EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2019
EMA/471389/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fiasp

International non-proprietary name: insulin aspart

Procedure No. EMEA/H/C/004046/II/0010

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
BG	blood glucose
CGM	continuous glucose monitoring
CI	confidence interval
DKA	diabetic ketoacidosis
E	number of adverse events or hypoglycaemic episodes
EMA	European Medicines Agency
EOT	end of text
ETD	estimated treatment difference
EU	European Union
Faster aspart	Fast-acting insulin aspart
FDA	Food and Drug Administration
Fiasp®	trade name for fast-acting insulin aspart
FPG	fasting plasma glucose
HbA1c	glycosylated haemoglobin
IG	interstitial glucose
ISPAD	International Society for Pediatric and Adolescent Diabetes
M	Module
MAA	marketing authorisation application
MESI	medical event of special interest
N	number of subjects
NPH	Neutral Protamine Hagedorn
PG	plasma glucose
PPG	postprandial glucose
PYE	Patient years of exposure
R	rate
s.c.	subcutaneous
SAE	serious adverse event
SMPG	self-measured plasma glucose
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
US	United States of America
%B/T	%B/T value is proportional to the antibody titre present in the sample; percent bound radioactivity (B) of the total amount of radioactivity (T)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 8 January 2019 an application for a variation

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB, Annex A

Extension of Indication to include treatment of children and adolescents aged 1 year and above based on data from the phase 3b clinical trial NN1218-4101, supported by data from the Clinical Pharmacology trials NN1218-4371 and clinical study NN1218-3888 which was included in the initial MAA.
As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC and the corresponding sections of the Package Leaflet are updated accordingly.
In addition, the Marketing authorisation holder (MAH) took the opportunity to make other non-related minor or editorial changes were implemented throughout the EU PI to increase readability/consistency.
An updated RMP was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet, Annex A and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable. There is no Paediatric Investigation Plan for Fiasp in the EU.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH have sought Scientific advice at the CHMP on the paediatric development programme (EMA/H/SA/2136/FU/1/2013/III).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Ingrid Wang

Timetable	Actual dates
Submission date	8 January 2019
Start of procedure:	27 January 2019
CHMP Co-Rapporteur Assessment Report	21 March 2019
CHMP Rapporteur Assessment Report	20 March 2019
PRAC Rapporteur Assessment Report	29 March 2019
PRAC members comments	3 April 2019
Updated PRAC Rapporteur Assessment Report	4 April 2019
PRAC Outcome	11 April 2019
CHMP members comments	15 Apr 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 April 2019
Request for supplementary information (RSI)	26 April 2019
PRAC Rapporteur Assessment Report	3 June 2019
Updated PRAC Rapporteur Assessment Report	7 June 2019
CHMP Rapporteur Assessment Report	11 June 2019
PRAC Outcome	13 June 2019
CHMP members comments	17 Jun 2019
Updated CHMP Rapporteur Assessment Report	20 Jun 2019
Opinion	27 Jun 2019

2. Scientific discussion

2.1. Introduction

Fast-acting insulin aspart (faster aspart) is insulin aspart in a new formulation, which has been developed as a mealtime insulin with a faster glucose-lowering effect compared to the original insulin aspart formulation with the global trade name NovoRapid. Faster aspart has received marketing authorisation in the EU in January 2017, under the tradename Fiasp, for the treatment of adult patients with diabetes mellitus.

The objective of the development of faster aspart was to more closely mimic the physiological mealtime insulin response compared to other available mealtime insulins. Moreover, the aim with faster aspart was to address some of the real-life challenges faced by individuals who require mealtime insulin, such as the option for post-meal dosing in situations when dosing at the start of the meal is not suitable or possible (e.g., when the size, composition or timing of the meal is unpredictable) or when patients are anxious about potential hypoglycaemia from pre-meal dosing.

Compared to NovoRapid, faster aspart contains two additional excipients: nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride (an amino acid). The addition of nicotinamide results in a faster initial absorption of insulin aspart following subcutaneous (s.c.) injection, leading to a greater early glucose-lowering effect compared to NovoRapid. The addition of L-arginine hydrochloride supports stabilisation of the faster aspart formulation. The insulin aspart molecule in faster aspart and NovoRapid is identical and therefore, once systemically absorbed, it has the same biological action at the insulin receptor as that of NovoRapid.

Diabetes mellitus in paediatric subjects

Type 1 diabetes mellitus (T1DM) is among the most common chronic diseases in children and adolescents. T1DM accounts for over 90% of all childhood and adolescent diabetes. Subjects with T1DM require lifelong treatment with insulin.

Type 2 diabetes mellitus (T2DM) is becoming increasingly common in adolescents, particularly in the peripubertal period although the disease remains relatively rare apart from in minority populations. Available data suggest that preadolescent children are unlikely to have T2DM even if obese. Due to the progressive nature of T2DM, the majority of subjects will eventually require insulin therapy to achieve targets for glycaemic control once beta-cell function deteriorates and insulin deficiency increases.

The challenge to obtain good glycaemic control in the absence of hypoglycaemia is greater in a paediatric population compared to an adult population due to growth, more variable lifestyle, need of assistance with insulin injection and hormonal changes. A basal-bolus insulin regimen is generally recommended for paediatric T1DM subjects aiming at resembling physiological insulin secretion.

Preferable, rapid-acting insulin analogues like faster aspart should be given immediately before meals. However, a significant proportion of people with diabetes regularly need to take their dose of bolus insulin either during or after a meal despite glycaemic control having a positive association with administration before the meal. Thus, there is an unmet medical need for a bolus insulin that allows subjects greater flexibility through the option of post-meal dosing. In the ISPAD 2018 guideline, the need for the option to dose after meal start is recognised, and it states that rapid acting insulin analogues may be given after the meal if needed, e.g., in toddlers and infants where the size and composition of a meal cannot be accurately predicted in advance.

Paediatric development programme

The clinical development programme for faster aspart in paediatric subjects consisted of one clinical pharmacology trial (trial 3888) and one therapeutic confirmatory trial (trial 4101). The clinical trial report for trial 3888 was submitted as part of the Marketing authorisation application (MAA), and the clinical trial report for trial 4101 has been submitted as a post-authorisation measure as an Article-46 paediatric study submission (EMEA/H/C/4046 P46 002).

In addition, a clinical pharmacology trial, trial 4371, with similar trial design and objectives as that of trial 3888 was conducted in alignment with recommendations from the FDA. From this trial, only safety results as well as the pharmacodynamic results from the meal test are included in the present application. The

clinical trial report has been submitted as a post-authorisation measure as an Article-46 paediatric study submission.

Objective and rationale

The purpose of this application is to update the current prescribing information to include specific information on the use of faster aspart in children from 1 year and above with diabetes mellitus.

Prior to initiation of the paediatric trials included in this application, the MAH consulted with the Committee for medicinal products for human use (EMA/H/SA/2136/FU/1/2013/III) and obtained agreement that the proposed trials would support the paediatric indication for faster aspart including children from 1 year of age and above with diabetes mellitus.

The clinical trials were conducted in children and adolescents with T1DM. Insulin treatment may be required to achieve good glycaemic control in children and adolescents with type 2 diabetes (T2DM) and insulin , together with metformin, are the only approved drugs for the treatment of diabetes in this population. According to the EMA diabetes guideline, additional data in paediatric patients with T2DM may not be needed if efficacy and safety of a novel insulin is demonstrated in adults with T2DM and in children with T1DM. As part of the clinical development programme for faster aspart, 2 therapeutic confirmatory trials in adult subjects with T2DM were conducted: trial 3853 in which 689 bolus insulin-naïve subjects were treated for 26 weeks with faster aspart versus NovoRapid in a basal-bolus regimen with a trial design comparable to that of trial 4101, and trial 4049 in which 236 bolus insulin-naïve subjects were treated with faster aspart + basal vs. basal only treatment. Both trials demonstrated that faster aspart was efficacious and safe in adult subjects with T2DM. This issue was discussed in the Scientific Advice and the CHMP agreed that this type of extrapolation (to children with T2DM, based on efficacy and safety having been demonstrated in adults with T2DM and in children and adolescents with T1DM) would be in line with the EMA diabetes guideline.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Insulin aspart is a protein consisting of amino acids derived from a biological system and therefore expected to be readily biodegradable. On this basis Novo Nordisk conclude that the use of Fiasp for treatment of diabetes is unlikely to result in significant risk to the environment. This is agreed.

2.2.2. Conclusion on the non-clinical aspects

There are no objections to approval of the Type II variation from a non-clinical point of view.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Trial ID Country	Type of study	Trial design and type of control	Test drugs and route of administration	Number of subjects (FAS) (M/F)	Healthy subjects or population	Duration of treatment
NN1218-3888 DE	PK	Single-centre, randomised, double-blind, single-dose, two-period cross-over trial in which children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with T1DM received faster aspart and NovoRapid®/NovoLog®	Single s.c. dose of faster aspart and NovoRapid®/NovoLog®, at dose level of 0.2U/kg body weight	40 (M: 22/F: 18) All subjects received both treatments: faster aspart; NovoRapid®/NovoLog®	T1DM Adults, children and adolescents 6 ≤ 64	Two periods with single-dose
NN1218-4101 BG, CZ, DE, EE, FI, IL, IN, IT, JP, LV, LT, PL, RS, RU, TR, UA, US	Efficacy and safety	Multi-centre, multi-national, randomised, partly double - blind (1:1:1), 3-armed parallel-group treat-to-target trial .The trial compared effect and safety of mealtime faster aspart versus mealtime NovoRapid®/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	Bolus treatment with faster aspart s.c. or NovoRapid®/Novolog® s.c in combination with basal insulin degludec s.c. Faster aspart, 100 U/mL, 3 mL Penfill® NovoRapid®/Novolog® 100 U/mL, 3 mL Penfill® s.c. Insulin degludec, 100 U/mL, pre-filled 3 mL PDS290 pen-injector (FlexTouch®) s.c.	Mealtime faster aspart: 260 (M:134/F:126) 1 - <6 years: 16 6 - <12 years: 100 12 - <18 years: 144 Postmeal faster aspart: 259 (M:137/F:122) 1 - <6 years: 16 6 - <12 years: 100 12 - <18 years: 143 NovoRapid®/NovoLog®: 258 (M:148/F:110) 1 - <6 years: 14 6 - <12 years: 101 12 - <18 years: 143	T1DM Children and adolescents 1 to <18 years	A 12 weeks run-in period with degludec and insulin aspart followed by a partly double blinded 26 week treatment period
NN1218-4371 DE	PK	Single-centre, randomised, double-blind, single-dose, two-period cross-over trial investigating the pharmacokinetic properties of faster aspart and NovoRapid® in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with type 1 diabetes	Single s.c. dose of faster aspart and NovoRapid®/NovoLog®, at dose level of 0.2U/kg body weight	43 (M:20/F:23) All subjects received both treatments: faster aspart; NovoRapid®/NovoLog® 6 ≤11years: 12 12 ≤17 years: 16 18 ≤ 64 years: 15	T1DM Adults, children and adolescents 6 ≤ 64	Two periods with single-dose

2.3.2. Pharmacokinetics

Two clinical pharmacology trials have been conducted in paediatric patients; trial 3888 and trial 4371. Trial 3888 was submitted with the initial MAA and is not further described in this AR. Study 4371, with a similar trial design and objectives, is described below.

Study 4371 was a randomised, single-centre, double-blind, single-dose, two-period cross-over trial investigating the pharmacokinetic and pharmacodynamic properties of faster aspart and NovoRapid in children (n=12), adolescents (n=16) and adults (n=15) with T1DM. Each subject was randomly allocated to a treatment sequence consisting of two dosing visits during which the subject received a single subcutaneous dose of either faster aspart or NovoRapid at a predefined fixed dose level (0.2 U/kg BW) in connection to intake of a standardised meal (meal test). The mean age was 10.0 years in the children age group (range 7-11 years), 14.9 in the adolescent group (range 12-17 years) and 19.7 in the adult group (range 18-23 years).

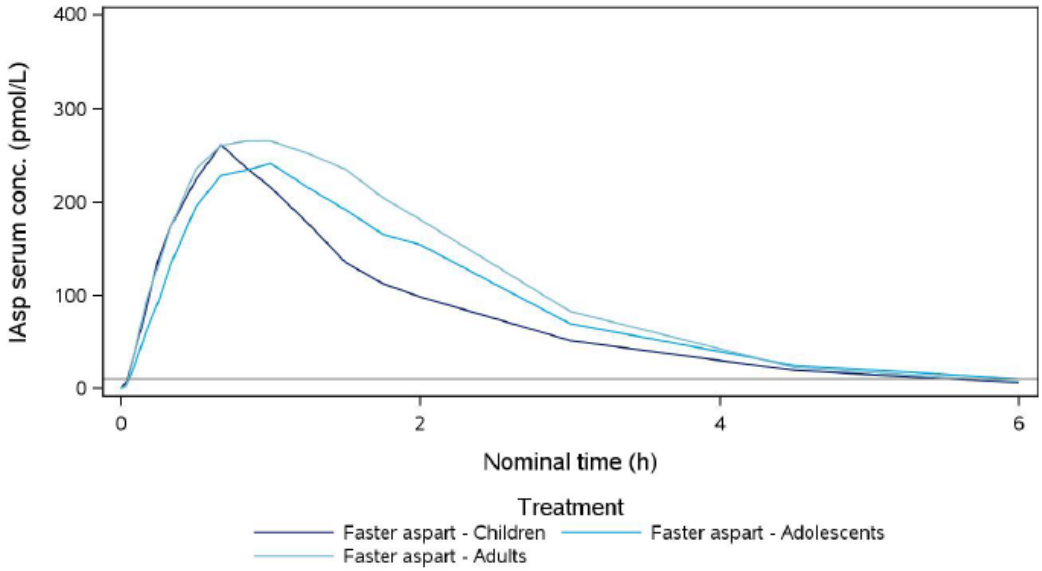
Age group comparisons (children vs adults, adolescents vs adults)

The age group comparisons showed similar pattern for insulin aspart as for NovoRapid.

Total insulin exposure

Based on free insulin aspart measurements, the total exposure (AUCIAsp,free,0-12h) after administration of faster aspart was 29% lower in children and 13% lower in adolescents compared to adults, Figure 1 and Table 1.

Figure 1 Mean free insulin aspart profiles – faster aspart ($IAsp_{free}$), 0-6 hours.



IAsp serum conc.: Free insulin aspart serum concentration, PK: Pharmacokinetic
Horizontal grey line at 10 pmol/L indicates the LLOQ.

