are discussed below.

1. Are Fiasp PK/PD differences from Novolog observed in adults preserved in pediatric population?

The PK/PD properties for Fiasp in pediatric T1DM patients were assessed in two studies 4371 and 3888. Study 4371 and 3888 were randomized, single-center, double-blind, single-dose, two-period cross-over study investigating the PK properties of Fiasp and NovoLog® in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with T1DM (Figure 3). In addition, PD properties were investigated using a meal test setting. In studies 4371 and 3888 (pediatric and adult subjects with T1DM), a SC dose of 0.2 Unit/kg body weight was used for both Fiasp and NovoLog®. This dose is close to the average pre-meal dose administered in the therapeutic confirmatory efficacy and safety studies with pediatric subjects (study 4101) and adult subjects.

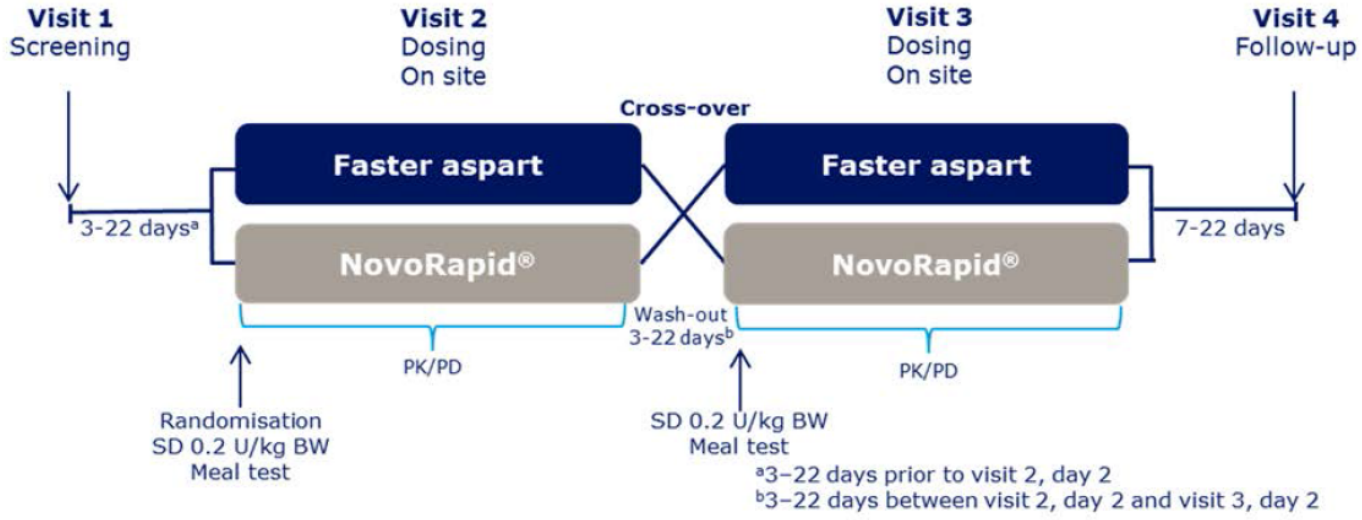
The subjects received an overnight infusion of human soluble insulin (Actrapid®) or glucose to ensure the PG level was within the target range 5.6–8.9 mmol/L (100–160 mg/dL). Fiasp or NovoLog® was administered immediately before intake of a standardized liquid meal. The liquid meal (Composition in study 4371: 62% carbohydrates, 16% protein, and 22% fat; Composition in study 3888: 68% carbohydrates, 17% protein, and 15% fat) was to be ingested as fast as possible preferably within 8 minutes after dosing. The amount of the meal was adjusted to subjects' body weight at visit 2 day 1. The PK and PD properties of Fiasp and NovoLog® were assessed by collecting blood samples for insulin aspart analysis for 6-12 hours after study product administration.

In study 4371, free as well as total serum insulin aspart was analyzed for the assessment of PK profiles. In study 3888, only free serum insulin aspart was analyzed. During the original NDA submission, the free

insulin aspart assay was deemed to unreliable (see OCP review dated 09/06/2017), and only total serum insulin aspart concentration were relied for PK conclusions. Thus, for description of comparative PK properties of Fiasp and NovoLog, study 4371 was relied upon, whereas for PD properties both studies 4371 and 3888 were utilized.

In order to describe the PK properties of Fiasp, elements of the PK profiles were evaluated by analyzing selected temporal components (i.e., onset, early, late and total exposure/action). The PD endpoints used to evaluate the PD properties of Fiasp based on meal test was analyzed focusing on the first 2 hours after dose administration. No interventions were made during the first 60 minutes following study product administration, and most of the interventions in children and adults occurred between 120 minutes and 180 minutes in study 4371 and 120 minutes and 300 minutes in study 3888.

Figure 3. Schematic of study design



Source: Module 5.3.3.3. Study report 4371, Page 31

The PK profile of Fiasp in children and adolescents with TIDM (study 4371) was left-shifted compared to that of NovoLog®, showing a greater early insulin absorption and exposure with Fiasp (Figures 4 and 5).

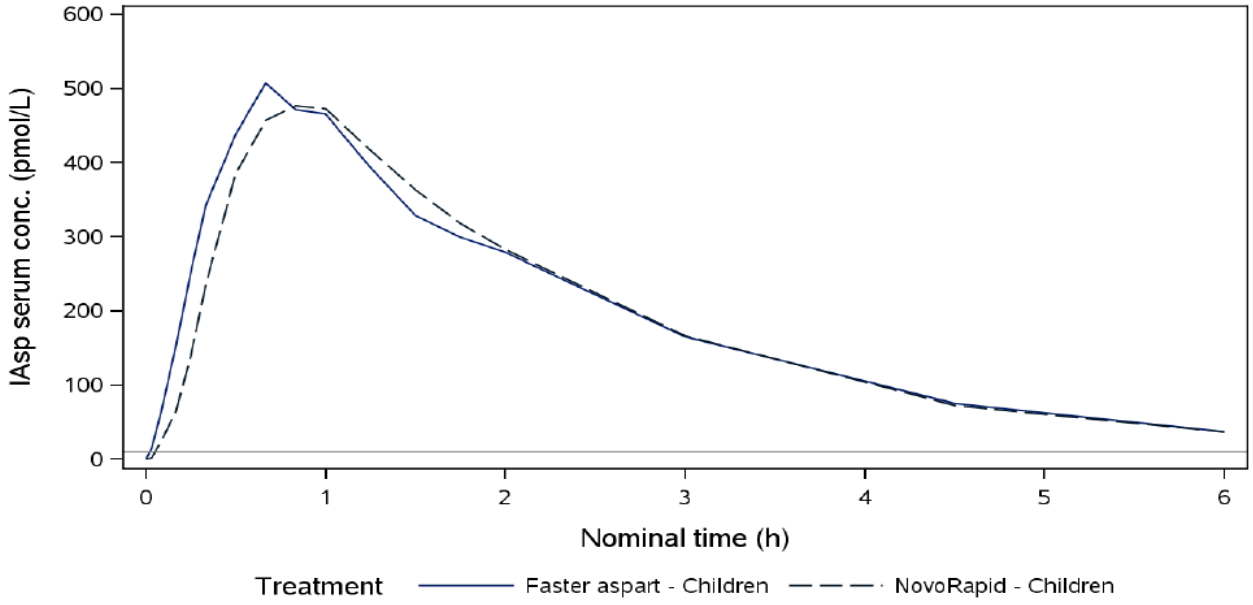
In children, estimates of mean onset of appearance were 2.4 minutes with Fiasp and 5.4 minutes with NovoLog®. The estimates of mean time to 50% $C_{max,IAsp}$ were 20.8 minutes with Fiasp and 27.1 minutes with NovoLog® in children. In adolescents, estimates of mean onset of appearance were 3.2 minutes with Fiasp and 5.0 minutes with NovoLog®. Estimates of mean time to 50% $C_{max,IAsp}$ were 21.9 minutes with Fiasp and 28.1 minutes with NovoLog® in adolescents (Table 2). In children and adolescents, the estimated early insulin aspart exposure was statistically significantly greater for Fiasp compared to NovoLog® for the first 30 minutes after administration (Table 3). This difference was less at 1 and 2 hours after SC administration.

In children, both duration of exposure (measured as time to late 50% $C_{max,IAsp}$) of insulin aspart and late insulin aspart exposure ($AUC_{IAsp,2\text{-}12}$ hours) were comparable between Fiasp and NovoLog®. In adolescents, the estimated time to late 50% $C_{max,IAsp}$ was 12.3 minutes shorter for Fiasp compared to NovoLog®. Exposure during the later part of the PK profile ($AUC_{IAsp,2–12h}$) of Fiasp was statistically significantly lower by 14% compared to NovoLog® (Table 4).

In children and adolescents, the total exposure of insulin aspart ($AUC_{IAsp,0-12h}$) and the maximum insulin aspart concentration ($C_{max,IAsp}$) were comparable for Fiasp and NovoLog® (Table 5).

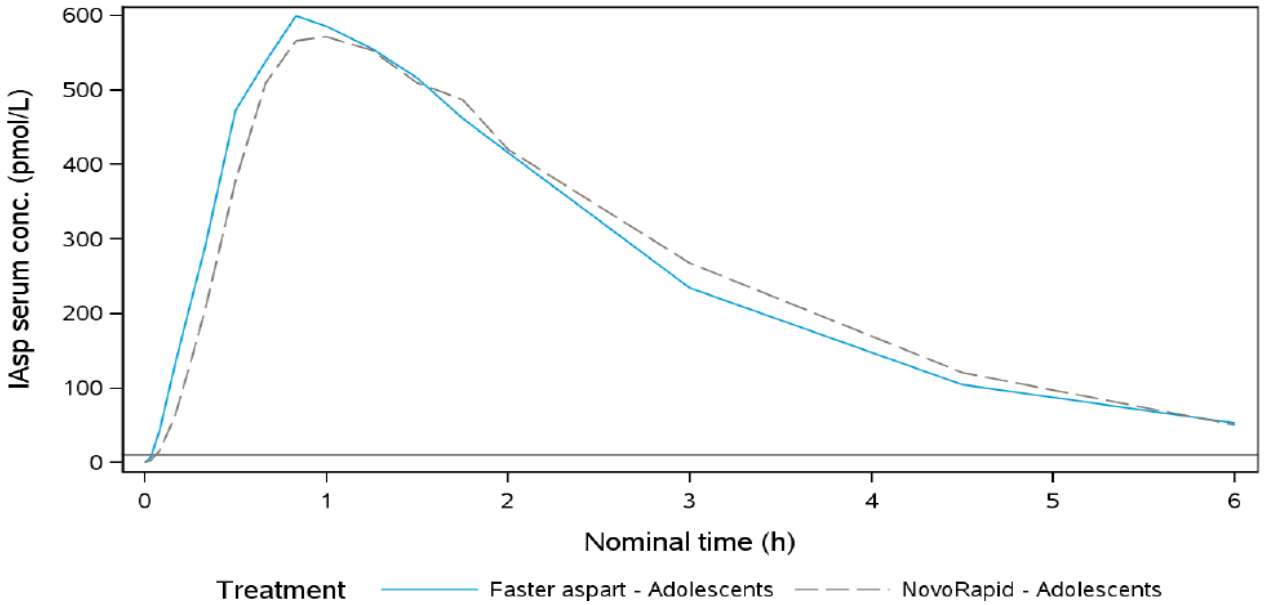
These PK differences between Fiasp and NovoLog® were generally similar to that observed in adults SC injection in the original NDA for Fiasp in adults (Refer to OCP review dated 09/06/2017).