Table 1. Statistical analyses of age group comparisons for total exposure and maximum concentration, faster aspart ($IAsp_{free}$).

	N	Estimate	95% CI
#AUCIAsp,free(0-12h) (pmol*h/L)			
LSMeans			
Faster aspart: Children	12	493	
Faster aspart: Adolescents	16	604	
Faster aspart: Adults	13	693	
Treatment ratio			
Faster aspart: Children / Adults		0.71	[0.61; 0.83]
Faster aspart: Adolescents / Adults		0.87	[0.78; 0.98]
Cmax Iasp,free (pmol/L)			
LSMeans			
Faster aspart: Children	12	258	
Faster aspart: Adolescents	16	253	
Faster aspart: Adults	13	292	
Treatment ratio			
Faster aspart: Children / Adults		0.88	[0.67; 1.17]
Faster aspart: Adolescents / Adults		0.87	[0.73; 1.03]

AUC: Area under the curve, CI: Confidence interval, IAsp: Free insulin aspart, N: Number of subjects contributing to analysis. The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect.
#AUC(0-12 hour) is the primary endpoint.

Early insulin exposure

For all AUCs covering the first 90 minutes after administration of faster aspart, early exposure based on free insulin aspart measurements in children and adolescents was not statistically significantly different from that in adults. There was a tendency towards lower exposure in children and adolescents compared to that in adults, which became statistically significant at 2 h after drug administration, Table 2.

Table 2. Statistical analyses of age group comparisons for early AUC endpoints, faster aspart ($IAsp_{free}$).

Endpoint	Children/Adults Ratio [95% CI]	Adolescents/Adults Ratio [95% CI]
AUCIAsp,free(0-15min)	0.81 [0.33;1.98]	0.69 [0.42; 1.16]
AUCIAsp,free(0-30min)	0.82 [0.43; 1.56]	0.75 [0.52; 1.09]
AUCIAsp,free(0-1h)	0.83 [0.55; 1.25]	0.82 [0.63; 1.06]
AUCIAsp,free(0-90min)	0.77 [0.57; 1.05]	0.82 [0.67; 1.02]
AUCIAsp,free(0-2h)	0.72 [0.57; 0.92]	0.82 [0.69; 0.97]

AUC: Area under the curve, CI: Confidence interval, IAsp: Free insulin aspart,
The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect.

Onset of insulin exposure

The onset of appearance for free insulin aspart after administration of faster aspart in children (4.2 min) and in adolescents (4.4 min) was not statistically significantly different from that for adults (3.7 min). The time to 50% Cmax in children (19.7 min) and in adolescents (20.9 min) was no statistically significantly different form that in adults (18.6 min).

Treatment group comparison (faster aspart versus NovoRapid)

Total insulin exposure

Based on the free insulin aspart measurements, the total insulin exposure (AUCIAsp, 0−12h) and the maximum observed free insulin aspart concentration (Cmax) were comparable for faster aspart and NovoRapid (treatment ratios: 0.99 [0.88; 1.11]95% CI and 1.01 [0.83; 1.23]95% CI, respectively).

Onset of insulin exposure

In children, the onset of appearance for free insulin aspart was 5.0 minutes earlier for faster aspart (4.2 minutes) compared to NovoRapid (9.2 minutes). The time to 50% Cmax for free insulin aspart was 6.4 minutes earlier for faster aspart (19.7 minutes) compared to NovoRapid® (26.2 minutes).

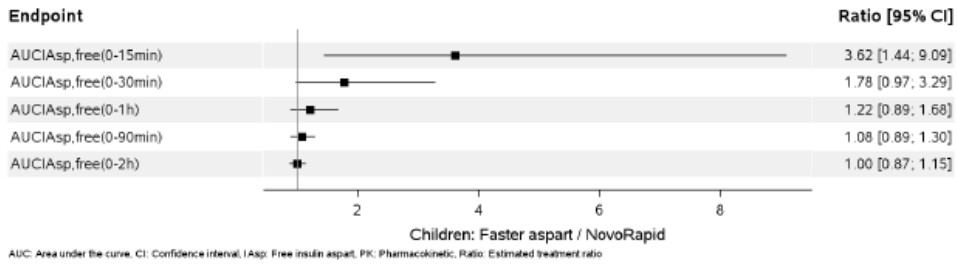
In adolescents, the onset of appearance for free insulin aspart was 2.4 minutes earlier for faster aspart (4.4 minutes) compared to NovoRapid (6.8 minutes). The time to 50% Cmax for free insulin aspart was 6.6 minutes earlier for faster aspart (20.9 minutes) compared to NovoRapid® (27.5 minutes).

Early insulin exposure

Insulin exposure based on free insulin aspart measurements was approximately 3.6 times greater in children for faster aspart compared to NovoRapid® during the first 15 minutes (AUCIAsp 0-15min) after trial product administration (

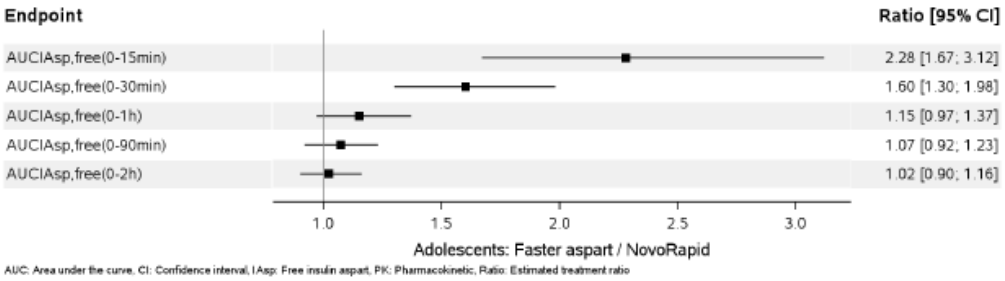
Figure 2). This result was statistically significant. There was a trend towards greater exposure for faster aspart compared to NovoRapid for AUCIAsp, 0-30 min, AUCIAsp, 0-1h, and AUCIAsp, 0-90min, although these differences were not statistically significant. Insulin exposure based on free insulin aspart measurements was comparable at 2 hours (AUCIAsp, 0-2h) after trial product administration.

Figure 2 Forest plot of statistical analysis of treatment comparison for early AUC endpoints – Children (IAspfree)



Insulin exposure based on free insulin aspart measurements was approximately 2.3 times greater in adolescents for faster aspart compared to NovoRapid® during the first 15 minutes and approximately 1.6 times greater during the first 30 minutes after trial product administration (Figure 3). These results were statistically significant. There was a trend towards greater exposure for faster aspart compared to NovoRapid® for AUCIAsp, 0-1h, and AUCIAsp, 0-90min, although these differences were not statistically significant. Insulin exposure based on free insulin aspart measurements was comparable at 2 hours (AUCIAsp, 0-2h) after trial product administration.

Figure 3 Forest plot of statistical analysis of treatment comparison for early AUC endpoints – Adolescents ($IAsp_{free}$)



2.3.3. Pharmacodynamics

Two studies providing PD data in paediatric subjects were submitted in support of the present application. Trial 3888 was submitted as part of the MAA. Only the pharmacodynamic (PD) results from the meal test in this study are described in the present application.

In addition, a clinical pharmacology trial with similar design and objectives as that of trial 3888, was conducted; trial 4371.

Both trial 3888 and trial 4371 were single dose cross-over studies investigating pharmacokinetic and pharmacodynamic properties of faster aspart and NovoRapid in children, adolescents and adults.

Study 3888

This single-centre cross-over study included 40 subjects and compared the pharmacodynamic properties of faster aspart and NovoRapid administered as a single subcutaneous injection (0.2 U/kg) immediately before a standardised meal in subjects with T1DM. For further details of this study, please refer to the EPAR for the MAA for Fiasp (EMEA/H/C/004046/0000).

The age range of the included subjects was 9 – 25 years. Pharmacodynamic properties were studied with plasma glucose sampled during a 12-hour period following a standardised meal. To describe the early and

total effect of faster aspart, the average postprandial plasma glucose increment during time, and the plasma glucose concentrations at 1 and 2 hours after start of the meal, were used.

The estimated mean PPG increment over 2 hours (ΔPGav, 0-2h) with faster aspart in adults was 2.36 mmol/L with faster aspart and 2.93 mmol/L with NovoRapid. The estimated treatment difference between faster aspart and NovoRapid for ΔPGav, 0-2h was not statistically significantly different (-0.57 mmol/L [-1.83; 0.69]95% CI). The treatment difference (faster aspart – NovoRapid) in mean PPG increment over 1 hour (ΔPGav, 0-1h) (-0.31mmol/L [-1.48; 0.86]95% CI) was smaller than at 2 hours.

The estimated mean changes from baseline in PG during the first and second hours of the meal test (ΔPGav, 0-1h and ΔPGav, 0-2h) were similar between children (9-11 years) and adults (18-25 years) but tended to be larger for adolescents (13-17 years) compared to adults, though this difference was not statistically significant.

The mean PG level did not differ significantly between children and adults at 1 hour and at 2 hours.

With regards to the mean changes in PG levels, adolescents tended to have higher PG levels than adults at both 1 hour and 2 hours, but these differences were not statistically significant.

A test for interaction between age group and treatment showed that the age group effect did not differ significantly between the treatments for the pharmacodynamic endpoints.

Study 4371 - Pharmacodynamic profiles – age group comparison – faster aspart

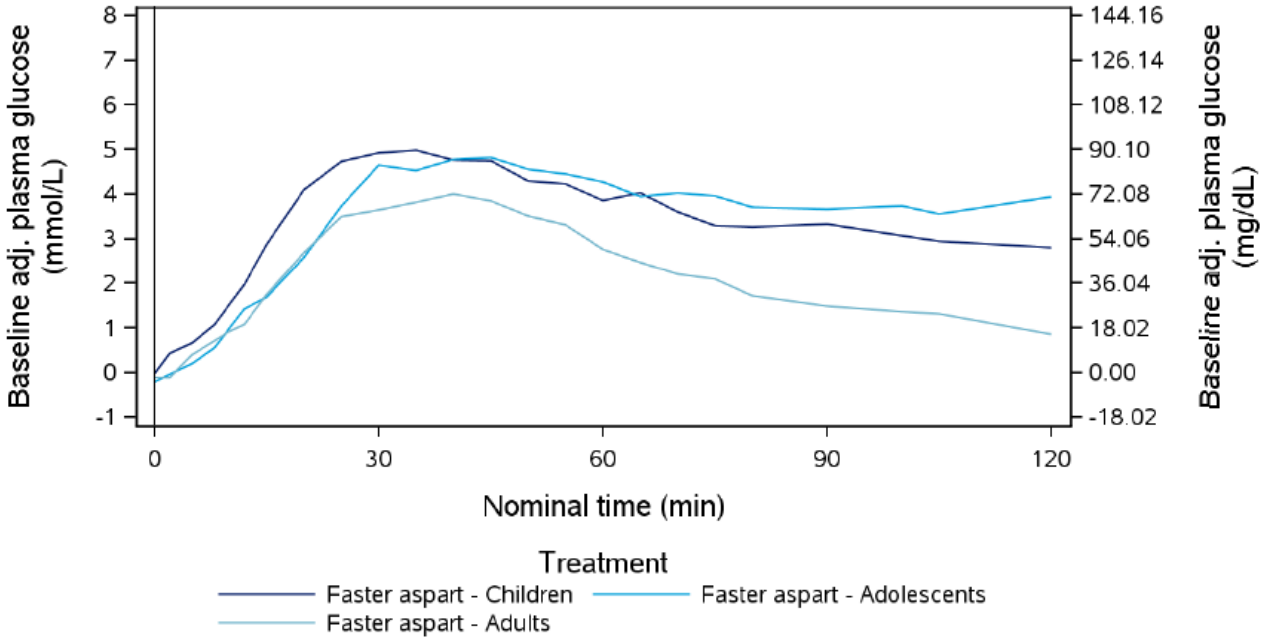
In study 4371, the PG concentration was measured over a period of 12 hours following the administration of a single dose of faster aspart given in connection with a standardised meal.

Seven (7) subjects (3 children and 4 adults) who were administered faster aspart received oral carbohydrate interventions during the meal test. No interventions were made during the first 60 minutes following trial product administration, and the majority of interventions in children and adults occurred between 120 minutes and 180 minutes. As 25.0% of children and 26.7% of adults received oral carbohydrate with the faster aspart treatment, the secondary endpoints of mean change in PG concentration from 0 to 6 hours after trial product administration and minimum PG levels were affected, as well as the 0 to 6 hour PG profiles.

In evaluation of the PG-lowering effect of the trial products, it is therefore more relevant to consider the PD endpoints covering the first 2 hours of the meal test. No insulin or glucose infusions were given as intervention during the meal test.

Mean baseline adjusted PG profiles for all age groups for faster aspart from 0 to 120 minutes are shown in Figure 4. During the first 2 hours after administration of faster aspart, the PG profile for children and adolescents appeared to be higher compared to that for adults.

Figure 4 Mean baseline adjusted plasma glucose profiles - faster aspart, 0-120 minutes (full analysis set)



Adj.: Adjusted, PD: Pharmacodynamic
The conversion factor between mmol/L and mg/dL is 18.02.
Baseline is the mean over PG concentrations measured in the time interval -15 to 0 minutes prior dosing.

Glucose-lowering effect – age group comparison – faster aspart

The one-hour glucose-lowering effect estimated by the change from baseline in PG (ΔPG1h) was not statistically significantly different between children and adults (age group difference: 1.13 [-1.63; 3.88]95% CI), or between adolescents and adults (age group difference: 1.52 [-0.05; 3.09]95% CI). Also, the two-hour glucose-lowering effect was not statistically significantly different between children and adults (age group difference: 1.93 [-0.92; 4.79]95% CI) but was statistically significantly lower in adolescents compared to adults (age group difference: 3.06 [0.83; 5.29]95% CI). The PG mean change endpoints (ΔPGav,0-1h and ΔPGav,0-2h) showed similar results.

The maximum PG excursion from 0 to 6 hours (ΔPGmax) was not statistically significantly different between children and adults (age group difference: 1.61 [-0.51; 3.73]95% CI), or between adolescents and adults (age group difference: 1.91 [0.24; 3.58]95% CI).

Pharmacodynamic profiles – treatment comparison – faster aspart vs NovoRapid

For all three age groups, the PG profiles for the first 2 hours were lower for faster aspart than for NovoRapid indicating a greater glucose-lowering effect with faster aspart compared to NovoRapid.