Figure 4. Mean total insulin aspart profiles (0 to 6 hours) in children with T1DM (study 4371)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 19

Figure 5. Mean total insulin aspart profiles (0 to 6 hours) in adolescents with T1DM (study 4371)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 20

Table 2. Mean onset of exposure in adults with T1DM in pediatrics T1DM (study 4371)

Children

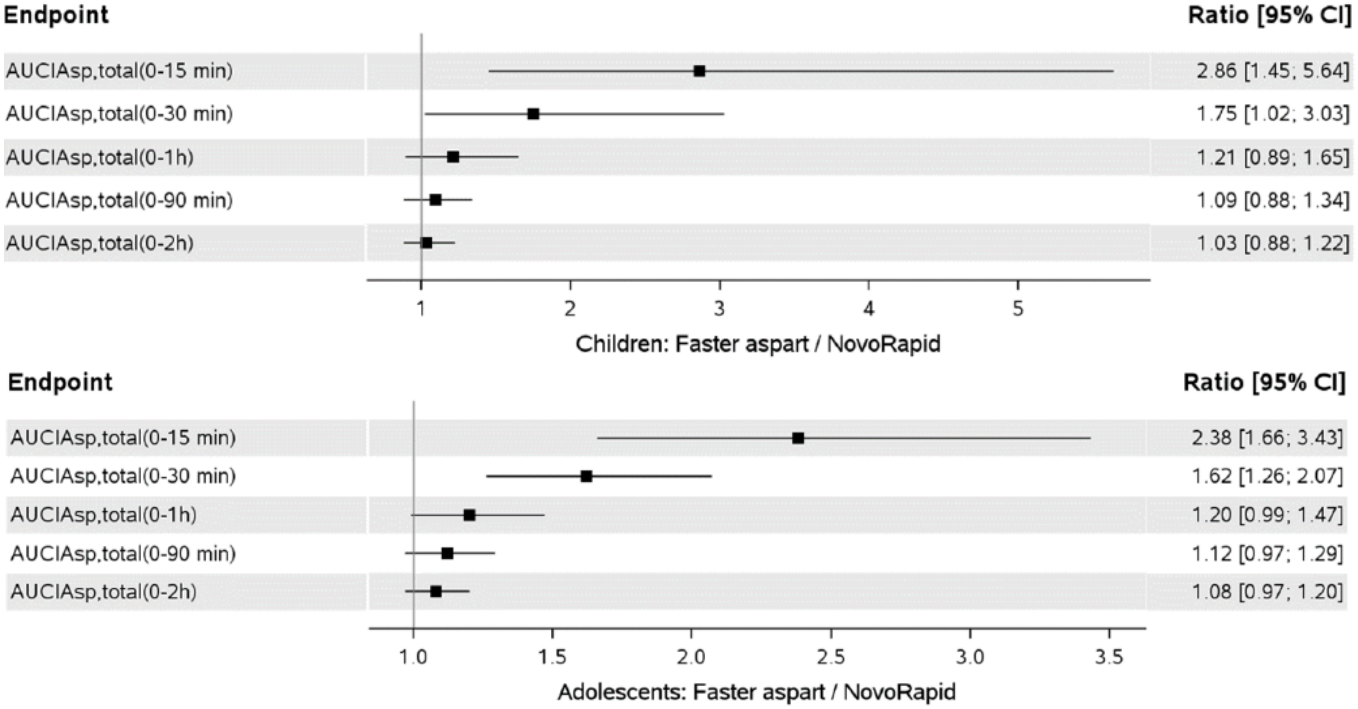
Endpoint	Number of subjects		Estimated mean (minutes)		Treatment difference [95% CI] (min)	Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart-NovoRapid®	Faster aspart/ NovoRapid®
Onset of appearance	12	12	2.4	5.4	-2.9 [-4.4; -1.5]	0.45 [0.24; 0.68]
Time to 50% $C_{max,IAsp}$	12	12	20.8	27.1	-6.3 [-13.1; 0.6]	0.77 [0.56; 1.01]
$t_{max,IAsp}$	12	12	48.1	64.8	-16.7 [-33.9; 0.6]	0.74 [0.53; 0.99]

Adolescents

Endpoint	Number of subjects		Estimated mean (minutes)		Treatment difference [95% CI] (min)	Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart-NovoRapid®	Faster aspart/ NovoRapid®
Onset of appearance	16	16	3.2	5.0	-1.8 [-3.2; -0.5]	0.64 [0.43; 0.88]
Time to 50% $C_{max,IAsp}$	16	16	21.9	28.1	-6.3 [-10.1; -2.5]	0.78 [0.66; 0.90]
$t_{max,IAsp}$	16	16	65.6	63.3	2.3 [-13.2; 17.8]	1.04 [0.81; 1.32]

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Pages 21 and 22

Table 3. Treatment ratios and 95% CI for insulin exposure (AUC_{IAsp}) in pediatrics T1DM (study 4371)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 23

Table 4. Duration of exposure and late exposure in pediatrics T1DM (study 4371)

Children

Endpoint	Number of subjects		Estimated mean		Treatment difference [95% CI]	Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart-NooRapid®	Faster aspart/ NovoRapid®
Time to late 50% $C_{max,IAsp}$ (min)	12	12	130.5	130.9	-0.5 [-34.1; 33.1]	
$AUC_{IAsp,2\text{-}12h}$ (pmol*h/L)	12	12	446	438		1.02 [0.85; 1.21]

Adolescents

Endpoint	Number of subjects		Estimated mean		Treatment difference [95% CI]	Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart-NovoRapid®	Faster aspart/ NovoRapid®
Time to late 50% $C_{max,IAsp}$ (min)	16	16	152.3	164.6	-12.3 [-39.0; 14.5]	
$AUC_{IAsp,2\text{-}12\ h}$ (pmol*h/L)	16	16	653	702		0.93 [0.80; 1.08]

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 24

Table 5. Treatment ratios and 95% CI for total ($AUC_{IAsp,0\text{-}t}$) and maximum ($C_{max,IAsp}$) insulin exposure in pediatrics T1DM (study 4371)

Children

Endpoint	Number of subjects		Estimated mean		Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart-NovoRapid®
$AUC_{IAsp,0\text{-}12h}$ (pmol*h/L)	12	12	1161	1139	1.02 [0.95; 1.10]
$C_{max,IAsp}$ (pmol/L)	12	12	536	534	1.00 [0.76; 1.33]

Adolescents

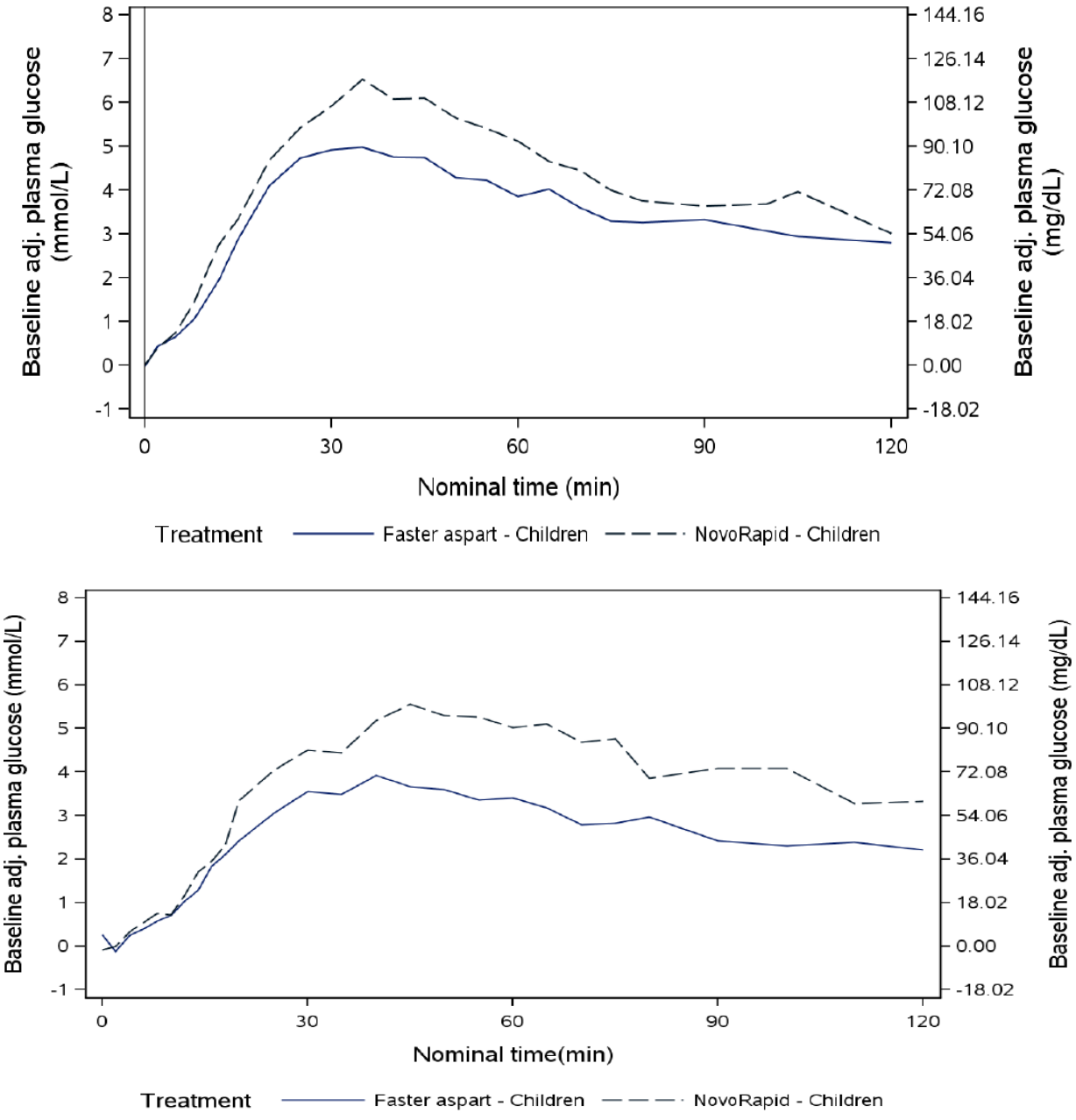
Endpoint	Number of subjects		Estimated mean		Treatment ratio [95% CI]
	Faster aspart	Novo Rapid®	Faster aspart	Novo Rapid®	Faster aspart-NovoRapid®
$AUC_{IAsp,0\text{-}12h}$ (pmol*h/L)	16	16	1461	1448	1.01 [0.96; 1.06
$C_{max,IAsp}$ (pmol/L)	16	16	555	540	1.03 [0.88; 1.20

Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 25

The PD properties of Fiasp and NovoLog® were compared in children and adolescents with T1DM during a meal test in the clinical pharmacology studies 4371 and 3888, as well as in a subgroup of pediatric subjects aged ≥8 years with T1DM in the therapeutic confirmatory study 4101 (see Figure 8 and

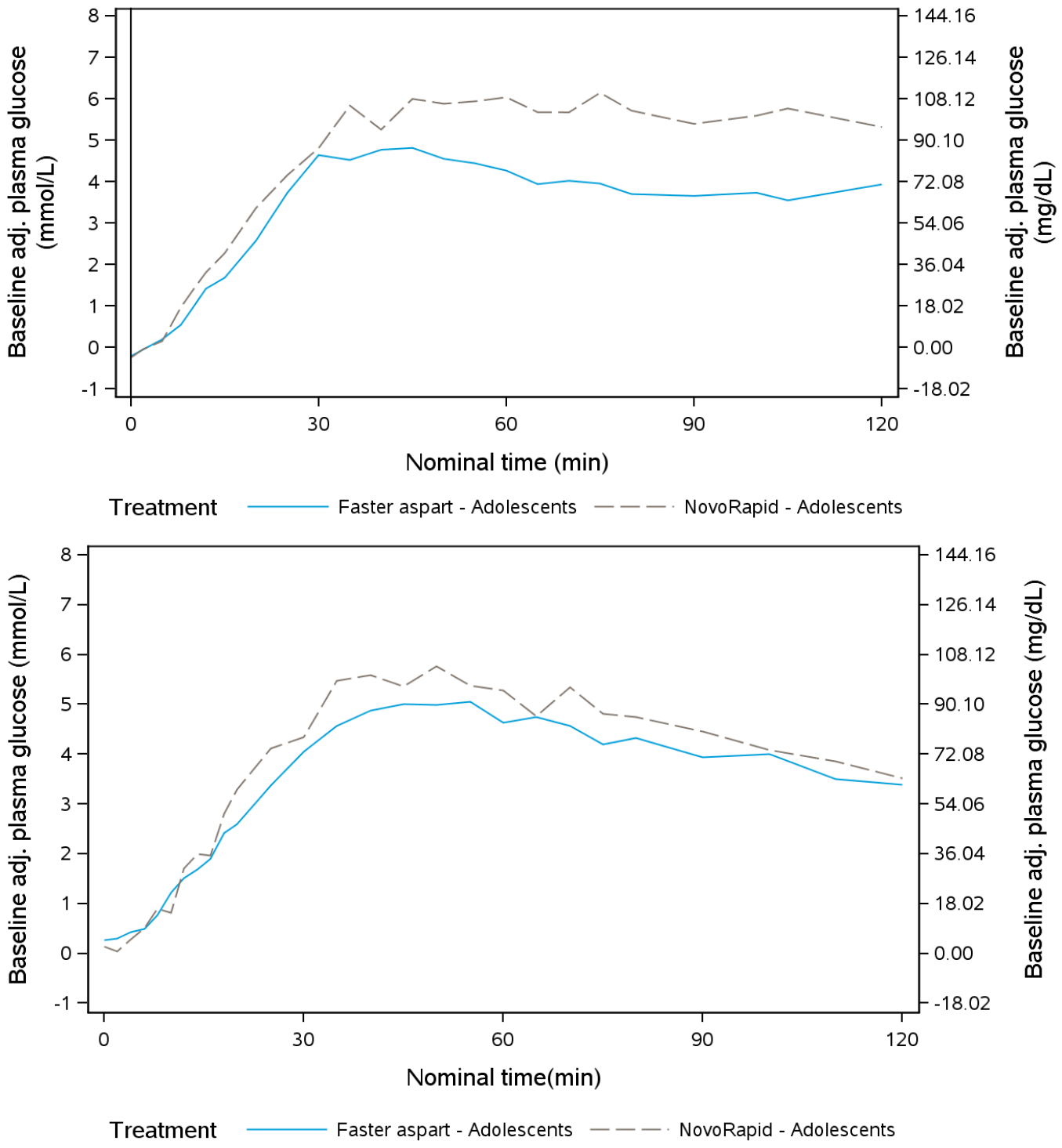
section 2.3.2 for further details on study 4101). For children and adolescents with T1DM in the clinical pharmacology studies 4371 and 3888, the plasma glucose (PG) profiles for the first 2 hours were lower for Fiasp compared to that for NovoLog®, indicating a trend for numerically lower PG excursion with Fiasp compared to NovoLog® (Figure 6 and 7). Note that beyond 2 hours the PD profile was impacted by oral carbohydrate interventions. No insulin or glucose infusions were given as intervention during the meal test. Given that meal test studies are less controlled as compared to euglycemic studies, the PD conclusions from studies 4371 and 3888 are limited in nature.

Figure 6. Mean baseline adjusted plasma glucose profiles for children with T1DM (top: study 4371; bottom: study 3888)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 34

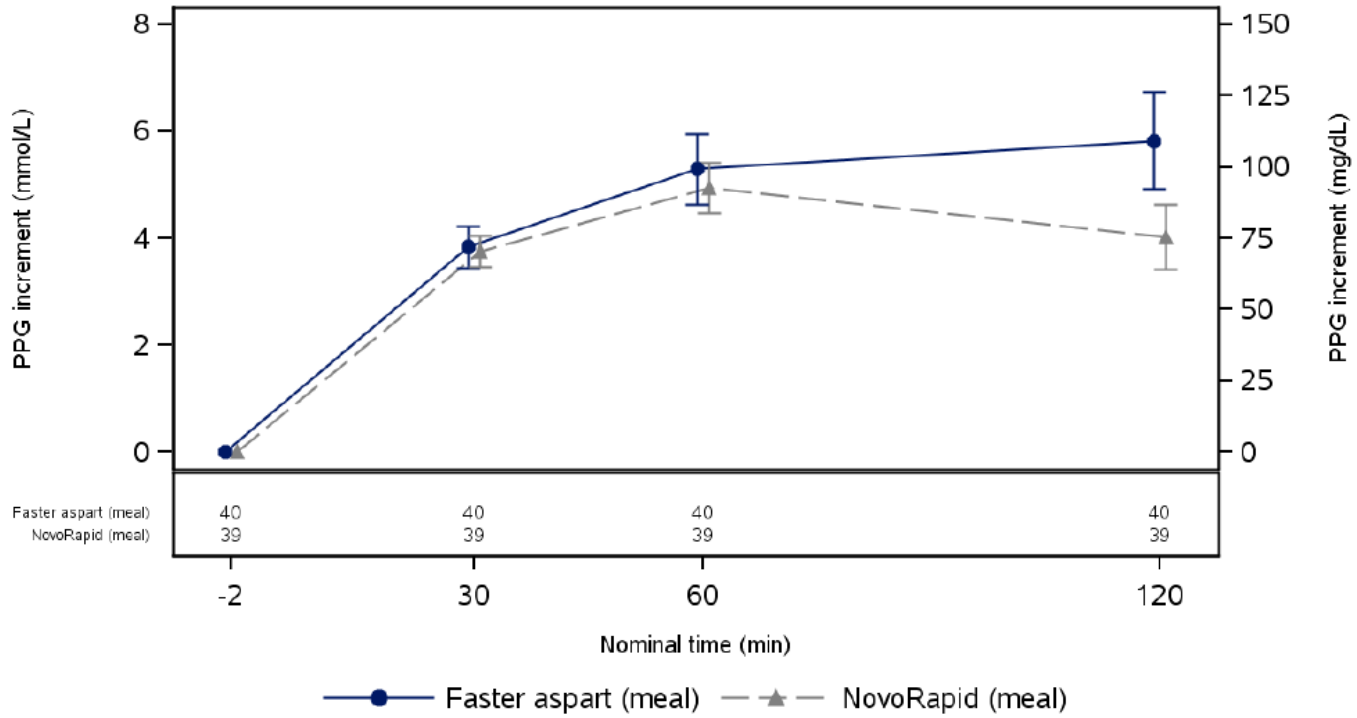
Figure 7. Mean baseline adjusted plasma glucose profiles for adolescents with T1DM (top: study 4371; bottom: study 3888)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 35

In the therapeutic confirmatory study 4101, PPG in a standardized meal test was evaluated at baseline and after 26 weeks of treatment in a subset of the study population aged 8 to <18 years of age. The PG profiles for the first 2 hours after 26 weeks of treatment are shown in Figure 8 and are generally similar up to 60 min for Fiasp and NovoLog.

Figure 8. Post prandial glucose increments at week 26, 0−2 hours in children and adolescents with T1DM (study 4101)



Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 36

2. Are Fiasp PK/PD properties observed in pediatric population comparable to adults?

The PK/PD profile of Fiasp was generally comparable between children, adolescents, and adults. This comparison was supported by data from studies 4371 and 3888. The study design for these two studies has been described above in section 2.3.1. The PK analysis indicated that AUC_{12h} and C_{max} was higher in pediatrics (~25-50%) compared to adults (Table 6 and Figure 9). The baseline mean total antibody level for children (30.3 %B/T) and adolescents (36.0 %B/T) were higher than for adults (18.9 %B/T). After adjusting for antibody level AUC_{12h} and C_{max} were comparable for children and adolescents compared to adults (Table 6). These findings are not unusual considering the total insulin assay measures free and antibody bound insulin and are consistent with the observations from original NDA submission where 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 SC administration of Fiasp (Refer to OCP review dated 09/06/2017). Total glucose lowering effect for Fiasp did not appear to be affected by the level of total anti-insulin aspart antibodies.