2.3.4. Discussion on clinical pharmacology

Two clinical pharmacology trials have been conducted in paediatric patients; trial 3888 and trial 4371. Trial 3888 was submitted with the initial MAA and is only briefly described in this AR.

Study 4371 included children from 7 years of age, adolescents and adults. Pharmacokinetic data show that total exposure was 29% lower in children and 13% lower in adolescents compared to adults. C_{max} was 12% and 13% lower in children and adolescents respectively, compared to adults. A similar pattern was seen for NovoRapid. The difference between children and adolescents compared to adults is not considered clinically relevant since insulin is individually titrated.

Faster aspart showed an earlier onset of exposure and a higher early insulin exposure whilst maintaining a similar total exposure and maximum concentration compared to NovoRapid across all age groups.

With regards to the PD, 1-hour PG-lowering effect did not differ between children and adults or between adolescents and adults. However, the 2-hour PG-lowering effect was lower in adolescents compared to adults. For NovoRapid, the age group comparison for PD parameters showed similar pattern of results as seen for faster aspart. When faster aspart was compared to NovoRapid, both the 1-hour and 2-hour PG lowering effect was greater with faster aspart than with NovoRapid across all age groups.

2.3.5. Conclusions on clinical pharmacology

The results provided with study 4371are well in accordance with the results from the previous paediatric study, 3888, included in the initial MAA. The pharmacodynamic data indicate that the glucose lowering effect of Fiasp is comparable in children, adolescents and adults.

2.4. Clinical efficacy

2.4.1. Main study

"Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes" - NN1218-4101

Methods

The trial compared effect and safety of mealtime faster aspart versus mealtime NovoRapid, 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 trial also included a 26-week open-label post-meal faster aspart dosing group in combination with insulin degludec.

The trial design is shown schematically in Figure 5.

The total trial duration for each subject was approximately 45 weeks:

- up to 2 weeks for screening
- a 12-week run-in period (optimising the insulin degludec dose)
- a 26-week treatment period
- a 7-day and a 30-day follow-up period

12-week run-in period

At visit 2, eligible subjects were enrolled in a 12-week run-in period and switched from their previous insulin treatment to insulin degludec once daily and mealtime NovoRapid. In this period, the investigator optimised the basal insulin on a weekly basis to individual FPG targets (Figure 5).

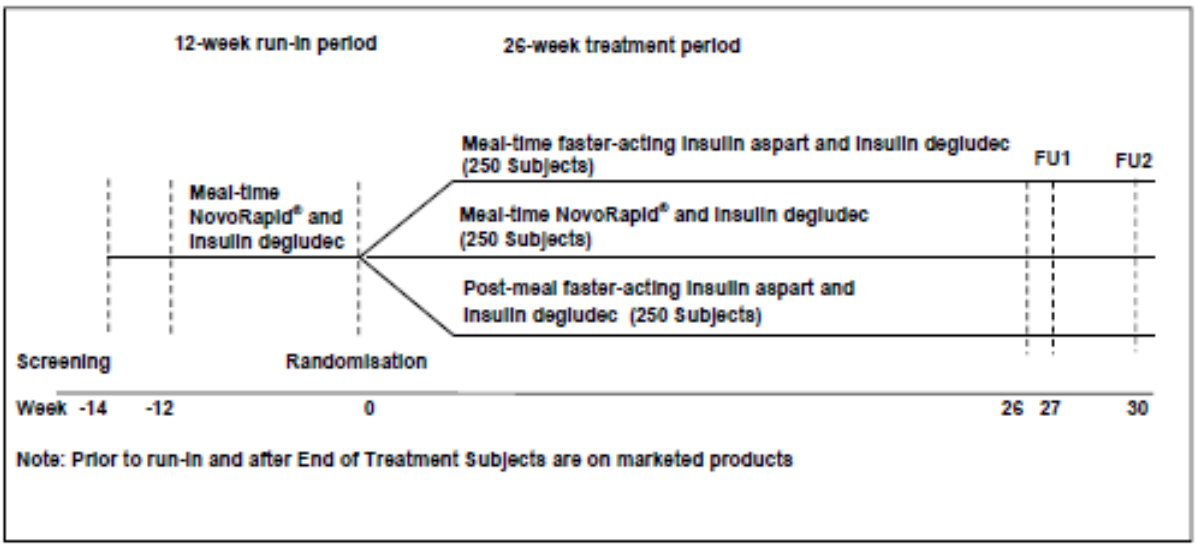
26-week treatment period

Subjects with HbA1c ≤ 9.5% (80 mmol/mol) who based on the investigators judgement had shown ability and willingness to adhere to the trial protocol were randomised (1:1:1) to receive mealtime faster aspart, post-meal faster aspart or mealtime NovoRapid, all in combination with insulin degludec (Figure 5).

In the 26-week treatment period, the investigator optimised the bolus insulin to individual pre-meal targets, in accordance with the titration guideline, as described in the trial protocol. Adjustment of basal

insulin dose was to be minimized during the treatment phase; however, basal insulin dose could be adjusted at the investigator's discretion if needed. Glycaemic pre-meal targets of 4.0-8.0 mmol/L (71-145 mg/dL) and glycaemic bedtime targets of 6.7-10.0 mmol/L (120-180 mg/dL) were to be attempted achieved as described in protocol.

Figure 5 Trial design



Study participants

The inclusion and exclusion criteria for the trial were chosen to allow enrolment of subjects from the intended target population in terms of baseline demographics, comorbidities, duration and severity of diabetes. Eligible subjects were 1 to less than 18 years of age (In Serbia: 2 to less than 18 years) with T1DM, treated on a basal-bolus insulin regimen and using a basal insulin analogue or NPH insulin for at least 90 days prior to screening with a total daily dose of insulin ≤2.0 U/kg prior to screening, and with HbA_{1c} ≤9.5 mmol/L (80 mmol/mol) at screening. Subjects had to fulfil an additional randomisation criterion related to their HbA_{1c} levels measured two weeks prior to randomisation: HbA_{1c} ≤9.5%. This criterion was set with the aim to select a trial population, which could be expected to be compliant with the trial regimen and could achieve adequate basal insulin coverage in the 12-week run-in basal insulin titration period where focus was not on bolus titration.

Treatments

The following investigational medical products (IMPs) were used in this trial:

- *Basal insulin*: Insulin degludec
- *Bolus insulin*: Faster aspart (test product) or NovoRapid (active comparator)

At selected sites, a subgroup of subjects wore a blinded CGM device. Subjects were not allowed to wear their own real time CGM during the run-in or treatment periods.

Basal insulin

Timing of dosing: All subjects received insulin degludec as basal insulin from visit 2 (run-in) and throughout the treatment period. Administration of insulin degludec was once-daily, preferably at the same time every day.

Dose: The titration guideline in the trial protocol was followed and titration was based on the SMPG profiles recorded by subjects, with no maximum dose specified:

- At visit 2, all subjects were switched from their previous basal insulin analogue or NPH insulin to insulin degludec.
- During the 12-week run-in period, basal insulin was titrated by the investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0-8.0 mmol/L (71-145 mg/dL).
- During the 26-week treatment period, adjustment at the discretion of the investigator was allowed if needed.

Bolus insulin

Timing of dosing: In the run-in period, all subjects received NovoRapid as bolus insulin. In the treatment period, subjects received mealtime faster aspart, post-meal faster aspart or mealtime NovoRapid as bolus insulin according to their randomisation:

- Mealtime dosing was defined as injecting 0-2 minutes before the meal.
- Post-meal dosing was defined as injecting 20 minutes after the start of the meal.

Administration of bolus insulin (faster aspart or NovoRapid) was done for each of the 3 main meals (i.e., breakfast, lunch and main evening meal). Additional bolus dosing was allowed at the discretion of the investigator.

Dose: The titration guideline in the trial protocol was followed and titration was based on the SMPG profiles recorded by subjects with no maximum dose specified:

- At visit 2, all subjects were switched from their pre-trial bolus insulin to mealtime NovoRapid. Subjects received diabetes training including training in carbohydrate counting. NovoRapid was only adjusted during the run-in period if the investigator found it necessary for safety reasons.
- At randomisation (visit 14), subjects were randomised 1:1:1 to receive mealtime faster aspart, post-meal faster aspart or mealtime NovoRapid.
- In the 26-week treatment period, the bolus insulin was titrated to the pre-meal target of 4.0−8.0 mmol/L (71–145 mg/dL), and the bed-time target of 6.7–10 mmol/L (120−180 mg/dL) in a treat-to-target fashion. Subjects were instructed to titrate the bolus insulin doses using the principles of flexible bolus dosing based on the meal carbohydrate content or to use the pre-defined bolus dosing algorithms.

Objectives

Objective

Primary objective

- To confirm the effect of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid both in combination with insulin degludec using a non-inferiority approach in children and adolescents with type 1 diabetes.

Secondary objectives

- To confirm the effect of treatment with post-meal faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid both in combination with insulin degludec, using a non-inferiority approach in children and adolescents with type 1 diabetes.

- To confirm superiority of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid, both in combination with insulin degludec in children and adolescents with type 1 diabetes.
- To compare the effect and safety of treatment with meal-time faster-acting insulin aspart vs. mealtime NovoRapid both in combination with insulin degludec in children and adolescents with type 1 diabetes.
- To compare the effect and safety of treatment with post-meal faster-acting insulin aspart vs. mealtime NovoRapid both in combination with insulin degludec in children and adolescents with type 1 diabetes.

Outcomes/endpoints

Primary endpoint

- Change from baseline in HbA1c 26 weeks after randomisation.

The primary endpoint addressed the primary objective and the 2 confirmatory secondary objectives (see section "Objectives" above).

Key secondary endpoints

- 8-point self-measured plasma glucose profile (SMPG)
- Postprandial glucose (PPG) based on SMPG, mean over all 3 meals and in individual meals (breakfast, lunch and main evening meal)
- PPG increment based on SMPG, mean over all 3 meals and in individual meals (breakfast, lunch and main evening meal)
- Fasting plasma glucose (FPG)
- 1,5-anhydroglucitol
- Bolus, basal, and total insulin doses
- PPG and PPG increment (meal test) in subgroup
- Interstitial glucose (IG) in subgroup

Sample size

The primary objective of the trial was to confirm the effect of treatment with mealtime faster aspart in terms of glycaemic control measured by change from baseline in HbA1c 26 weeks after randomisation by comparing it to treatment with mealtime NovoRapid, both in combination with insulin degludec, using a non-inferiority approach in children and adolescents with T1DM. The sample size was determined using a non-inferiority limit of 0.4%.

The trial also aimed to confirm the effect of treatment with post-meal faster aspart as measured by change from baseline in HbA1c 26 weeks after randomisation and to confirm superiority of mealtime faster aspart, both in combination with insulin degludec in children and adolescents with T1DM. This was done using a hierarchical testing procedure with 3 steps.

The sample size was determined to ensure sufficient power for the first step and the second step in the hierarchical testing procedure.

Power for the non-inferiority steps were based on a t-statistic under the assumption of a one-sided test of size 2.5%. A zero mean treatment difference for the comparison between mealtime faster aspart and mealtime NovoRapid was expected, and for the comparison of post-meal faster aspart and mealtime NovoRapid a mean difference of 0.05% in favour of mealtime NovoRapid was expected.

Based on experience from previous trials, and taking into account that the in-trial observation period included data collected after treatment discontinuation, the SD for change in HbA1c was assumed to be 1.3%. With this SD, a sample size of 250 subjects per group (750 in total) ensured more than 93% power to show non-inferiority, given that the actual treatment difference was 0%. This sample size ensured a power of 85% to show non-inferiority of post-meal faster aspart compared to mealtime NovoRapid.

The number of subjects to prematurely discontinue trial product was expected to be less than 10% based on previous trials. The number of subjects to withdraw from the trial was expected to be less than 5%.

Sample size calculation for the continuous glucose monitoring and meal test subgroup

The CGM and meal test subgroup was included in the trial in order to compare additional assessments for evaluation of postprandial and overall glucose regulation between the treatment groups. As this additional assessment was exploratory in nature, this subgroup was not strictly powered to demonstrate a statistical significant difference between treatment groups in any particular endpoint. In all, 50 subjects per treatment group was chosen as this number was considered enough to provide sufficient information for evaluation in this exploratory analysis, and as this was a similar number to what had been included in previous trials using CGM subgroups.

Randomisation

Subjects with HbA1c ≤ 9.5% (80 mmol/mol) who based on the investigators judgement had shown ability and willingness to adhere to the trial protocol were randomised (1:1:1) to receive mealtime faster aspart, post-meal faster aspart or mealtime NovoRapid, all in combination with insulin degludec. The randomisation was stratified by age group (1≤ age < 3 years, 3≤ age <6 years, 6≤ age <12 years and 12≤ age <18 years) based on subject's age at randomisation.

Blinding (masking)

Rationale for the method of treatment assignment and blinding

It was not considered feasible to blind the post-meal arm due to the high number of injections required to make a double-blind, double dummy trial and increased burden on the subjects; as such, a partly double-blind trial design was chosen.

The bolus treatment was double-blind for the mealtime faster aspart and NovoRapid treatment groups and open-label for the post-meal faster aspart treatment group. According to standard pharmacovigilance procedures, specific members of the Novo Nordisk A/S Global Safety department were not blinded to SUSARs (for reporting purpose), whereas the clinical study group and the investigator remained blinded throughout the trial.

The treatment code for a particular subject could be broken in a medical emergency if knowing the actual treatment would influence the treatment of the subject. If the code was broken, the subject was to discontinue trial product and a discontinuation of trial product session was to be completed in IV/WRS.

The blind was unintentionally broken for one subject in the mealtime faster aspart group.

A subgroup of subjects (150 in total), age ≥ 8 years old at screening (visit 1) had blinded CGM and a standardised meal test at 2 occasions during the trial.

Statistical methods

Analysis sets

- Full analysis set (FAS) includes all randomised subjects. In exceptional cases randomised subjects could have been excluded from the FAS. In such cases the reason for exclusion was to be justified and documented. Subjects in the FAS contributed to the evaluation 'as randomised'.
- Per protocol (PP) analysis set includes all subjects in the FAS that comply with inclusion and exclusion criteria. Subjects in the PP set contributed to the evaluation "as treated".

Primary endpoint

Change from baseline in HbA1c 26 weeks after randomisation.

Primary estimand

Treatment difference between faster aspart and NovoRapid, assessed by change from baseline in HbA1c 26 weeks after randomisation for all randomised subjects, regardless of treatment discontinuation or use of ancillary therapies. The primary estimand was assessed using the in-trial observation period, which included data collected after a subject discontinued trial product.