Note that for all the results of age group comparisons in study 4371 presented below, the PK endpoints based on total insulin aspart concentrations were adjusted for antibody level.

The estimated onset of appearance of Fiasp and estimated time to 50% $C_{max,IAsp}$ were comparable across children, adolescents, and adults (Table 7). Likewise, the total exposure ($AUC_{IAsp,0-12h}$) of Fiasp was comparable across age groups, with estimated age group ratios of 0.97 [0.80; 1.17]95%CI for children versus adults and 1.07 [0.85; 1.34]95%CI for adolescents versus adults (Table 7). The estimated age group ratio for the maximum concentration ($C_{max,IAsp}$) was 1.12 [0.82; 1.53]95%CI for children versus adults and 1.04 [0.77; 1.40] 95%CI for adolescents versus adults (Table 7).

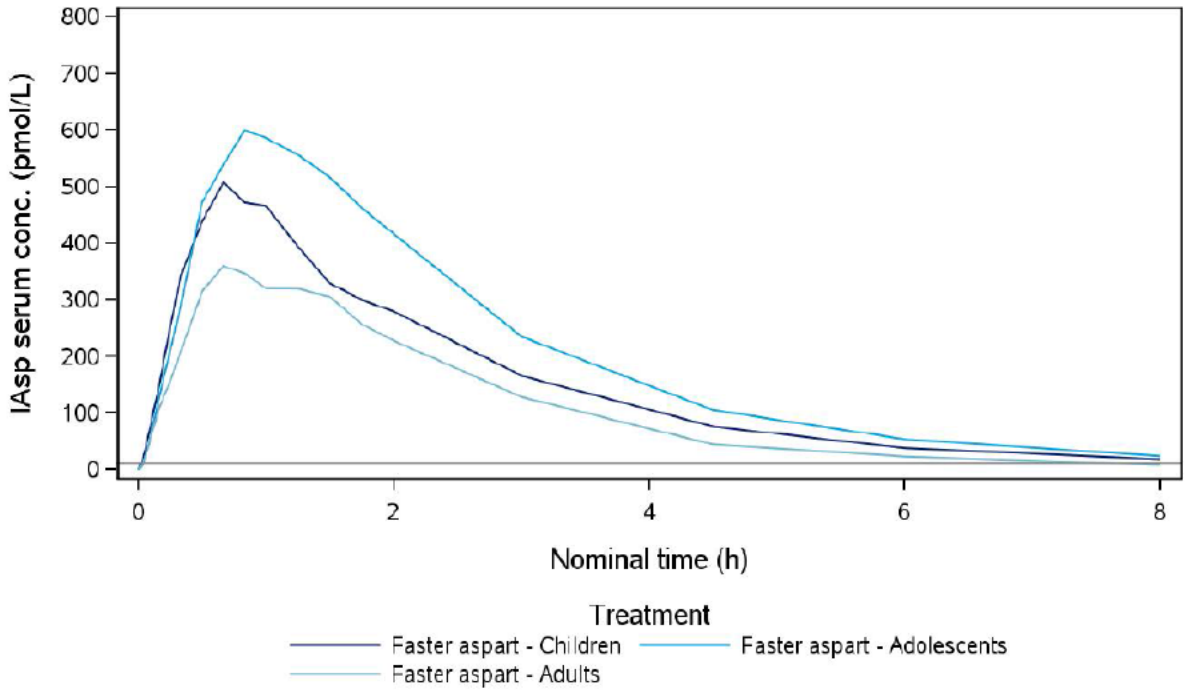
A similar pattern was observed for NovoLog® (see Study 4371). When comparing the total exposure and maximum concentration for Fiasp versus NovoLog® (Study 4371), the estimated treatment ratio was similar across age groups and there was no statistically significant interaction between age group and treatment.

Table 6. AUC and C_{max} comparison in age groups by ADA status.

Total Fiasp exposure	Estimate [95% CI]	
AUC_{0-12hr}	Not ADA adjusted	ADA adjusted
Fiasp: Children / Adults	1.24 [0.90; 1.71]	0.97 [0.80; 1.17]
Fiasp: Adolescents / Adults	1.56 [1.13; 2.17]	1.07 [0.85; 1.34]
NovoLog: Children / Adults	1.15 [0.84; 1.58]	0.89 [0.74; 1.08]
NovoLog: Adolescents / Adults	1.47 [1.06; 2.03]	1.00 [0.79; 1.25]
C_{max}		
Fiasp: Children / Adults	1.36 [0.96; 1.94]	1.12 [0.82; 1.53]
Fiasp: Adolescents / Adults	1.41 [1.00; 2.00]	1.04 [0.77; 1.40]
NovoLog: Children / Adults	1.38 [0.98; 1.97]	1.10 [0.80; 1.50]
NovoLog: Adolescents / Adults	1.40 [0.99; 1.98]	0.99 [0.74; 1.33]

Source: Reviewer's summary of data submitted in Module 5.3.3.3. Study report 4371

Figure 9. Mean total insulin aspart profiles – Fiasp (IAsptotal), 0-8 hours.



Source: Module 5.3.3.3. Study report 4371, Page 109

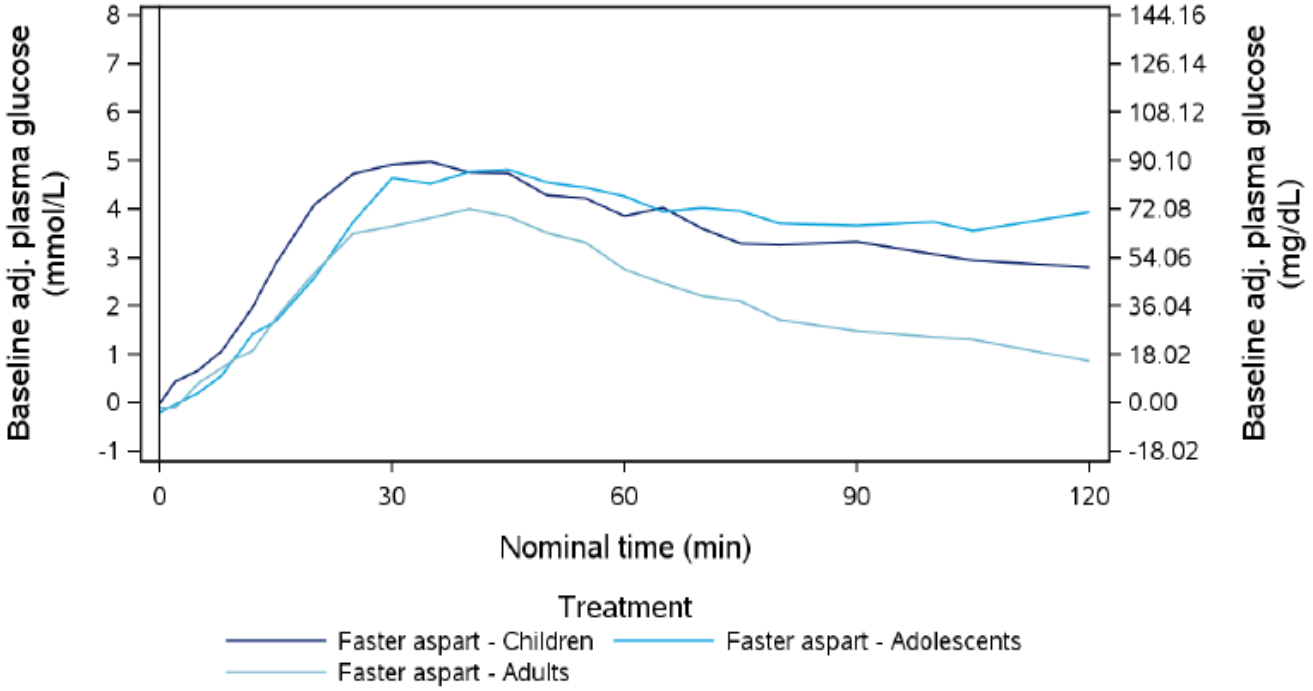
Table 7. Onset and total exposure of insulin aspart across age groups in subjects with T1DM (study 4371)

Endpoint	Children	Adolescents	Adults
Number of subjects	12	16	13
Onset of appearance (min)	2.5	3.2	3.3
Time to 50% $C_{max,Iasp}$ (min)	20.7	21.1	22.6
Total exposure	**Ratio Children vs adults [95% CI]**	**Ratio Adolescents vs adults [95% CI]**	**Age-by-treatment interaction p-value**
$AUC_{IAsp,\ 0\text{-}12h}$	0.97 [0.80; 1.17]	1.07 [0.85; 1.34]	0.095
$C_{max,IAsp}$	1.12 [0.82; 1.53]	1.04 [0.77; 1.40]	0.850

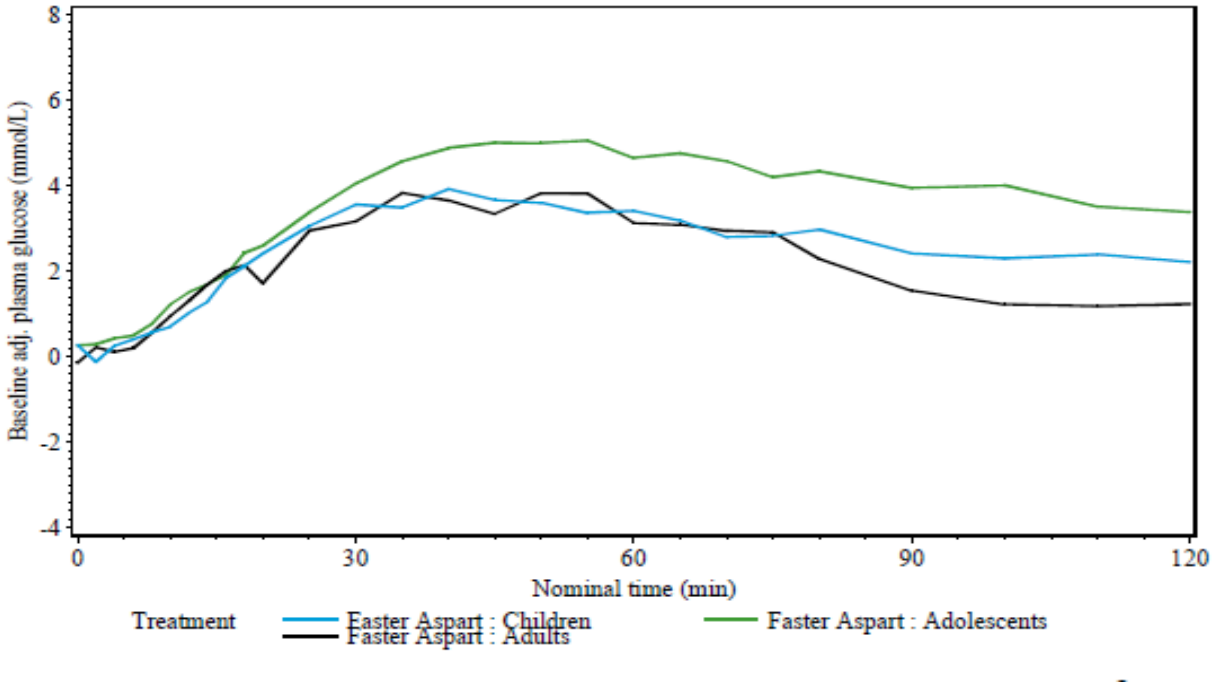
Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 26

Mean baseline adjusted PG profiles for all age groups for Fiasp from 0 to 120 minutes are shown in Figure 10. During the first 2 hours after administration of Fiasp, the PG profile for children and adolescents appeared to be higher compared to that for adults in study 4371 but not in study 3888.

Figure 10. PD - plasma glucose - single-dose - baseline adjusted mean profiles (-1 to 6 hours), study 4371 (top) and study 3888 (bottom)



Source: Module 5.3.3.3. Study report 4371, Page 120

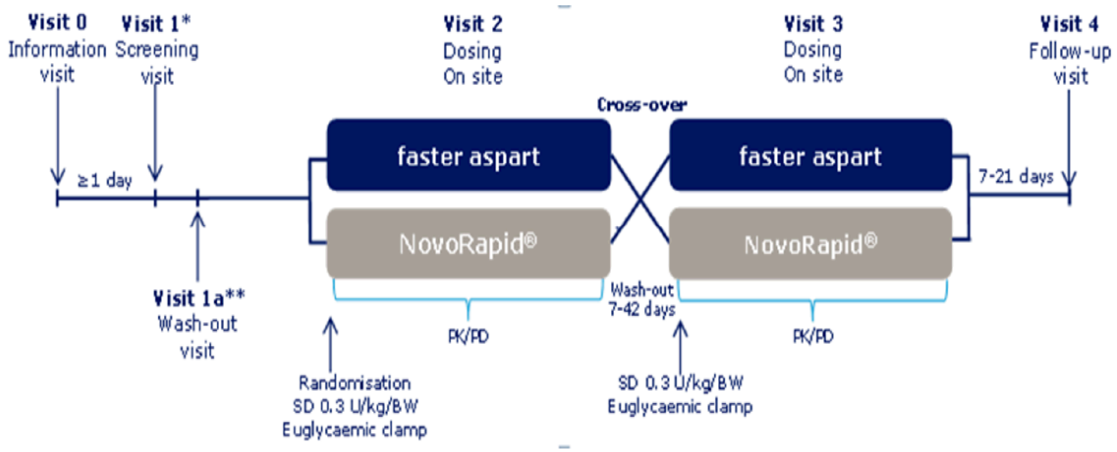


Source: Module 5.3.3.3. Study report 3888, Page 92

3. Do Fiasp PK/PD differences from Novolog observed in T1DM adults preserved in T2DM population?

To support the relevance of the safety and efficacy data from pediatric T1DM and adult T2DM to pediatric T2DM patients the sponsor conducted study 4265 in adult T2DM patients. Study 4265 evaluated the PK/PD of Fiasp and Novolog in adult T2DM using a euglycemic clamp. This was a randomized, single-center, double-blind, single-dose, two-period, cross-over, active-comparator study investigating the PK and PD properties of Fiasp in a euglycemic clamp setting in subjects with T2DM (Figure 11). The dosing visits were separated by a wash-out period of 7−42 days during which the subjects could resume the insulin regimen followed immediately before the first dosing visit (i.e. with no oral antidiabetic drug therapy except metformin in any of the subjects). For both the IMPs, the dose level was 0.3 Unit/kg body weight.

Figure 11. Schematic of study 4265 design



Source: Module 5.3.4.2. Study report 4265, Page 26

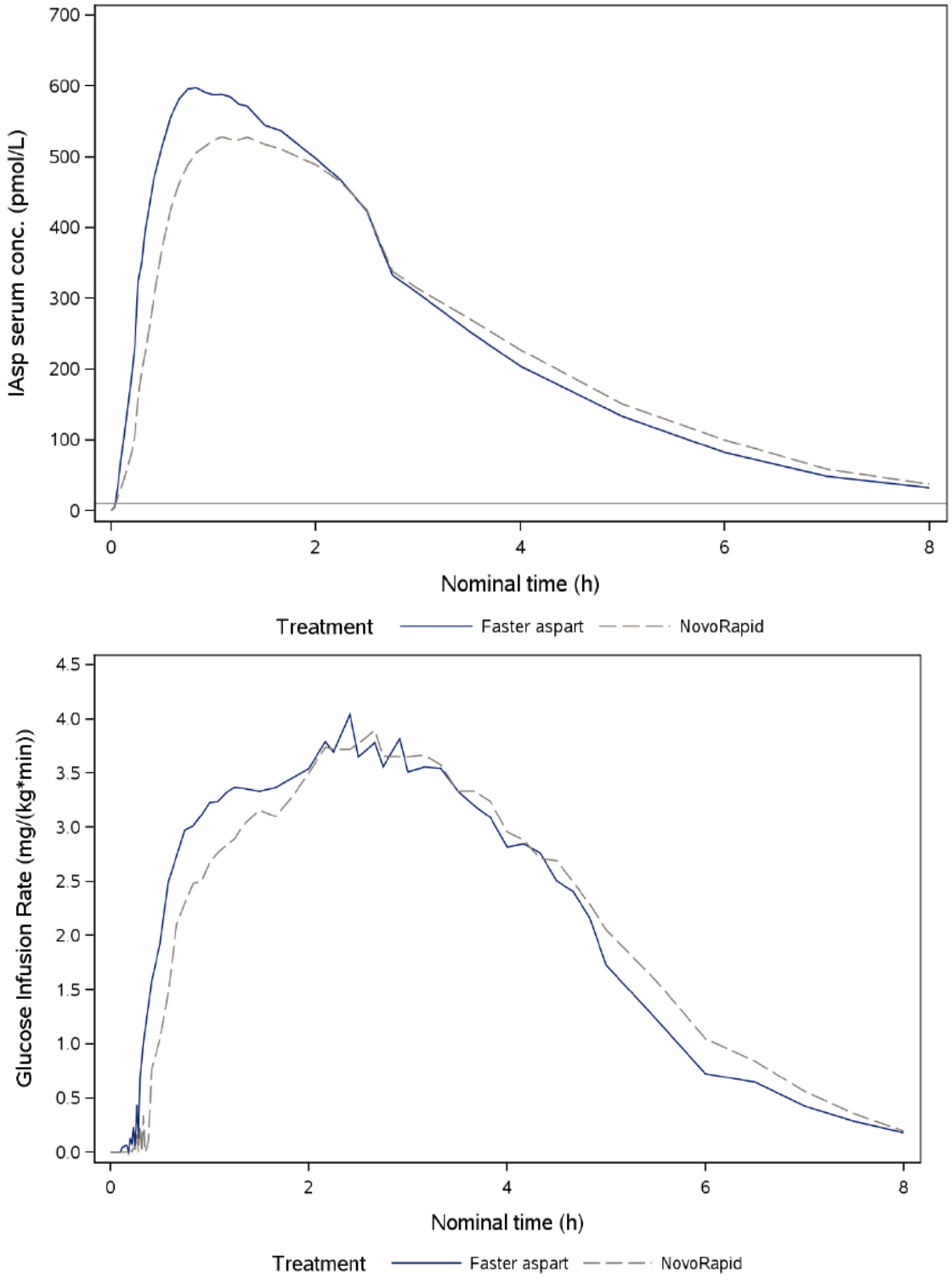
The mean age of the 61 subjects randomized and exposed to treatment was 61.8 years. The majority of subjects were male (73.8%), and all subjects were white. The mean BMI was 29.6 kg/m^2. Mean duration of diabetes was 20.8 years, and mean HbA1c at baseline was 7.6%. In total, 19 subjects had C-peptide value <0.3 nmol/L, 33 subjects between ≥0.3 − <0.6 nmol/L and 9 subjects between ≥0.6 − ≤0.9 nmol/L. No subject had C-peptide value >0.9 nmol/L.

The PK profiles of Fiasp in study 4265 in adults with T2DM was left-shifted compared to NovoLog®, showing a greater early insulin exposure with Fiasp (Figure 12).

In adults with T2DM, Fiasp showed earlier onset of exposure, greater early exposure compared to NovoLog® with a comparable total insulin exposure (Table 8). In adults with T2DM, the mean onset of appearance of insulin aspart was 3.1 minutes for Fiasp compared to 4.3 minutes for NovoLog®. The time to 50% $C_{max,IAsp}$ was 19.0 minutes for Fiasp compared to 26.7 minutes for NovoLog®. However, the estimated time to late 50% $C_{max,IAsp}$ (duration of exposure) was 30 minutes shorter with Fiasp compared to NovoLog®. Exposure during the last part of the PK profile ($AUC_{IAsp,2\text{-}12h}$) of Fiasp was statistically significantly lower by 11% compared to NovoLog®. In adults with T2DM, the total insulin exposure (measured as $AUC_{IAsp,0\text{-}12h}$) was similar between Fiasp and NovoLog®, while the maximum insulin aspart concentration ($C_{max,IAsp}$) was 12% higher for Fiasp compared to NovoLog®. However, this 12% difference is not considered to be a clinically relevant difference, supported by the observation that total glucose-lowering effect in study 4265 was similar for Fiasp and NovoLog (see below). In adults with T2DM, the median terminal half-life was 80.6 minutes for Fiasp and 85.9 minutes for NovoLog®.