Secondary estimand

Treatment difference between faster aspart and NovoRapid, assessed by change from baseline in HbA1c 26 weeks after randomisation for all randomised subjects, if subjects continued on treatment until 26 weeks. The secondary estimand was assessed using the on-treatment observation period.

Efficacy endpoints except insulin dose were based on the in-trial observation period and repeated using the on-treatment observation period. Insulin dose and all safety endpoints were based on on-treatment observation period. The hierarchical testing procedure below was performed under the framework of the primary estimand.

Hierarchical testing procedure and analysis used for the primary endpoint

The primary objective was addressed using a non-inferiority approach to compare the change from baseline in HbA1c 26 weeks after randomisation between mealtime faster aspart and mealtime NovoRapid (non-inferiority limit 0.4%). If the primary objective was confirmed (step 1), type I error rate was controlled by using a hierarchical (fixed sequence) testing approach to address the secondary confirmatory objectives of non-inferiority of post-meal faster aspart vs mealtime NovoRapid (step 2), respectively superiority of mealtime faster aspart vs mealtime NovoRapid (step 3). Accordingly, rejection of the null hypothesis was confirmed only for steps where all previous null hypotheses had been rejected in favour of faster aspart.

Analysis was based on a statistical model using multiple imputations where the subjects without any available HbA1c measurements at scheduled visits had their HbA1c value imputed from the available information from the treatment the subject had been randomised to (resembling in essence a mixed model of repeated measurements analysis). Analyses were adjusted for region, strata (age), as factors, and baseline HbA1c as a covariate.

Key supportive secondary analyses

Change from baseline in 8-point self-measured plasma glucose (SMPG) profile endpoints: Change from baseline in mean PPG and PPG increment over all three meals were analysed using a model similar to the primary endpoint except with the corresponding baseline value as covariate.

Safety endpoints

A treatment-emergent adverse event was defined as an event that had an onset date on or after the first day of exposure to randomised treatment, and no later than seven days after the last day of randomised treatment.

A hypoglycaemic episode was defined as treatment-emergent if the onset of the episode occurred on or after the first day of IMP administration after randomisation and no later than one day after the last day on IMP. Hypoglycaemic episodes were defined as nocturnal if the time of the onset was between 23:00 and 07:00 both included. Severe or BG confirmed hypoglycaemia was defined as an episode that was severe according to the ISPAD criterion or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia. The number of treatment-emergent severe or BG confirmed hypoglycaemic episodes (all, daytime, nocturnal) were analysed using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode was considered treatment emergent as offset. The model included treatment, region and strata (age) as factors, and was based on the FAS. Where data allowed, separate analyses were performed for severe episodes.

Results

Participant flow

Run-in period

A total of 834 subjects entered the run-in period of the trial. Of those, 57 subjects were run-in failure. Thus, 777 subjects were later randomised to the treatment period. The most common reason for failure during the run-in period was 'failure to meet randomisation criteria' (31 subjects). During the run-in period subjects were treated with insulin degludec once daily and mealtime NovoRapid.

Randomisation and completion

In all, 777 subjects were assigned to the 3 treatment groups in a 1:1:1 ratio: mealtime faster aspart (260 subjects), post-meal faster aspart (259 subjects) and NovoRapid (258 subjects). All 777 randomised subjects were exposed to trial product (Table 3).

A total of 760 (97.8%) of the randomised subjects completed the trial period: 256 (98.5%) of the subjects in the mealtime faster aspart group, 251 (96.9%) of the subjects in the post-meal faster aspart group and 253 (98.1%) of the subjects in the NovoRapid group.

A similar proportion of subjects completed both the trial and treatment period in each treatment group (Table 3).

Table 3 Subject disposition

	Faster aspart (meal) N (%)	Faster aspart (post) N (%)	NovoRapid (meal) N (%)	Total N (%)
Screened				933
Screening failures				99
Run-in failures				57
Randomised	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
Exposed*	261	258	258	777
Prematurely discontinued randomised treatment	6 (2.3)	9 (3.5)	6 (2.3)	21 (2.7)
Adverse event	0	0	0	0
Hypoglycaemic episode	0	0	0	0
Protocol violation	0	0	0	0
Included in the trial in violation of criteria	0	0	0	0
Intention of becoming pregnant	0	0	0	0
Participation in another clinical trial throughout the trial	0	0	0	0
Other protocol violations	0	0	0	0
Decision of subject	0	3 (1.2)	3 (1.2)	6 (0.8)
Decision of parent/guardian	3 (1.2)	2 (0.8)	0	5 (0.6)
Pregnancy	0	0	0	0
Other	3 (1.2)	4 (1.5)	3 (1.2)	10 (1.3)
Withdrawn from trial	4 (1.5)	8 (3.1)	5 (1.9)	17 (2.2)
Adverse event	0	0	0	0
Lost to follow-up	0	0	0	0
Withdrawal by subject	0	1 (0.4)	4 (1.6)	5 (0.6)
Withdrawal by parent/guardian	4 (1.5)	4 (1.5)	1 (0.4)	9 (1.2)
Other	0	3 (1.2)	0	3 (0.4)
Completed treatment period	254 (97.7)	250 (96.5)	252 (97.7)	756 (97.3)
Completed trial period	256 (98.5)	251 (96.9)	253 (98.1)	760 (97.8)

%: Percentage of randomised subjects, *: Includes subjects 'as treated', N: Number of subjects
Treatment period: The period from visit 14 (Week 0) to visit 40 (Week 26) without premature discontinuation of randomised treatment.
Trial period: The period from visit 14 (Week 0) to visit 42 (Week 30).

Age groups

As a consequence of the small number of subjects below 3 years of age (n=4, two each in the faster aspart groups), only results for the age groups 1 to < 6 years, 6 to < 12 years and 12 to < 18 years are presented. In all, 46 subjects in the age group 1 to < 6 years, 301 subjects in the age group 6 to < 12 years and 430 subjects in the age group 12 to < 18 years were randomised and exposed to treatment (Table 4).

Table 4 Subject disposition – summary – by age groups

	Faster aspart (meal) N (%)	Faster aspart (post) N (%)	NovoRapid (meal) N (%)	Total N (%)
Children (1 - <6 years)				
Randomised	16 (100.0)	16 (100.0)	14 (100.0)	46 (100.0)
Exposed*	16	16	14	46
Prematurely discontinued randomised treatment	0	0	0	0
Withdrawn from trial	0	0	0	0
Completed treatment period	16 (100.0)	16 (100.0)	14 (100.0)	46 (100.0)
Completed trial period	16 (100.0)	16 (100.0)	14 (100.0)	46 (100.0)
Children (6 - <12 years)				
Randomised	100 (100.0)	100 (100.0)	101 (100.0)	301 (100.0)
Exposed*	101	99	101	301
Prematurely discontinued randomised treatment	0	3 (3.0)	2 (2.0)	5 (1.7)
Withdrawn from trial	0	3 (3.0)	1 (1.0)	4 (1.3)
Completed treatment period	100 (100.0)	97 (97.0)	99 (98.0)	296 (98.3)
Completed trial period	100 (100.0)	97 (97.0)	100 (99.0)	297 (98.7)
Adolescents (12 - <18 years)				
Randomised	144 (100.0)	143 (100.0)	143 (100.0)	430 (100.0)
Exposed*	144	143	143	430
Prematurely discontinued randomised treatment	6 (4.2)	6 (4.2)	4 (2.8)	16 (3.7)
Withdrawn from trial	4 (2.8)	5 (3.5)	4 (2.8)	13 (3.0)
Completed treatment period	138 (95.8)	137 (95.8)	139 (97.2)	414 (96.3)
Completed trial period	140 (97.2)	138 (96.5)	139 (97.2)	417 (97.0)

%: Percentage of randomised subjects, *: Includes subjects 'as treated', N: Number of subjects
Treatment period: The period from visit 14 (Week 0) to visit 40 (Week 26) without premature discontinuation of randomised treatment.
Trial period: The period from visit 14 (Week 0) to visit 42 (Week 30).
For non-randomised subjects age at screening is used instead of age at randomisation.

Premature discontinuation

A total of 21 (2.7%) subjects prematurely discontinued randomised treatment: 6 (2.3%) subjects in the mealtime faster aspart group, 9 (3.5%) subjects in the post-meal faster aspart group and 6 (2.3%) subjects in the NovoRapid group (Table 3).

The reasons for premature treatment discontinuation of trial product were 'decision of subject' (6 subjects), 'decision of parent/guardian' (5 subjects) and 'other' (10 subjects). No subjects prematurely discontinued treatment due to an AE, a hypoglycaemic episode, a protocol violation or due to pregnancy (Table 3).

The most common reason for prematurely discontinuation was due to reasons unrelated to treatment (mainly personal reasons).

Withdrawals

In total, 17 (2.2%) subjects withdrew from the trial at or after randomisation: 4 (1.5%) subjects in the mealtime faster aspart group, 8 (3.1%) subjects in the post-meal faster aspart group and 5 (1.9%) subjects in the NovoRapid group. No subjects withdrew from the trial due to an AE (Table 3).

The most frequent reason for withdrawal was 'withdrawal by parent/guardian' (in all 9 subjects): 4 (1.5%) subjects in the mealtime faster aspart group, 4 (1.5%) subjects in the post-meal faster aspart group and 1 (0.4%) subject in the NovoRapid group. An overview of the reasons for withdrawal is shown in Table 3.

Screen failures

A total of 933 subjects were screened, of which 99 subjects were screening failures (Table 3). The majority of subjects (82 subjects) failed during screening because they did not meet one of the inclusion

criteria, of which the most common was inclusion criterion 7 (HbA1c was outside the allowed range) (74 subjects).

Recruitment

The trial was conducted at 150 sites in 17 countries.

Initiation date: 04 May 2016

Primary completion date: 05 February 2018

Global completion/termination date: 03 March 2018

Conduct of the study

Protocol amendments

There were 4 amendments to the protocol.

Table 5 Amendments of the protocol

Amendment number	Issue date	Timing of change (before/after FPFV)	Countries affected	Key changes
1	16-Feb-2016	Before FPFV	Global	Added 'or equal to' in the definition of confirming of non-inferiority in trial protocol Section 17: General consideration.
2	30-Mar-2016	Before FPFV	Global	A mistake identified in the blood sampling volume at visit 14 and visit 40 for the subjects participating in the CGM and meal test subgroup. Consequently the required minimum weight for participation in the CGM and meal test subgroup was increased to ensure the blood volume collected at visit 14 and visit 40 did not exceed 1% of the subjects total blood volume.
3	29-Jul-2016	After FPFV	Serbia	Changes the inclusion criterion number 2 in order to include subjects from 2 years old and below 18 years old at the time of signing informed consent and below 18 years old at the time of randomisation.
4	13-Jan-2017	After FPFV	Global	An inaccuracy was identified in the layman language for reporting hypoglycaemic episodes. There was a need to clarify the run-in failure criteria, to provide more guidance on when to report a MESI, and that the FPG sample was to be collected using the FPG home sampling kit no matter if the FPG sample was taken at home or at site. The statistical section was updated to clarify the analyses made for the primary and secondary estimands, the supportive secondary CGM and meal test related efficacy endpoints. A clarification was made to which treatment emergent hypoglycaemic episodes should be included in the analyses. Appendix B was updated to reflect the changes that occurred due to the change in CGM supplier shortly before trial initiation.

Abbreviations: CGM = continuous glucose monitoring; FPFV = first patient first visit; FPG = fasting plasma glucose; MESI = medical event of special interest

Protocol deviations

Important protocol deviations at trial level

At trial level, 1 important PD belonging to the category "other" was reported. There were 4 deviations in the Appendix B (CGM and meal test) of the protocol version 2.0 which was discovered by monitors.

Important protocol deviations at trial site and subject level

There were 94 and 875 important PDs at site and subject level, respectively. The number of PDs related to informed consent was rather high (122). According to the MAH, the site personnel were retrained on the informed consent procedure and missing or incorrect informed consent forms were corrected.

None of the PDs were by the MAH considered to have an overall impact on the trial conduct, subject safety or data interpretation and neither of the PDs were considered to be in violation of the defined estimands.

Baseline data

Demographics and baseline characteristics

Overall, the 3 treatment groups were similar with respect to demographics and baseline characteristics (Table 6, Table 7).

At baseline (visit 14), the mean age of the subjects was 11.68 years (range: 2−17 years). The mean body weight was 46.48 kg (range: 12.3−103.4 kg) and the mean BMI was 19.66 kg/m^2 (range: 11.8−33.5 kg/m^2). Mean HbA1c at baseline was 7.56 % (59.13 mmol/mol) (range: 4.9−10.6 % (30.1−92.4 mmol/mol)). Please note, the HbA1c criterion for screening and randomisation (HbA1c ≤ 9.5 %), was based on HbA1c values measured at screening and visit 12. The mean HbA1c at visit 1 was 7.71 % (range: 5.1−9.5 %) and 7.59 % (range: 4.9−9.5 %) at visit 12. Mean FPG was 7.81 mmol/L (140.66 mg/dL) (range: 1.1−21.3 mmol/L (18.9−384.0 mg/dL)). The mean duration of diabetes was 4.38 years (range: 0.5−16.3 years).

In all, 464 of 777 subjects used flexible dosing (carbohydrate counting) at baseline with a similar number of subjects in each treatment group (152, 156 and 156 subjects in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups). Overall, 53.9% of the subjects were male. 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%).