The mean GIR profiles for Fiasp were left-shifted compared to NovoLog®, indicating a greater early glucose-lowering effect with Fiasp compared to NovoLog®/ NovoLog® (Figure 12). Fiasp showed earlier onset of glucose-lowering effect, greater early glucose-lowering effect compared to NovoLog® while maintaining a comparable total and maximum glucose-lowering effect (Table 8). Onset of action was 22.4 minutes for Fiasp compared to 31.3 minutes for NovoLog®. Time to 50% GIR_{max} was 39.3 minutes for Fiasp and 51.1 minutes for NovoLog. The $tGIR_{max}$ was 150.9 minutes for Fiasp compared to 155.7 minutes for NovoLog®. However, the estimated time to late 50% GIR_{max} was 14.4 minutes earlier with Fiasp compared to that with NovoLog®. In study 4265, the total glucose-lowering effect (measured as $AUC_{GIR,0\text{-}t}$) and the maximum observed GIR (GIR_{max}) for Fiasp was comparable to NovoLog®.
Overall, the PK/PD profile of Fiasp and differences observed with Novolog in subjects with T2DM were consistent with those observed in subjects with T1DM.

Figure 12. Mean PK (top) and mean GIR (bottom) profiles of Fiasp and NovoLog in study 4265.



Source: Module 5.3.4.2. Study report 4265, Pages 111 and 120

Table 8. PK (left) and PD (right) parameters from study 4265.

	Fiasp	NovoLog
	Estimated mean (min)	
Onset of Appearance	3 1	4.3
Time to 50% C_{max}	19	26.7
T_{max}	62 7	84.5
Time to late 50% C_{max}	180	210
	Ratio [95% CI]	
AUC_{15min}	2 5	
AUC_{30min}	1 85	
AUC_{1hr}	1 4	
C_{max}	1 12 [1.3,1.2]	
AUC_{0-12}	1 00 [0.9,1.1]	

	Fiasp	NovoLog
	Estimated mean (min)	
Onset of Action	22.4	31.3
Time to 50% GIR_{max}	39.3	51.1
$TGIR_{max}$	150.9	155.69
Time to late 50% GIR_{max}	283.3	297.7
	Ratio [95% CI]	
$AUC_{GIR,30min}$	2.47	
$AUC_{GIR,60min}$	1.48	
$AUC_{GIR,90min}$	1.35	
GIR_{max}	1.03 [0.9,1.1]	
$AUC_{GIR,0-12}$	1.01[0.9,1.1]	

Source: Reviewer's summary of data submitted in Module 5.3.4.2. Study report 4265

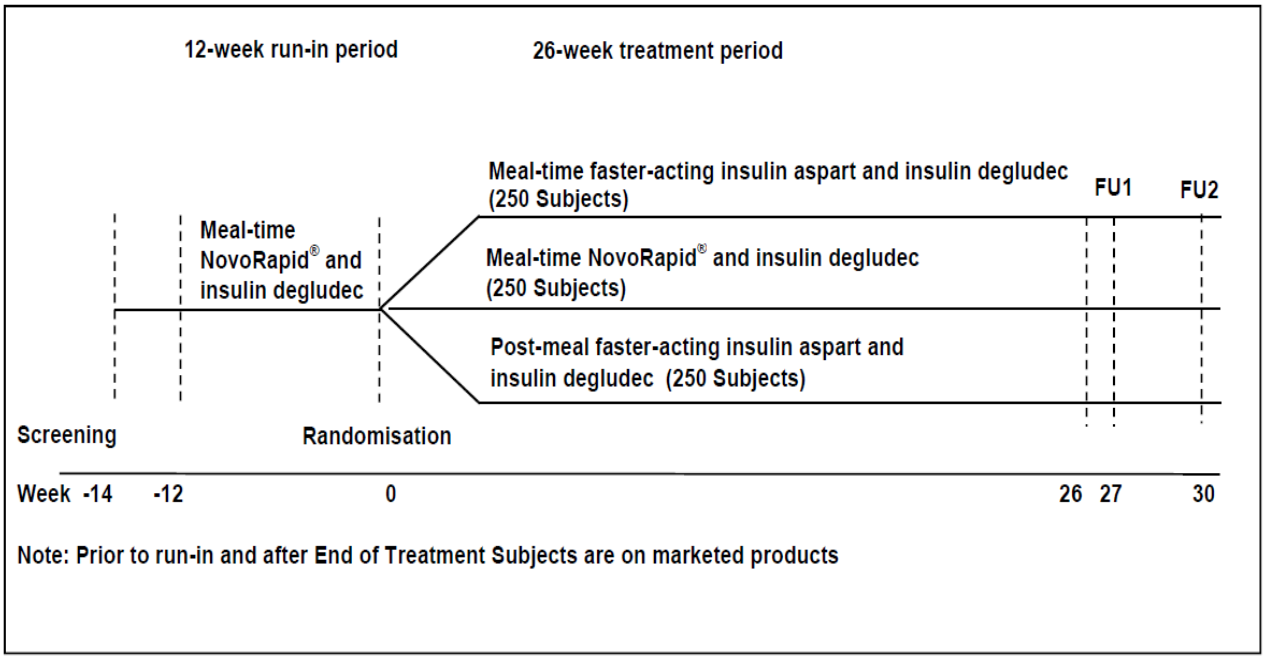
2.3.2. What are the relevant components of the efficacy comparison between Fiasp and NovoLog in study 4101 as they may relate to the PK/PD observations?

While the acceptability of the efficacy/safety claims is deferred to Statistical/Clinical reviews, certain relevant observations from Study 4101 are described here. This was a 26-week, randomized, partly double-blind, multicenter, multinational, active controlled, treat-to-target, 3-armed parallel-group study with a 12-week run-in period (Figure 13). The study compared effect and safety of mealtime Fiasp versus mealtime NovoLog®, both in combination with insulin degludec once daily in a basal-bolus regimen, in subjects with T1DM aged 1 year to less than 18 years of age.

The study also included a 26-week open-label postmeal Fiasp dosing group in combination with insulin degludec. Mealtime dosing was defined as injecting the bolus insulin 0−2 minutes before the meal and postmeal dosing was defined as injecting the bolus insulin 20 minutes after the start of the meal. During the treatment period, the bolus insulin was titrated to the pre-meal glycemic target of 4.0–8.0 mmol/L [71–145 mg/dL] and bedtime glycemic target of 6.7-10.0 mmol/L [120–180 mg/dL] in a treat-to-target approach. The study also compared glycemic control of mealtime Fiasp or postmeal Fiasp versus mealtime NovoLog® in relation to a standardized meal test and continuous glucose monitoring (CGM) in a subgroup of subjects aged ≥ 8 years at the time of screening. A total of 833 subjects were planned to enter the run-in period, and 750 subjects were planned for randomization.

The population consisted of male (53.9%) and female (46.1%) children and adolescents aged 2 to < 18 years with T1DM, with a mean age of 11.68 years (range 2 to 17 years), mean BMI of 19.66 kg/m^2 (range 11.8 to 33.5 kg/m^2), mean duration of diabetes of 4.38 years (range 0.52 to 16.3 years) and mean HbA1c of 7.56 % (range: 4.9−10.6 %) (59.13 mmol/mol; range: 30.1 to 92.4 mmol/mol). The majority of the subjects were White (81.3%) or Asian (16.2%) and of non-Hispanic or non-Latino ethnicity (94.2%). The majority of subjects were enrolled in the US (25.1%), Russia (13.4%) and Japan (8.5%). There were ~143 patients in 12 to <18 years age category, ~100 patients in 6 to <12 years category and ~16 patients in 1 to <6 years category, in each treatment arm.

Figure 13. Schematic of study 4101 design



Source: Module 5.3.5.1. Study report 4101, Page 55

At week 26, insulin doses for Fiasp versus NovoLog® were as follows:

- The mean daily bolus insulin dose at week 26 was 23.3 Units (0.48 Unit/kg) for mealtime Fiasp, 23.5 Units (0.49 Unit/kg) for postmeal faster as part and 22.5 Units (0.47 Unit/kg) for NovoLog®. No apparent differences between treatment groups were identified among the observed doses at each main meal.
- The mean daily basal insulin dose at week 26 was 21.6 Units (0.43 Unit/kg) for mealtime Fiasp, 21.5 Units (0.43 Unit/kg) for postmeal faster as part and 20.7 Units (0.41 Unit/kg) for NovoLog®.
- The mean daily total insulin dose at week 26 was 44.8 Units (0.92 Unit/kg) for mealtime Fiasp, 45.0 Units (0.9 Unit/kg) for postmeal faster as part and 43.2 Units (0.88 Unit/kg) for NovoLog®.

At week 26, the mean basal: bolus split ratio was similar between treatment groups (47: 53 for mealtime Fiasp, 47: 53 for postmeal Fiasp and 46: 54 for NovoLog®). For further understanding of dose, the daily dose was separated by various pediatric age categories. The mean plots for daily bolus, basal and total dose for insulin in study 4101 for various pediatric age categories are shown in Figure 14. Note that in age category of 1 to <6 years only 16 patients received Fiasp whereas 14 received NovoLog. Out of these 16 patients, only 2 patients between 1 to < 3 years age received Fiasp, therefore the interpretation of the difference observed in daily dose in this age category is limited by the small sample size. Overall, there were no clinically meaningful differences apparent in the mean daily doses between Fiasp as compared to NovoLog in age categories.

The main results of the study, as reported, are as follows:

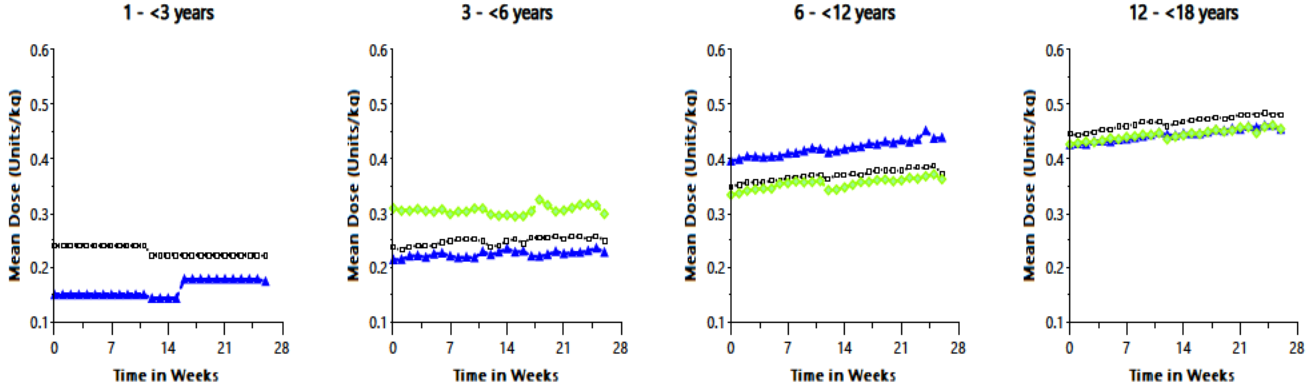
- Fiasp dosed at mealtime (estimated treatment difference (ETD): -0.17 % [-0.30; -0.03]95% CI) or postmeal (ETD: 0.13 % [-0.01; 0.26]95% CI) was confirmed to be effective, as both

administrations were confirmed to be non-inferior to mealtime NovoLog®, with regards to change from baseline to 26 weeks in HbA1c (Figure 15).

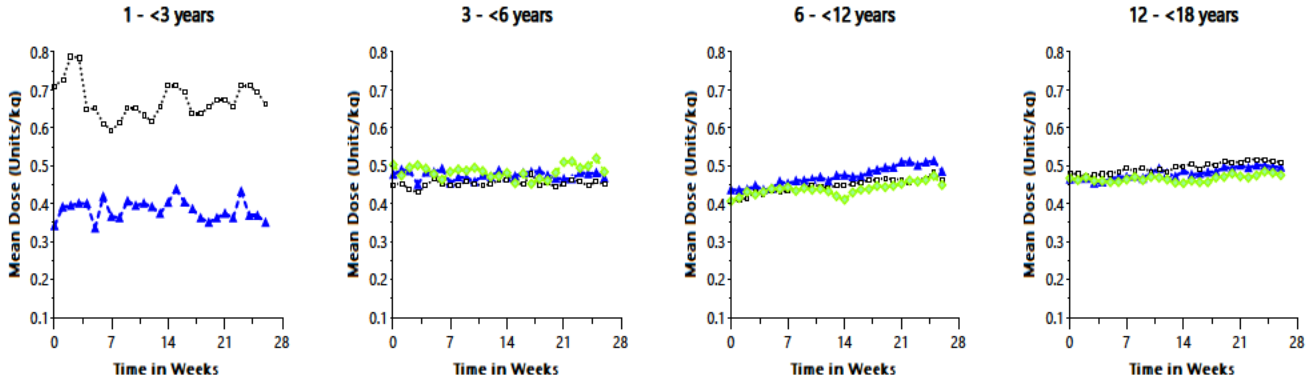
- Superiority of mealtime Fiasp versus mealtime NovoLog® was also confirmed for change from baseline to 26 weeks in HbA1c with ETD -0.17 % [-0.30; -0.03]95% CI.
- A statistically significant difference was demonstrated for mean 1-hour PPG increment over all 3 meals (SMPG) in favor of mealtime Fiasp compared to mealtime NovoLog® after 26 weeks of treatment. For postmeal Fiasp, this comparison was statistically significantly different in favor of mealtime NovoLog®.
- No statistically significant differences in overall rate of severe or BG confirmed hypoglycemic episodes were seen between mealtime Fiasp and NovoLog® or between postmeal Fiasp and NovoLog®. No statistically significant difference in rate of nocturnal severe or BG confirmed hypoglycemic episodes was observed between mealtime Fiasp and NovoLog®; for postmeal Fiasp, the rate was statistically significantly higher compared to mealtime NovoLog®. The overall safety profiles for Fiasp and NovoLog® were similar and as expected for insulin aspart.

Figure 14. Mean plot of daily insulin dose (basal, bolus and total) in Unit/kg by treatment week in study 4101. Black line shows Fiasp post meal, blue lines show Fiasp mealtime and green lines show Novolog mealtime.

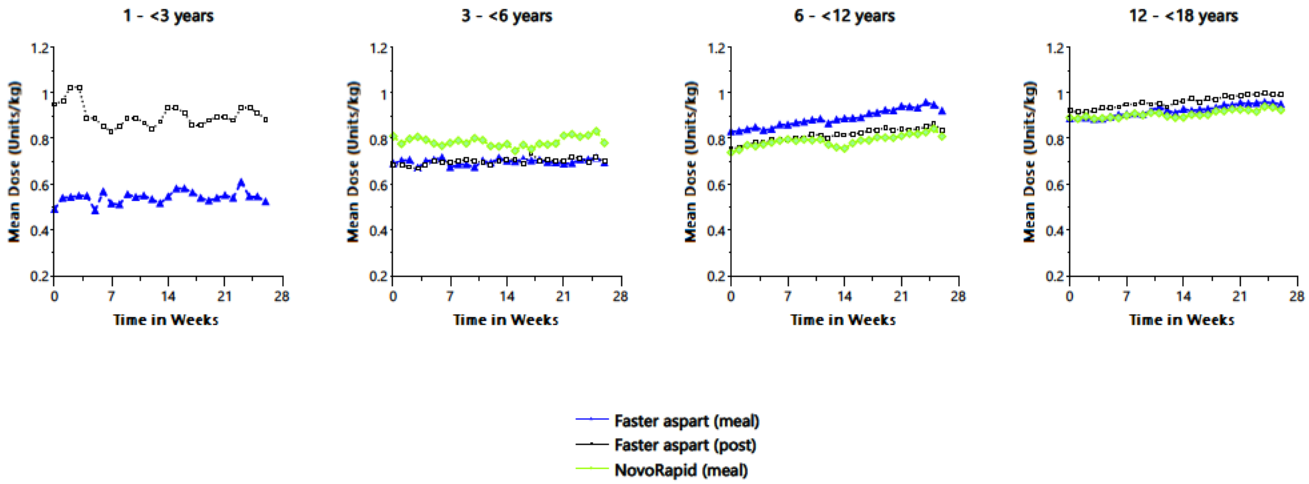
Daily Basal Insulin dose



Daily Bolus Insulin dose

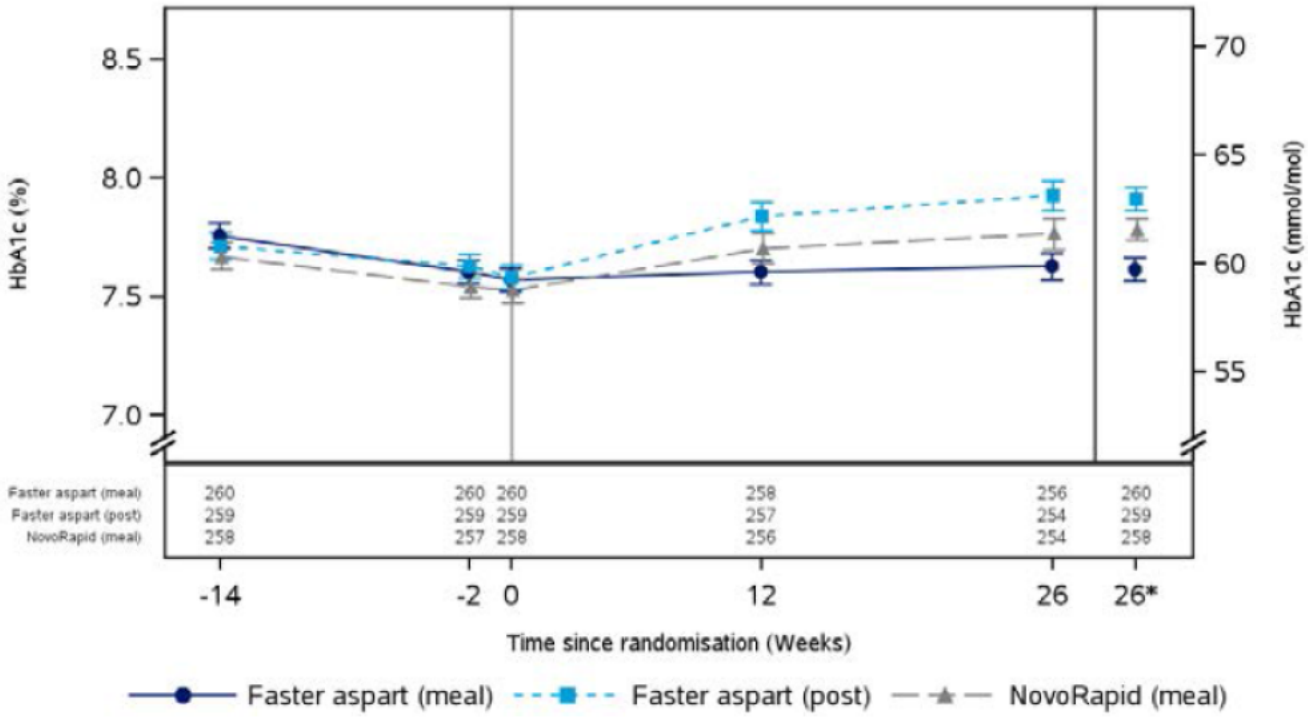


Total daily insulin dose



Source: Reviewer's analysis of data submitted within module 5.3.5.1. study report 4101

Figure 15. HbA1c by treatment week - observed mean and ls mean plot in study 4101