Table 6 Demographics and baseline characteristics - summary - full analysis set

	Faster aspart (meal) N (%)	Faster aspart (post) N (%)	NovoRapid (meal) N (%)	Total N (%)
Number of subjects	260	259	258	777
Age group				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
1 - <6 years	16 (6.2)	16 (6.2)	14 (5.4)	46 (5.9)
6 - <12 years	100 (38.5)	100 (38.6)	101 (39.1)	301 (38.7)
12 - <18 years	144 (55.4)	143 (55.2)	143 (55.4)	430 (55.3)
BMI group				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
<25 kg/m^2	238 (91.5)	234 (90.3)	233 (90.3)	705 (90.7)
25-29.9 kg/m^2	17 (6.5)	23 (8.9)	22 (8.5)	62 (8.0)
30-34.9 kg/m^2	5 (1.9)	2 (0.8)	3 (1.2)	10 (1.3)
Sex				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
Female	126 (48.5)	122 (47.1)	110 (42.6)	358 (46.1)
Male	134 (51.5)	137 (52.9)	148 (57.4)	419 (53.9)
Country of residence				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
Bulgaria	15 (5.8)	15 (5.8)	18 (7.0)	48 (6.2)
Czech Republic	6 (2.3)	15 (5.8)	15 (5.8)	36 (4.6)
Estonia	8 (3.1)	5 (1.9)	4 (1.6)	17 (2.2)
Finland	5 (1.9)	4 (1.5)	4 (1.6)	13 (1.7)
Germany	8 (3.1)	8 (3.1)	2 (0.8)	18 (2.3)
India	22 (8.5)	18 (6.9)	19 (7.4)	59 (7.6)
Israel	11 (4.2)	9 (3.5)	11 (4.3)	31 (4.0)
Italy	9 (3.5)	10 (3.9)	10 (3.9)	29 (3.7)
Japan	24 (9.2)	19 (7.3)	23 (8.9)	66 (8.5)
Latvia	6 (2.3)	2 (0.8)	5 (1.9)	13 (1.7)
Lithuania	2 (0.8)	4 (1.5)	4 (1.6)	10 (1.3)
Poland	7 (2.7)	9 (3.5)	6 (2.3)	22 (2.8)
Serbia	5 (1.9)	9 (3.5)	6 (2.3)	20 (2.6)
Russia	32 (12.3)	35 (13.5)	37 (14.3)	104 (13.4)
Turkey	13 (5.0)	15 (5.8)	8 (3.1)	36 (4.6)
Ukraine	20 (7.7)	20 (7.7)	20 (7.8)	60 (7.7)
United States	67 (25.8)	62 (23.9)	66 (25.6)	195 (25.1)
Ethnicity				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
Hispanic or Latino	16 (6.2)	17 (6.6)	12 (4.7)	45 (5.8)
Not Hispanic or Latino	244 (93.8)	242 (93.4)	246 (95.3)	732 (94.2)
Race				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
White	206 (79.2)	217 (83.8)	209 (81.0)	632 (81.3)
Asian	46 (17.7)	37 (14.3)	43 (16.7)	126 (16.2)
Black or African American	6 (2.3)	4 (1.5)	5 (1.9)	15 (1.9)
American Indian or Alaska Native	0	1 (0.4)	1 (0.4)	2 (0.3)
Other	2 (0.8)	0	0	2 (0.3)
Age group (STRATA)				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
1 - <3 years	2 (0.8)	2 (0.8)	0	4 (0.5)
3 - <6 years	14 (5.4)	14 (5.4)	14 (5.4)	42 (5.4)
6 - <12 years	100 (38.5)	100 (38.6)	101 (39.1)	301 (38.7)
12 - <18 years	144 (55.4)	143 (55.2)	143 (55.4)	430 (55.3)

%: Percentage of subjects, BMI: Body mass index (kg/m^2), N: Number of subjects
Baseline is at randomisation (Visit 14 - Week 0).

Table 7 Baseline and diabetes characteristics - descriptive statistics - full analysis set

	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	Total
Number of subjects	260	259	258	777
Age (yrs)				
N	260	259	258	777
Mean (SD)	11.72 (3.74)	11.62 (3.65)	11.70 (3.44)	11.68 (3.61)
Median	12.00	12.00	12.00	12.00
Min ; Max	2.0 ; 17.0	2.0 ; 17.0	4.0 ; 17.0	2.0 ; 17.0
Height (m)				
N	260	259	258	777
Mean (SD)	1.50 (0.21)	1.50 (0.21)	1.50 (0.19)	1.50 (0.20)
Median	1.54	1.52	1.54	1.54
Min ; Max	0.9 ; 1.9	0.9 ; 1.9	1.0 ; 1.9	0.9 ; 1.9
Body weight (kg)				
N	260	259	258	777
Mean (SD)	46.74 (18.17)	46.43 (18.96)	46.28 (17.18)	46.48 (18.10)
Median	45.75	44.70	44.95	45.30
Min ; Max	12.3 ; 96.8	12.3 ; 103.4	15.0 ; 91.5	12.3 ; 103.4
Body weight (lb)				
N	260	259	258	777
Mean (SD)	103.03 (40.07)	102.36 (41.80)	102.04 (37.87)	102.48 (39.90)
Median	100.86	98.55	99.10	99.87
Min ; Max	27.1 ; 213.4	27.1 ; 228.0	33.1 ; 201.7	27.1 ; 228.0
BMI (kg/m^2)				
N	260	259	258	777
Mean (SD)	19.69 (3.75)	19.66 (4.02)	19.64 (3.78	19.66 (3.85)
Median	18.89	18.52	18.91	18.81
Min ; Max	11.8 ; 32.7	12.9 ; 33.5	12.9 ; 31.6	11.8 ; 33.5
Duration of diabetes (yrs)				
N	260	259	258	777
Mean (SD)	4.45 (3.50)	4.38 (3.15)	4.31 (3.14)	4.38 (3.26)
Median	3.29	3.78	3.44	3.45
Min ; Max	0.5 ; 15.0	0.5 ; 15.3	0.5 ; 16.3	0.5 ; 16.3
HbA1c (%)				
N	260	259	258	777
Mean (SD)	7.57 (0.80)	7.58 (0.84)	7.53 (0.83)	7.56 (0.82)
Median	7.55	7.60	7.45	7.50
Min ; Max	4.9 ; 10.0	5.6 ; 9.6	5.3 ; 10.6	4.9 ; 10.6
HbA1c (mmol/mol)				
N	260	259	258	777
Mean (SD)	59.26 (8.69)	59.38 (9.13)	58.76 (9.07)	59.13 (8.96)
Median	59.02	59.57	57.93	58.48
Min ; Max	30.1 ; 85.8	37.7 ; 81.4	34.4 ; 92.4	30.1 ; 92.4
FPG (mmol/L)				
N	186	198	180	564
Mean (SD)	7.58 (3.56)	8.03 (3.35)	7.79 (3.48)	7.81 (3.46)
Median	6.91	7.55	7.47	7.38
Min ; Max	1.9 ; 21.3	1.9 ; 19.1	1.1 ; 18.7	1.1 ; 21.3
FPG (mg/dL)				
N	186	198	180	564
Mean (SD)	136.67 (64.22)	144.61 (60.31)	140.43 (62.67	140.66 (62.35)
Median	124.52	135.96	134.52	132.99
Min ; Max	34.1 ; 384.0	35.0 ; 344.0	18.9 ; 337.0	18.9 ; 384.0

BMI: Body mass index (kg/m^2), FPG: Fasting plasma glucose, N: Number of subjects, SD: Standard deviation, yrs: Years

Anti-diabetic treatment at screening

The majority of randomised subjects received insulin glargine (50.2%) or insulin detemir (24.7%) as basal insulin at screening. The majority of subjects received insulin aspart (49.5%) or insulin lispro (28.2%) as bolus insulin at screening. There were no marked differences with regard to the anti-diabetic treatment at screening across the 3 treatment groups.

Diabetes complications before or at screening

Overall, 8.1% of the randomised subjects reported one or more diabetes complications. There were no marked differences with regard to the diabetic complications before or at screening across the 3 treatment groups.

Concomitant illness and medication

The most frequent concomitant illnesses, across treatment groups, were seen in the SOC 'skin and subcutaneous tissue disorders' (reported by 10.3% of the subjects; mainly related to 'lipodystrophy acquired' [2.1%] and 'lipohypertrophy' [1.9%]) and the SOC 'endocrine disorders' (reported by 8.5% of the subjects; mainly related to 'autoimmune thyroiditis' [4.1%] and 'hypothyroidism' [3.6%]). The proportion of subjects with concomitant illnesses was comparable across the 3 treatment groups.

At baseline, the most commonly reported concomitant medications used were drugs from the categories 'alimentary tract and metabolism' (8.0% of the subjects), 'systemic hormonal preparations, excluding sex hormones and insulins' (7.6% of the subjects) and 'respiratory system' (6.4% of the subjects). The proportion of subjects reporting concomitant medication at baseline was comparable across the 3 treatment groups.

Continuous glucose monitoring subgroup

In all, 135 subjects aged ≥ 8 years of age at screening (visit 1) used a blinded CGM. This subgroup had 2 standardised meal tests; one at baseline (visit 14) and another at the end-of-treatment (visit 40).

At baseline (visit 14), the mean age of the subjects was 12.58 years (range: 8−17 years). The mean body weight was 51.26 kg (range: 26.4−95.2 kg) and the mean BMI was 20.35 kg/m^2 (range: 14.3−30.8 kg/m^2). Mean HbA1c at baseline was 7.39 % (range: 5.4−9.4 %) and mean FPG was 6.89 mmol/L (124.12 mg/dL) (range: 1.1−14.9 mmol/L (18.9−269.0 mg/dL)). The mean duration of diabetes was 4.53 years (range: 0.5−14.0 years).

Overall, 57.8% of the subjects were male. The majority of the subjects were White (97.8%) and of non-Hispanic or non-Latino ethnicity (95.6%). The majority of subjects were from the US (38.5%), Ukraine (23.7%) and Bulgaria (15.6%).

The 3 treatment groups in the CGM subgroup were considered similar with respect to demographics and baseline characteristics.

Numbers analysed

Table 8 Analysis sets

	Faster aspart (meal) N (%)	Faster aspart (post) N (%)	NovoRapid (meal) N (%)	Total N (%)
Randomised	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
Completed treatment period	254 (97.7)	250 (96.5)	252 (97.7)	756 (97.3)
Completed trial period	256 (98.5)	251 (96.9)	253 (98.1)	760 (97.8)
Full analysis set	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
Per protocol analysis set*	261	258	258	777
Safety analysis set*	261	258	258	777

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

Outcomes and estimation

Efficacy results

Two estimands were defined in trial 4101 (see Statistical methods). The efficacy results in the following are structured around the framework of the primary estimand, focusing on the results for subjects in the trial, regardless of treatment adherence. Efficacy results related to the period where subjects were on treatment can be found in (Table 10). Results based on these 2 approaches were comparable due to the high completion rate and the small difference between number of subjects who discontinued treatment and who withdrew from trial.

Change in HbA1c (primary endpoint) - hierarchical testing

The results of the hierarchical testing procedure showed that mealtime faster aspart was non-inferior to mealtime NovoRapid, both in combination with insulin degludec, in terms of change from baseline to 26 weeks after randomisation in HbA1c (primary endpoint; Step 1). Non-inferiority of post-meal faster aspart versus mealtime NovoRapid, both in combination with insulin degludec, was confirmed in terms of change from baseline to 26 weeks after randomisation in HbA1c (Step 2). Superiority of mealtime faster aspart versus mealtime NovoRapid, both in combination with insulin degludec, was confirmed in terms of change from baseline to 26 weeks after randomisation in HbA1c (Step 3), see Table 9.

Table 9 Confirmatory statistical analyses 26 weeks after randomisation - in trial - all subjects (FAS)

Endpoint	Estimate [95% CI]	Conclusion
PRIMARY		
Step 1) Change from baseline in HbA_{1c} (%)		
Treatment difference at week 26		
Faster aspart (meal) - NovoRapid (meal)	-0.17 [-0.30; -0.03]	Non-inferiority confirmed with 1-sided p-value <0.001
CONFIRMATORY SECONDARY		
Step 2) Change from baseline in HbA_{1c} (%)		
Treatment difference at week 26		
Faster aspart (post) - NovoRapid (meal)	0.13 [-0.01; 0.26]	Non-inferiority confirmed with 1-sided p-value <0.001
Step 3) Change from baseline in HbA_{1c} (%)		
Treatment difference at week 26		
Faster aspart (meal) - NovoRapid (meal)	-0.17 [-0.30; -0.03]	Superiority confirmed with 1-sided p-value 0.007

NovoRapid® is known as NovoLog® in the US
CI: Confidence interval
*p-values are from the 1-sided test for non-inferiority and superiority respectively evaluated at the 2.5% level.

Table 10 Statistical analysis 26 weeks after randomisation addressing the secondary estimand– on-treatment (FAS)

	Estimate	95% CI		p-value*
Change from baseline in HbA1c (%), treatment difference at week 26				
Faster aspart (meal) - NovoRapid (meal)	-0.17	[-0.31;	-0.04]	0.012
Faster aspart (post) - NovoRapid (meal)	0.12	[-0.01;	0.26]	0.069

Abbreviations: CI: Confidence interval, N: Number of subjects
Note: *p-values are from the 2-sided test for treatment difference evaluated at the 5% level.

HbA1c over time

Run-in

During the run-in period, all subjects were treated with insulin degludec and NovoRapid. During the 14 weeks prior to randomisation (up to 2 weeks screening and 12-week run-in), the overall observed mean HbA1c changed from 7.71% to 7.56%. In subjects subsequently randomised to mealtime faster aspart the corresponding changes in HbA1c was from 7.76% to 7.57% (61.27 to 59.26 mmol/mol), from 7.71% to 7.58% (60.81 to 59.38 mmol/mol) in subjects subsequently randomised to post-meal faster aspart,

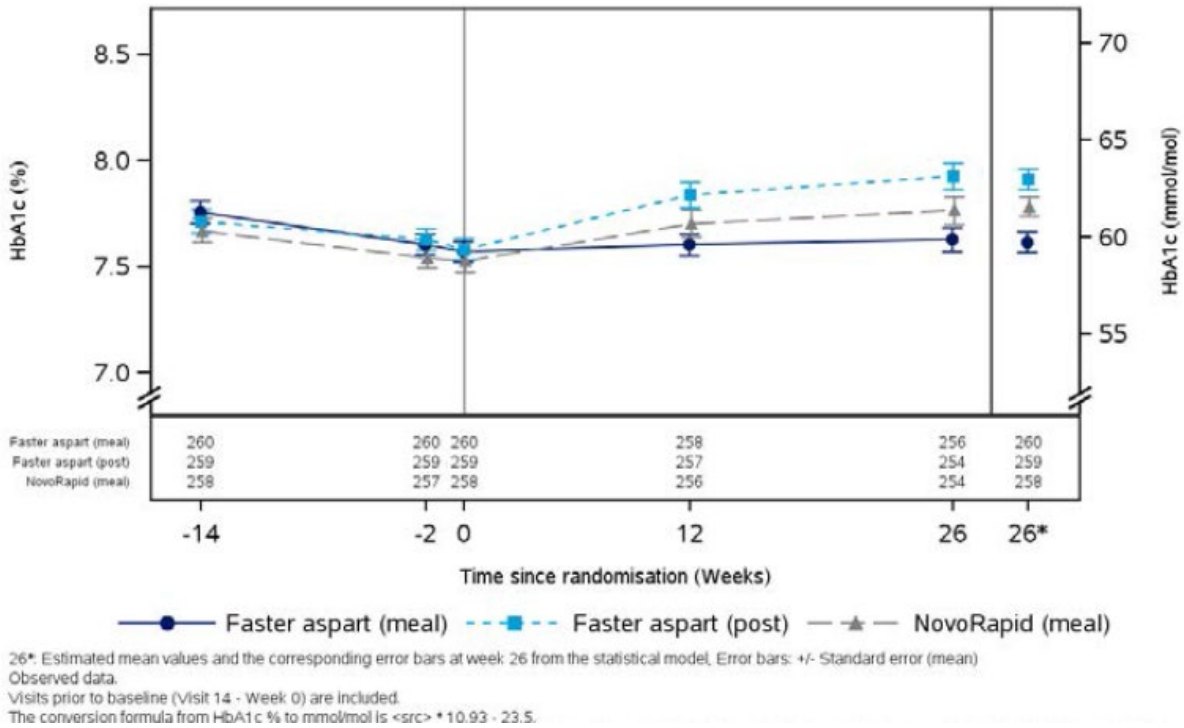
and from 7.67% to 7.53% (60.35 to 58.76 mmol/mol) in subjects subsequently randomised to mealtime NovoRapid (Figure 6).