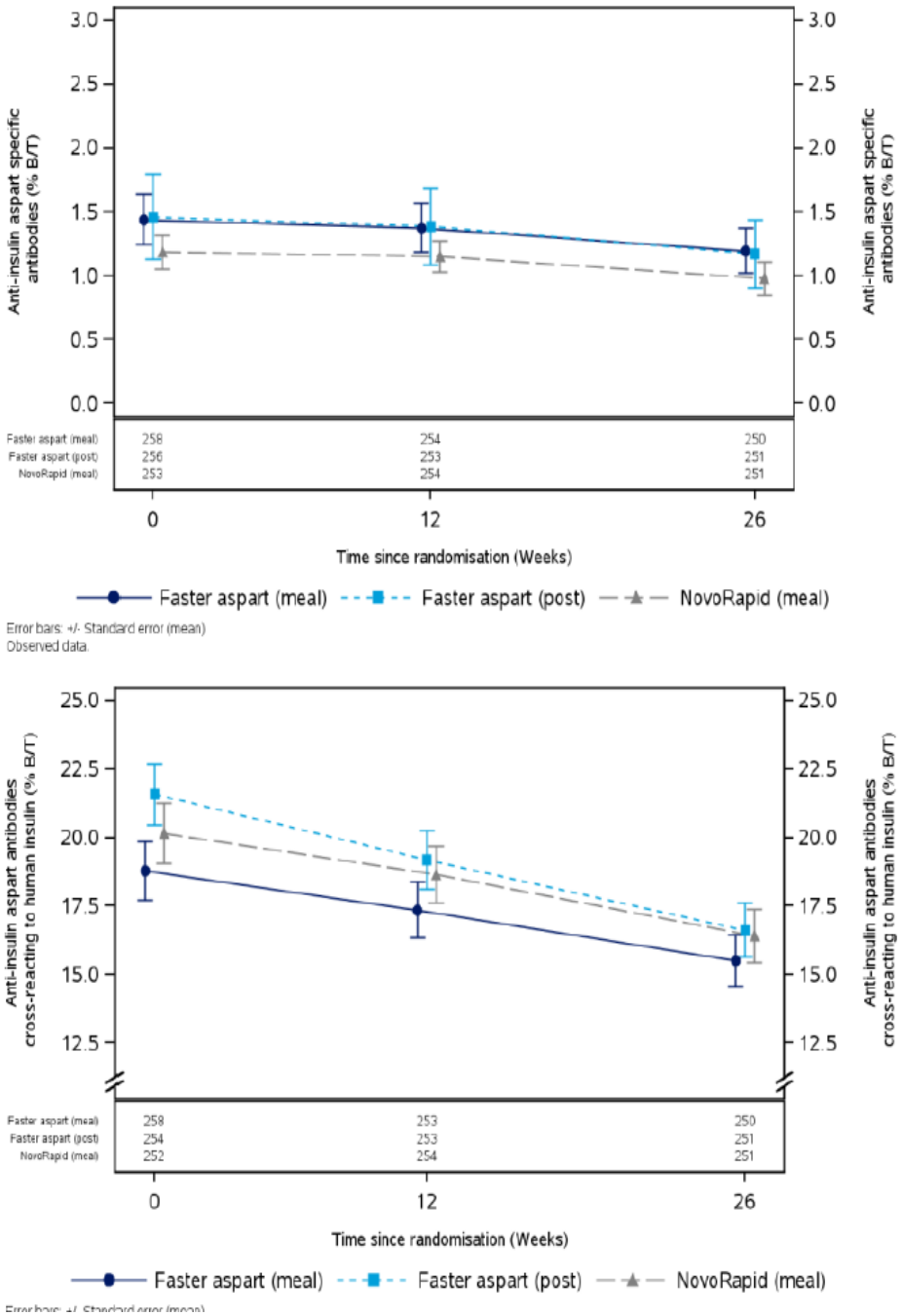


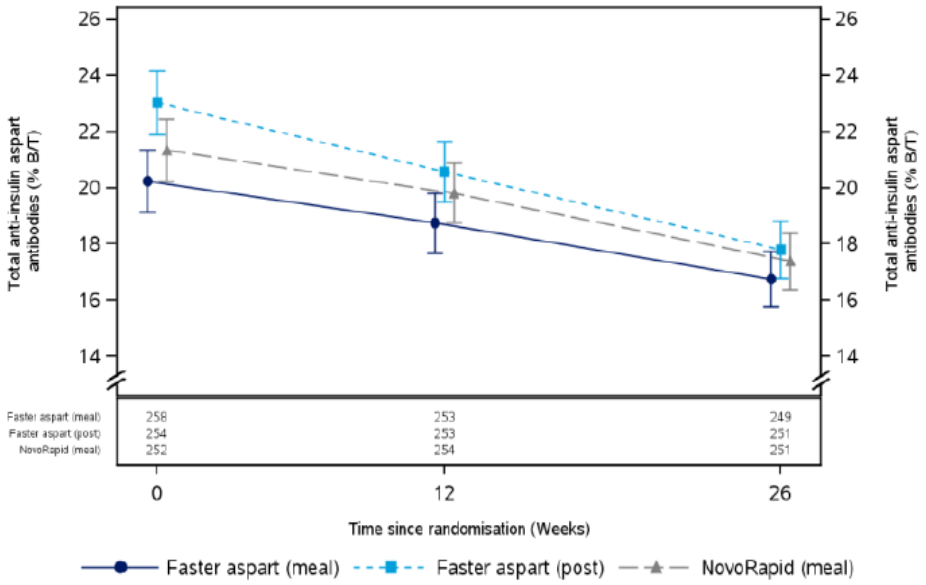
Source: Module 5.3.5.1. Study report 4101, Page 138

Samples for antibodies were collected at baseline (week 0), approximately half way through the study (week 12) and at the end-of-study visit (week 26). Overall, there were no differences in anti-insulin aspart specific antibodies, anti-insulin aspart antibodies cross-reacting to human insulin and total anti-insulin aspart antibodies (specific and cross-reacting with human insulin) across the 3 treatment groups at baseline and after 12 and 26 weeks of treatment (Figure 16). The percentage of subjects categorized as

positive for specific antibodies was similar between the 3 treatment groups (13.6–20.5%), irrespective of the timing of the sample or whether the response was sustained or a single occurrence (Table 9). At baseline, the percentage of subjects categorized as positive for cross-reacting antibodies was 93.0–96.2%, and 96.1–98.1% of the subjects were categorized as positive at any time during the treatment period. In line with the results for specific antibodies, the percentage of subjects categorized as positive for cross-reacting antibodies was similar between the 3 treatment groups. There was no apparent relation between the level of antibodies and either bolus or total daily insulin dose.

Figure 16. Anti-insulin aspart specific antibodies (top), anti-insulin aspart antibodies cross-reacting to human insulin (middle) and total anti-insulin aspart antibodies (bottom) – safety analysis set





Source: Module 2.7.4 Summary of clinical safety page 64

Table 9. Incidence of anti-insulin aspart antibody positive subjects – safety analysis set

		Anti-insulin aspart antibody positive		
	Safety Set	Baseline N (%)	Anytime N (%)	Sustained N (%)
Anti-insulin aspart antibodies cross-reacting to human insulin (% B/T)				
Faster aspart (meal)	261	251 (96.2)	256 (98.1)	252 (96.6)
Faster aspart (post)	258	240 (93.0)	248 (96.1)	241 (93.4)
NovoRapid (meal)	258	244 (94.6)	251 (97.3)	246 (95.3)
Anti-insulin aspart specific antibodies (% B/T)				
Faster aspart (meal)	261	41 (15.7)	48 (18.4)	41 (15.7)
Faster aspart (post)	258	42 (16.3)	51 (19.8)	35 (13.6)
NovoRapid (meal)	258	44 (17.1)	53 (20.5)	43 (16.7)
Total anti-insulin aspart antibodies (% B/T)				
Faster aspart (meal)	261	241 (92.3)	250 (95.8)	240 (92.0)
Faster aspart (post)	258	234 (90.7)	241 (93.4)	236 (91.5)
NovoRapid (meal)	258	238 (92.2)	248 (96.1)	244 (94.6)

%: Percentage of subjects, N: Number of subjects
Faster aspart (meal+post): combination of the mealtime and postmeal faster aspart treatment arms.
Limits: Cross-reacting antibodies > 0.7 % B/T, Specific antibodies > 1.9 % B/T, Total antibodies > 1.9 % B/T.

Source: Module 2.7.4 Summary of clinical safety, page 65

2.3.3. Does the clinical pharmacology information submitted support the pediatric indication for the use of Fiasp as CSII?

The sponsor has submitted prior approval efficacy supplement (S-11) to support CSII use in Insulin pump for Fiasp in pediatric patients with diabetes mellitus. In accordance with the agreed iPSP (dated 08/28/2015 in DARRTS), Novo Nordisk has proposed to extrapolate efficacy results from the adult pump study in T1DM to pediatric T1DM based on the following:

- Efficacy data from the completed Phase 3b pump efficacy and safety study in adult subjects with T1DM (NN1218-3854). This study was submitted under Supplement 08 (NDA 208751).

- The completed single dose pump PK/PD study in adult subjects with T1DM (NN1218-4349). This study was also submitted under Supplement 08 (NDA 208751).
- Efficacy data from the completed subcutaneous pediatric efficacy and safety study in subjects with T1DM (NN1218-4101)

Novo Nordisk has also proposed to leverage the safety and dosing information from studies NN1218-3854 and 4101 to support the CSII use of Fiasp with pediatric patients. Furthermore, study NN1218-3852 (long-term efficacy) is used to provide reference data for supporting dosing recommendations. From clinical pharmacology perspective the observed consistency in PK/PD profile of Fiasp among children, adolescents, and adults, supports the proposed extrapolation of adult CSII data towards an indication for CSII use in pediatric patients. However, the final acceptability of S-11 is deferred to Clinical and CDRH review disciplines.

2.4. Bioanalytical

2.4.1. Are the bioanalytical methods properly validated to measure Fiasp in the plasma samples?

The methods of bioanalysis for the studies included in this application were the same as in the original NDA. In brief, samples were analyzed by an indirect sandwich ELISA using an analyte-specific capture antibody and a biotinylated analyte-specific detection antibody. Following addition of avidin-peroxidase, the antibody-antigen complex is visualized by 3,3',5,5'-Tetramethylbenzidine substrate. The quantification is performed using the optical density values at 450 nm.

The analytical method for determination of insulin aspart (also referred to as "total insulin aspart") is described in SM3-349 and was validated in (b) (4) method validation studies. The assay validation and analysis of samples were performed in accordance with current practice and were reviewed at the time of original NDA submission (see OCP review dated 09/06/2017 for further details).

From study 4371, a total of 1720 samples were received frozen on dry ice and stored at (b) (4) at -20°C. Study samples were stored from sample collection (first collection date 16-Jan-2018) to the end of sample analysis (last analysis date 27-Jul-2018) for a duration not exceeding 192 days. Study samples were analyzed without exceeding long-term, short term or freeze-thaw stability. The %bias for QC samples was -1.8% to 1.2% and CV% was 7.1 to 8.0%. The overall performance of the ELISA method met the acceptance criteria and the results obtained were of the required integrity and quality.

From study 4265, a total of 4718 samples were received frozen on dry ice and stored at (b) (4) at -20°C. Study samples were stored from sample collection (first collection date 17-Nov-2016) to the end of sample analysis (last analysis date 28-Mar-2018) for a duration not exceeding 497 days. Study samples were analyzed without exceeding long-term, short term or freeze-thaw stability. The %bias for QC samples was -0.1% to -6.1% and CV% was 5.7 to 8.7%. The overall performance of the ELISA method met the acceptance criteria and the results obtained were of the required integrity and quality.

3. Label Recommendations

The following proposed clinical pharmacology related labeling is acceptable.

Specific Populations

Age (b) (4) gender, BMI, and race did not meaningfully affect the pharmacokinetics and pharmacodynamics of FIASP.

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/s/

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11/08/2019 11:39:17 PM

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