Minor changes in the observed mean HbA1c was also seen during the 14 weeks prior to randomisation in all 3 age groups across treatment groups.

Week 26

After 26 weeks of treatment, the observed mean HbA1c (at "last in-trial visit") in the mealtime faster aspart group remained stable compared to baseline (from 7.57% at randomisation to 7.63% [59.88 mmol/mol]), whereas the observed mean HbA1c increased slightly in the post-meal faster aspart (from 7.58% to 7.91% [62.97 mmol/mol]) and NovoRapid (from 7.53% to 7.76% [61.30 mmol/mol]) groups compared to baseline (Figure 6).

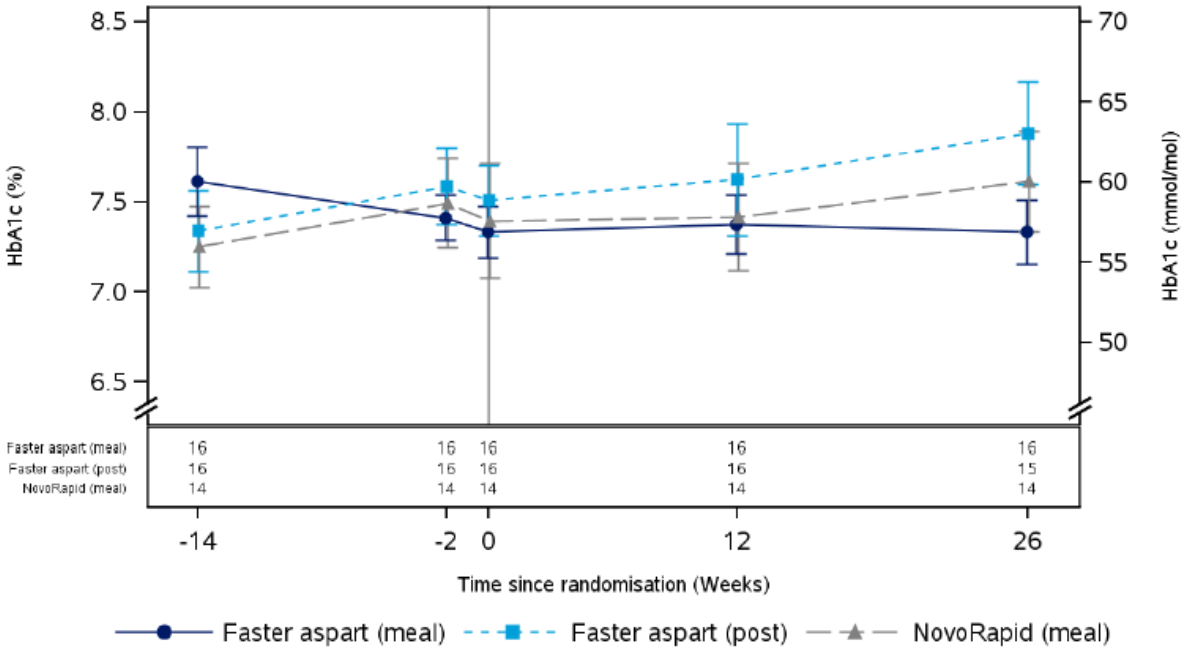
Figure 6 HbA1c by treatment week - observed mean and lsmean plot - in-trial (FAS)



26*: Estimated mean values and the corresponding error bars at week 26 from the statistical model. Error bars: +/- Standard error (mean)
Observed data.
Visits prior to baseline (Visit 14 - Week 0) are included.
The conversion formula from HbA1c % to mmol/mol is <src> * 10.93 - 23.5.

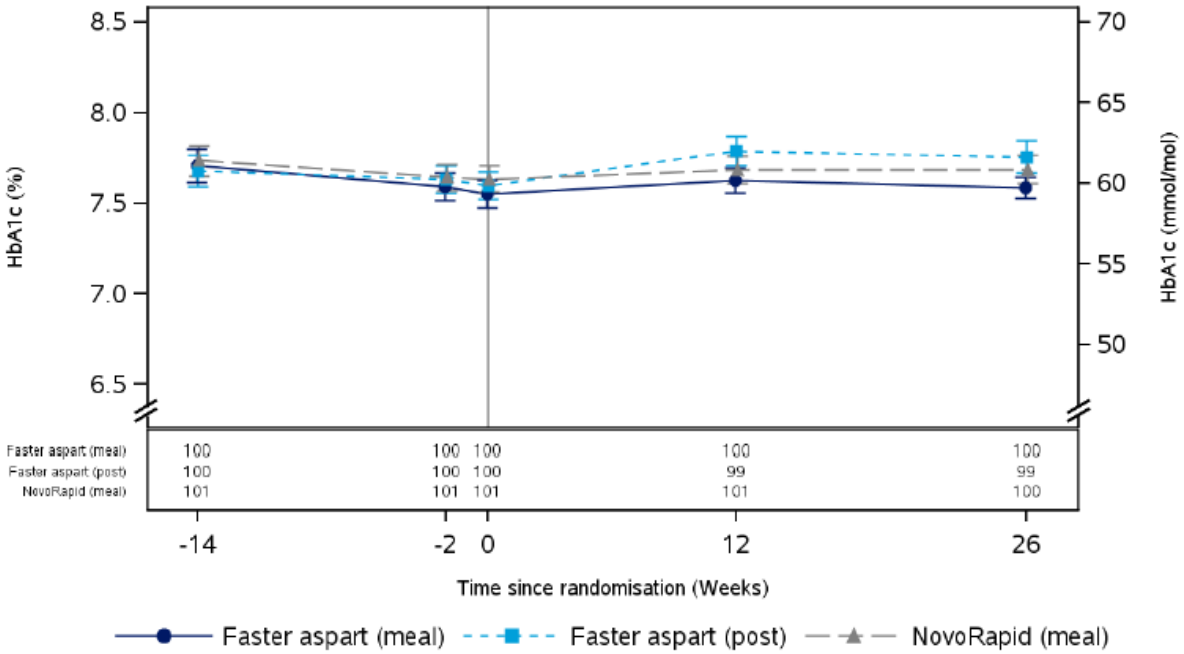
In the age group 6 to <12 years, all 3 treatment groups appeared stable in observed mean HbA1c from baseline to week 26 with no other differences between age groups observed (Figure 7, Figure 8 and Figure 9).

Figure 7 HbA1c by treatment week - mean plot - in-trial - children (1 - <6 years) - full analysis set



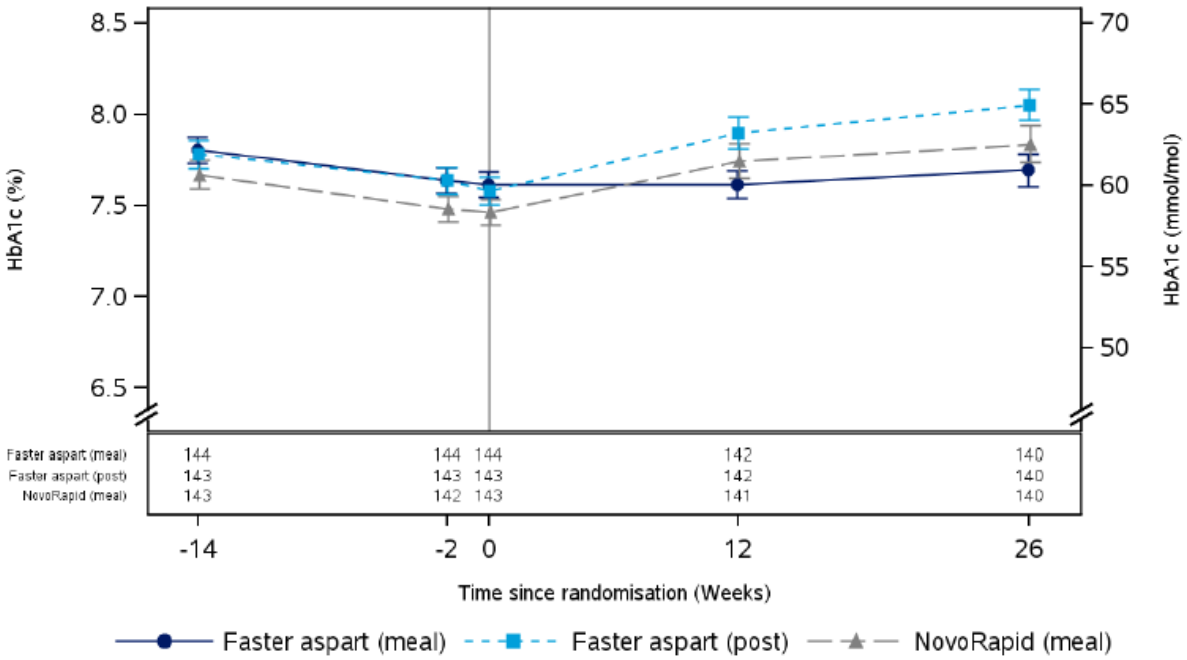
Error bars: +/- Standard error (mean)
Observed data.
Visits prior to baseline (Visit 14 - Week 0) are included.
The conversion formula from HbA1c % to mmol/mol is <src> * 10.93 - 23.5.

Figure 8 HbA1c by treatment week - mean plot - in-trial - children (6 - <12 years) - full analysis set



Error bars: +/- Standard error (mean)
Observed data.
Visits prior to baseline (Visit 14 - Week 0) are included.
The conversion formula from HbA1c % to mmol/mol is <src> * 10.93 - 23.5.

Figure 9 HbA1c by treatment week - mean plot - in-trial - adolescents (12 - <18 years) - full analysis set



Error bars: +/- Standard error (mean)
Observed data.
Visits prior to baseline (Visit 14 - Week 0) are included.
The conversion formula from HbA1c % to mmol/mol is <src> * 10.93 - 23.5.

The change from baseline to week 26 in HbA1c was estimated to 0.06 %-points (0.62 mmol/mol) with mealtime faster aspart, 0.35 %-points (3.84 mmol/mol) with post-meal faster aspart and 0.22 %-points (2.44 mmol/mol) with NovoRapid (Table 11 and Figure 6).

The estimated treatment difference 26 weeks after randomisation was -0.17 %-points (-1.82 mmol/mol) between mealtime faster aspart and NovoRapid and 0.13 %-points (1.40 mmol/mol) between post-meal faster aspart and NovoRapid (Table 11).

Table 11 HbA1c 26 weeks after randomisation

	FAS	N	Estimate	95% CI	p-value*
HbA1c (%)					
At week 26					
Faster aspart (meal)	260	260	7.62		
Faster aspart (post)	259	259	7.91		
NovoRapid (meal)	258	258	7.78		
Change from baseline at week 26					
Faster aspart (meal)	260	260	0.06		
Faster aspart (post)	259	259	0.35		
NovoRapid (meal)	258	258	0.22		
Treatment difference at week 26					
Faster aspart (meal) - NovoRapid (meal)			-0.17	[-0.30; -0.03]	0.014
Faster aspart (post) - NovoRapid (meal)			0.13	[-0.01; 0.26]	0.061
HbA1c (mmol/mol)					
At week 26					
Faster aspart (meal)	260	260	59.75		
Faster aspart (post)	259	259	62.97		
NovoRapid (meal)	258	258	61.57		
Change from baseline at week 26					
Faster aspart (meal)	260	260	0.62		
Faster aspart (post)	259	259	3.84		
NovoRapid (meal)	258	258	2.44		
Treatment difference at week 26					
Faster aspart (meal) - NovoRapid (meal)			-1.82	[-3.28; -0.36]	0.014
Faster aspart (post) - NovoRapid (meal)			1.40	[-0.06; 2.86]	0.061

CI: Confidence interval, N: Number of subjects
*p-values are from the 2-sided test for treatment difference evaluated at the 5% level. Change from baseline in HbA1c is analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model includes treatment, region and strata (age group) as factors, and baseline HbA1c as a covariate. Multiple imputation is used to sequentially impute missing values of change from baseline in HbA1c to week 12 and 26 for each treatment group separately with region and strata (age group) as factors, and baseline HbA1c and earlier changes from baseline in HbA1c as covariates. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

Sensitivity analysis

Sensitivity analyses were performed to assess the robustness of the primary analysis with regards to deviations from the model assumptions, by reducing the factors included (reduced model) and the assumption that missing data is missing at random (switch to inferior treatment, conditional switch to NovoRapid and unconditional switch to NovoRapid). The results of the sensitivity analyses supported the conclusions of the primary analysis.

Tipping point analysis

The robustness of the primary analysis addressing the primary estimand with regards to the MAR assumption was investigated using tipping point analyses. In the tipping point analysis, a multiple imputation model similar to the primary analysis was repeated with gradually increasing penalty added to imputed values at week 26 for subjects in the faster aspart arms until the non-inferiority hypotheses were rejected. The penalty value, also known as the tipping point, are the point at which the assumption about the treatment effect in subjects in the faster aspart groups with missing values at week 26 change the conclusion of faster aspart groups from being non-inferior to NovoRapid.

A tipping point analysis were also performed for step three in the hierachical testing procedure, superiority of meal time faster aspart compared to NovoRapid, where the penalty added to the imputed values in the faster aspart group causing the treatment effect to not be statistically significantly different is the tipping point.

With penalties reaching HbA1c values that were not clinically plausible, these analyses supported the conclusion of the primary analysis (Table 12).

Table 12 HbA1c 26 weeks after randomisation – statistical analysis – tipping point for non-inferiority and superiority – in-trial (FAS)

	HbA_{1c} (%) Penalty	ETD at week 26 Estimate	95% CI
Multiple imputation (tipping point when penalising subjects with an imputed value at week 26)			
Tipping point for non-inferiority			
Faster aspart (meal) - NovoRapid (meal)	19.04	0.13	[-0.14; 0.40]
Faster aspart (post) - NovoRapid (meal)	6.04	0.25	[0.09; 0.40]
Tipping point for superiority			
Faster aspart (meal) - NovoRapid (meal)	1.97	-0.14	[-0.27; 0.00]

Abbreviations: CI = confidence interval; ETD = estimated treatment difference.
Note: Change from baseline in HbA_{1c} is analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model includes treatment, region and strata (age group) as factors, and baseline HbA_{1c} as a covariate. Multiple imputation is used to sequentially impute missing values of change from baseline in HbA_{1c} to week 12 and 26 for each treatment group separately with region and strata (age group) as factors, and baseline HbA_{1c} and earlier changes from baseline in HbA_{1c} as covariates. For each subject in the faster aspart arm with an imputed value of change from baseline in HbA_{1c} at week 26, the penalty (meal and post, respectively) that changes the conclusion from non-inferiority to inferiority or superiority to non-superiority is added. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.

Percentage of subjects reaching HbA1c target

For all treatment groups, the total proportion of subjects achieving the HbA1c target (< 7.5%) was higher at baseline (44.6%, 43.6% and 50.0%) compared to after 26 weeks of treatment (Table 13). For mealtime faster aspart, the proportion of subjects achieving this target increased for age group 1 to <6 years, decreased for age group 6 to <12 years, and was stable for age group 12 to <18 years from baseline to after 26 weeks of treatment.

There was no statistically significant difference in the proportion of subjects achieving the HbA1c target 26 weeks after randomisation between mealtime faster aspart and NovoRapid (OR: 1.33 [0.87; 2.01]) or between post-meal faster aspart and NovoRapid (OR: 0.66 [0.43; 1.02]).

There was also no statistically significant difference between faster aspart and NovoRapid in the proportion of subjects achieving HbA1c targets without severe hypoglycaemic episodes 26 weeks after randomisation (OR: 1.37 [0.91; 2.08]95% CI and 0.68 [0.44; 1.04]95% CI).

Table 13 Subjects achieving HbA1c targets by treatment week - summary - on-treatment - full analysis set

	Faster aspart (meal) N (%)	Faster aspart (post) N (%)	NovoRapid (meal) N (%)	Total N (%)
Number of subjects	260	259	258	777
HbA1c <7.5%				
Visit 14 (Week 0)				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
Yes	116 (44.6)	113 (43.6)	129 (50.0)	358 (46.1)
No	144 (55.4)	146 (56.4)	129 (50.0)	419 (53.9)
Visit 26 (Week 12)				
N	255 (100.0)	257 (100.0)	255 (100.0)	767 (100.0)
Yes	105 (41.2)	94 (36.6)	106 (41.6)	305 (39.8)
No	150 (58.8)	163 (63.4)	149 (58.4)	462 (60.2)
Visit 40 (Week 26)				
N	258 (100.0)	258 (100.0)	256 (100.0)	772 (100.0)
Yes	109 (42.2)	80 (31.0)	101 (39.5)	290 (37.6)
No	149 (57.8)	178 (69.0)	155 (60.5)	482 (62.4)
HbA1c <7.5% without severe hypoglycaemic episodes				
Visit 40 (Week 26)				
N	258 (100.0)	258 (100.0)	256 (100.0)	772 (100.0)
Yes	108 (41.9)	78 (30.2)	98 (38.3)	284 (36.8)
No	150 (58.1)	180 (69.8)	158 (61.7)	488 (63.2)

%: Percentage of subjects, N: Number of subjects
Without severe hypoglycaemic episodes: Without treatment emergent severe hypoglycaemic episodes.

Supportive secondary efficacy endpoints

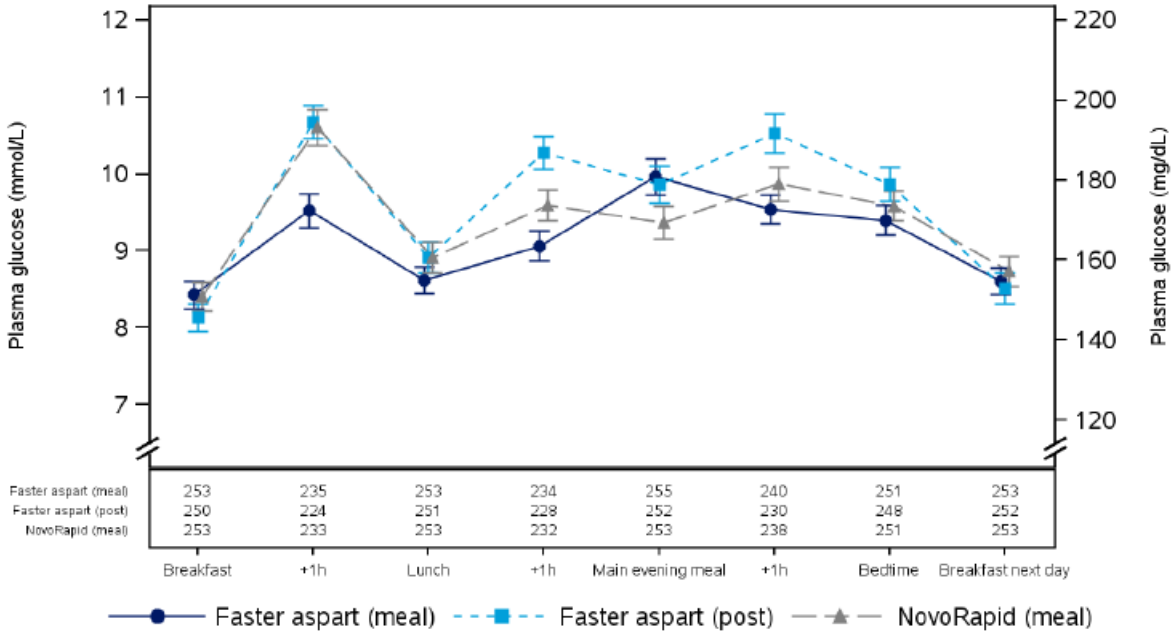
8-point self-measured plasma glucose profiles including postprandial glucose and postprandial glucose increment

Subjects measured the SMPG 8 times (8-point profiles) on 2 consecutive days (8-8-point profiles) prior to the visits at baseline (week 0), week 12 and week 26.

At baseline, the 8-point profiles for the 3 treatment groups appeared similar. At 26 weeks after randomisation, the observed mean SMPG was lower at 1 hour after breakfast, lunch and main evening meal with mealtime faster aspart compared to NovoRapid (Figure 10). With post-meal faster aspart, the observed mean SMPG was higher at 1 hour after lunch and main evening meal compared to NovoRapid at 26 weeks after randomisation.

No major differences were observed between age groups in the 8-point profiles.

Figure 10 8-point self-measured plasma glucose profile at week 26 – mean plot (FAS)



Error bars: +/- Standard error (mean)
The output is based on the mean of two 8-point profiles for each Subject.
Observed data.
The conversion factor from PG mmol/L to mg/dL is 18.02.

Postprandial glucose and postprandial glucose increment over all 3 meals and in individual meals (breakfast, lunch and main evening meal) from 8-point self-measured plasma glucose profile

At week 26, the observed mean 1-hour PPG and 1-hour PPG increment were lower for mealtime faster aspart compared to NovoRapid at all individual meals (breakfast, lunch and evening meal) and for "all meals", while the post-meal faster aspart group showed higher 1-hour PPGs and PPG increments compared to NovoRapid.

- 1-hour PPG mean over all meals was 9.26 mmol/L (166.82 mg/dL) for mealtime faster aspart, 10.50 mmol/L (189.23 mg/dL) for post-meal faster aspart, and 9.98 mmol/L (179.77 mg/dL) for NovoRapid.
- 1-hour PPG increment mean over all meals was 0.33 mmol/L (6.03 mg/dL) for mealtime faster aspart, 1.60 mmol/L (28.80 mg/dL) for post-meal faster aspart, and 1.14 mmol/L (20.52 mg/dL) for NovoRapid.

For mealtime faster aspart, a statistically significant difference in favour of mealtime faster aspart over NovoRapid was found for change from baseline to week 26 in 1-hour PPG after breakfast, lunch, and "all meals"(ETD: -0.70 mmol/L [-1.14; -0.27]95% CI; -12.69 mg/dL[-20.58; -4.80]95% CI), as well as for change from baseline to week 26 in 1-hour PPG increment after breakfast, main evening meal, and "all meals" (ETD: -0.93 mmol/L [-1.35; -0.52]95% CI; -16.79 mg/dL [-24.27; -9.30]95% CI).

For post-meal faster aspart, a statistically significant difference in favour of NovoRapid was found for change from baseline to week 26 in 1-hour PPG after lunch, main evening meal, and "all meals" (ETD: 0.67 mmol/L [0.23; 1.12]95% CI; 12.12 mg/dL [4.13; 20.12]95% CI), as well as for change from baseline to week 26 in 1-hour PPG increment after "all meals" (ETD: 0.43 mmol/L [0.02; 0.85]95% CI; 7.84 mg/dL [0.29; 15.38]95% CI).

Fluctuation in the 8-point profile

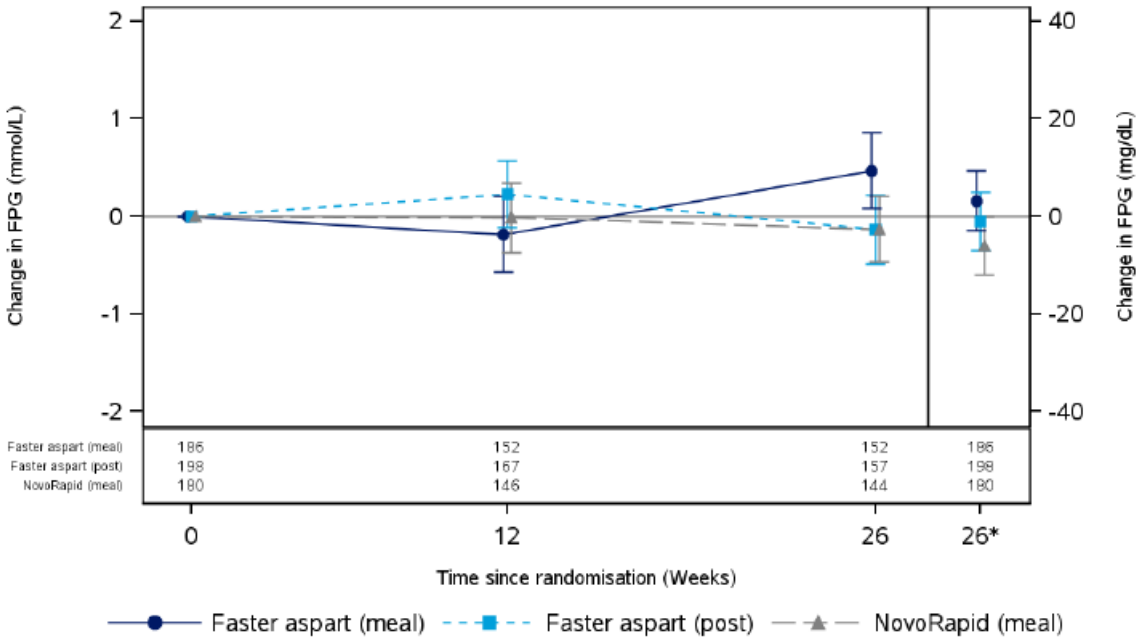
At week 26, there were no statistically significant differences in the fluctuation in the 8-point profile (SMPG) for mealtime faster aspart versus NovoRapid or for post-meal faster aspart versus NovoRapid.

Fasting plasma glucose

The mean FPG was fairly stable between baseline and week 26 for all 3 treatment groups. At baseline, the observed mean FPG was 7.58 mmol/L (136.67 mg/dL) with mealtime faster aspart, 8.03 mmol/L (144.61 mg/dL) with post-meal faster aspart and 7.79 mmol/L (140.43 mg/dL) with NovoRapid. At week 26, the observed mean FPG was 7.80 mmol/L (140.60 mg/dL) with mealtime faster aspart, 7.93 mmol/L (142.85 mg/dL) with "post-meal faster aspart" and 7.88 mmol/L (142.03 mg/dL) with NovoRapid (Figure 11). There was no statistically significant difference between mealtime faster aspart and NovoRapid or post-meal faster aspart and NovoRapid in the change from baseline to week 26 in FPG.

No major differences between age groups in estimated change from baseline in FPG 26 weeks after randomisation was observed (data not shown in the AR)

Figure 11 Fasting plasma glucose by treatment week - change from baseline – observed mean and LS-mean plot



26*: Estimated mean values and the corresponding error bars at week 26 from the statistical model, Change: Change from baseline, Error bars: +/- Standard error (mean), FPG: Fasting plasma glucose
Observed data.
The conversion factor from FPG mmol/L to mg/dL is 18.02.

1,5-anhydroglucitol

From baseline to week 26, the observed mean 1,5-anhydroglucitol was stable for mealtime faster aspart (from 4.95 to 4.89 µg/mL) and decreased for post-meal faster aspart (from 5,07 to 4.25 µg/mL) and NovoRapid (from 5.13 to 4.50 µg/mL).

The estimated change from baseline to week 26 in 1,5-anhydroglucitol was -0.07, -0.89, and -0.60 µg/mL for mealtime faster aspart, post-meal faster aspart and NovoRapid, respectively. The change from baseline to week 26 in 1.5-anhydroglucitol with mealtime faster aspart was statistically significantly different from that with NovoRapid (ETD: 0.52 µg/mL [0.09; 0.95]95% CI), whereas no statistically significant difference was found for the decrease from baseline to week 26 with post-meal faster aspart and NovoRapid (ETD: -0.29 µg/mL [-0.73; 0.14]95% CI).

Insulin dose

At week 26, subjects in the three treatment groups were treated with similar doses (U/kg) of daily bolus, daily basal, and total daily insulin doses:

- The mean daily bolus insulin dose at week 26 was 23.3 U (0.48 U/kg) for mealtime faster aspart, 23.5 U (0.49 U/kg) for post-meal faster as part and 22.5 U (0.47 U/kg) for NovoRapid. 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 U (0.43 U/kg) for mealtime faster aspart, 21.5 U (0.43 U/kg) for post-meal faster as part and 20.7 U (0.41 U/kg) for NovoRapid.
- The mean daily total insulin dose at week 26 was 44.8 U (0.92 U/kg) for mealtime faster aspart, 45.0 U (0.92 U/kg) for post-meal faster as part and 43.2 U (0.88 U/kg) for NovoRapid.

At week 26, the mean basal: bolus split ratio was similar between treatment groups (47: 53 for mealtime faster aspart, 47: 53 for post-meal faster aspart and 46: 54 for NovoRapid).

- Continuous glucose monitoring and meal test subgroup

High, low or at target interstitial glucose based on continuous glucose monitoring for 11 to 13 days

Percentage of time spent within IG target range 4.0−10.0 mmol/L (71−180 mg/dL) at week 26 was 53% with mealtime faster aspart, 53% with post-meal faster aspart, and 51% with NovoRapid.

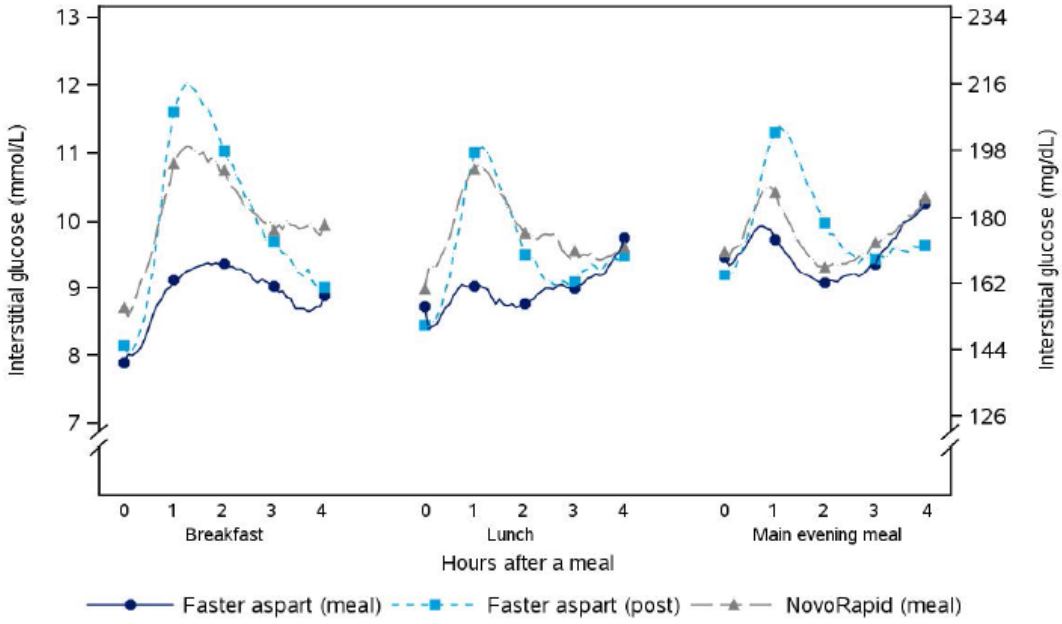
There were no observed differences in incidence of episodes or percentage of time spend with low IG (IG ≤2.5, 3.0, 3.9 mmol/l [45, 54, 70 mg/dL]) and high IG (IG >10.0, 12.0, 13.9 mmol/l [180, 216, 250 mg/dL]) between the 3 treatment groups at week 26, or in change from baseline to week 26 in mean of the IG profile or variation in the IG profile.

Time spend in low IG (IG ≤ 3.9 mmol/L [70 mg/dL]) was reduced from baseline to week 26 with no statistically significant difference between mealtime faster aspart and NovoRapid or post-meal faster aspart and NovoRapid.

Interstitial glucose after a meal based on continuous glucose monitoring for 11 to 13 days

Observed mean IG increment (0−1 hours after start of the meal) and (0−2 hours after start of the meal) was lower with mealtime faster aspart compared to NovoRapid at all individual meals (breakfast, lunch and evening meal) and for "all meals", while the post-meal faster aspart group showed higher increments compared to NovoRapid at week 26.

Figure 12 Prandial interstitial glucose profile at week 26 - mean plot (FAS)

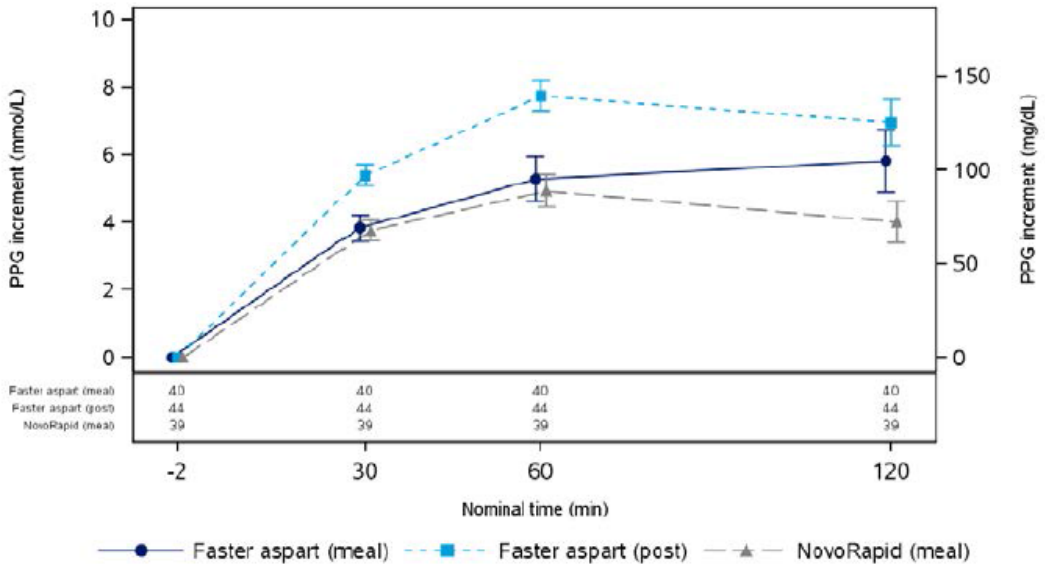


Observed data.
The conversion factor from Interstitial glucose mmol/L to mg/dL is 18.02.

Postprandial glucose and postprandial glucose increment (meal-test)

At week 26, the observed mean PPG profiles were similar for mealtime faster aspart and NovoRapid, whereas the post-meal faster aspart profile was higher at all time points (30-min, 60-min and 120-min) when compared with NovoRapid. A similar profile was seen for the mean PPG increment (Figure 13).

Figure 13 Postprandial glucose increments (meal test) at week 26 - mean plot - in-trial (FAS)



Error bars: +/- Standard error (mean), PPG: Postprandial glucose
Observed data, except for cases where glucose or glucagon is administered. If glucose or glucagon is administered then the last measurement before rescue intervention is carried forward.
The conversion factor from PG mmol/L to mg/dL is 18.02.

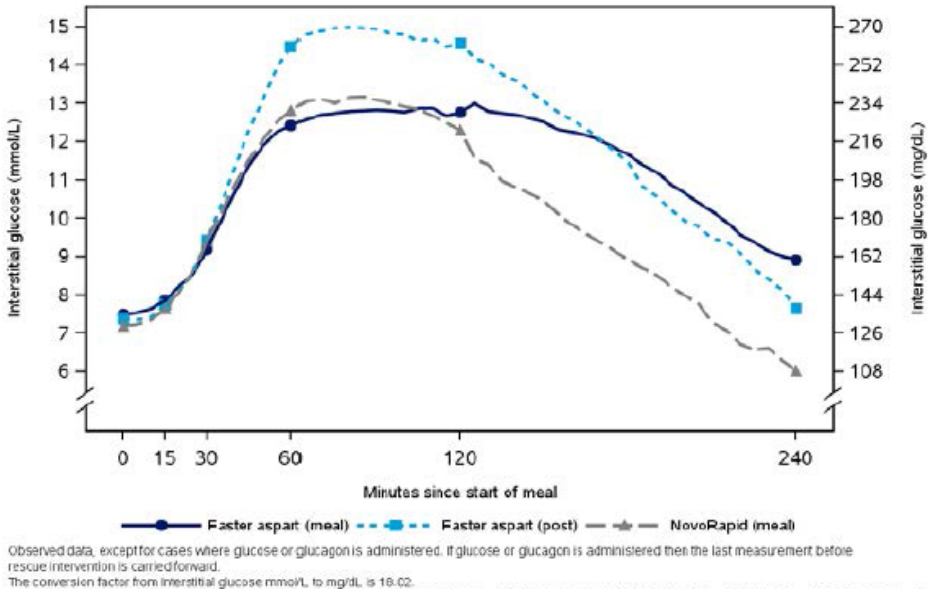
There was no statistically significant difference between mealtime faster aspart and NovoRapid in change from baseline to week 26 in 30-min, 1-hour (60-min) or 2- hour (120-min) PPG or PPG increment (meal test).

For post-meal faster aspart, there was a statistically significant difference in favour of NovoRapid at all 3 time points for both PPG and PPG increment (meal test).

Interstitial glucose during a meal-test based on continuous glucose monitoring

There were no statistically significant differences between mealtime faster aspart and NovoRapid in change from baseline to week 26 in in $AUC_{IG,0-2h}$, $AUC_{IG,0-4h}$, $AUC_{IG,0-15min}$, $AUC_{IG,0-30min}$, $AUC_{IG,0-1h}$ and corresponding increments. For post-meal faster aspart, there were statistically significant differences in favour of NovoRapid for change from baseline to week 26 in $AUC_{IG,0-2h}$ and $AUC_{IG,0-4h}$, whereas $AUC_{IG,0-15min}$, $AUC_{IG,0-30min}$, $AUC_{IG,0-1h}$ and corresponding increments were not statistically significantly different (Figure 14).

Figure 14 Prandial interstitial glucose profile at week 26 - mean plot (FAS)



For mealtime faster aspart, the decrease in the time to IG peak from baseline to week 26 observed for NovoRapid, was statistically significantly different in favour of NovoRapid, whereas no difference was seen between post-meal faster aspart and NovoRapid.

There was no statistically significant difference in the decrease in the IG peak from baseline to week 26 between mealtime faster aspart and NovoRapid. For post-meal faster aspart, the IG peak increased from baseline to week 26, and the difference was statistically significant in favour of NovoRapid.

Ancillary analyses

N/A

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14 Summary of Efficacy for trial

Title: Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes			
Study identifier	NN1218-4101, EudraCT number 2014-002568-33		
Design	This was a 26-week, randomised, partly double-blind, multicentre, multinational, active controlled, treat-to-target, 3-armed parallel-group trial with a 12-week run-in period. The trial compared effect and safety of mealtime faster aspart versus mealtime NovoRapid, 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 trial also included a 26-week open-label postmeal faster aspart dosing group in combination with insulin degludec.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks 12 weeks not applicable
Hypothesis	Non-inferiority/Superiority		
Treatments groups	Mealtime faster aspart		Bolus mealtime faster aspart/Basal insulin degludec. 260 patients randomized
	Post-meal faster aspart		Bolus post-meal faster aspart/Basal insulin degludec. 259 patients randomized
	Mealtime NovoRapid		Bolus mealtime NovoRapid/Basal insulin degludec. 258 patients randomized
Endpoints and definitions	Primary endpoint/ Confirmatory secondary	HbA1c (%/ mmol/mol)	Change from baseline in HbA1c 26 weeks after randomisation.
	Secondary endpoint	1-hour PPG (mmol/L)	Postprandial glucose (PPG) based on SMPG, mean over all 3 meals and in individual meals (breakfast, lunch and main evening meal)
	Secondary endpoint	1-hour PPG increment (mmol/L)	PPG increment based on SMPG, mean over all 3 meals and in individual meals (breakfast, lunch and main evening meal)
Database lock	06 April 2018		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The Full analysis set (FAS) included all randomised subjects. Subjects in the FAS contributed to the evaluation 'as randomised'. The Per protocol (PP) analysis set included all subjects in the FAS that complied with inclusion and exclusion criteria. Subjects in the PP set contributed to the evaluation "as treated". Primary analysis time point: 26 weeks after randomisation.			
Descriptive statistics and estimate variability	Treatment group	Mealtime faster aspart	Post-meal faster aspart	Mealtime NovoRapid
	Number of subjects	260	259	258
	HbA1c (mean; %/mmol/mol)	0.05 / 0.62	0.35 / 3.78	0.23 / 2.49
	SD	0.80 / 8.76	0.83 / 9.05	0.82 / 9.01
	1-hour PPG (mean)	9.26	10.50	9.98
	SD	2.11	2.66	2.58
	1-hour PPG increment (mean)	0.33	1.60	1.14

	SD	2.05	2.25	2.32
Effect estimate per comparison	Primary endpoint (Non-inferiority) Change in HbA1c	Comparison groups	Mealtime faster aspart vs NovoRapid	
		Estimated treatment difference (%-points)	-0.17	
		95% CI	-0.30; -0.03	
		P-value	<0.001	
	Confirmatory secondary endpoint (Non-inferiority) Change in HbA1c	Comparison groups	Post-meal faster aspart vs NovoRapid	
		Estimated treatment difference (%-points)	0.13	
		95% CI	-0.01; 0.26	
		P-value	<0.001	
	Confirmatory secondary endpoint (Superiority) Change in HbA1c	Comparison groups	Mealtime faster aspart vs NovoRapid	
		Estimated treatment difference (%-points)	-0.17	
		95% CI	-0.30; -0.03	
		P-value	<0.001	
	Secondary endpoint 1-hour PPG (all meals)	Comparison groups	Mealtime faster aspart vs NovoRapid	
		Estimated treatment difference (mmol/L)	-0.70	
		95% CI	-1.14; -0.27	
		P-value	0.002	
	Secondary endpoint 1-hour PPG (all meals)	Comparison groups	Post-meal faster aspart vs NovoRapid	
		Estimated treatment difference (mmol/L)	0.67	
		95% CI	0.23; 1.12	
		P-value	0.003	
	Secondary endpoint 1-hour PPG increment (all meals)	Comparison groups	Mealtime faster aspart vs NovoRapid	
		Estimated treatment difference (mmol/L)	-0.93	
		95% CI	-1.35; -0.52	
		P-value	<0.001	
	Secondary endpoint 1-hour PPG increment (all meals)	Comparison groups	Post-meal faster aspart vs NovoRapid	
		Estimated treatment difference (mmol/L)	0.43	
		95% CI	0.02; 0.85	
		P-value	0.042	
Notes	Two estimands were used in this trial for the primary endpoint; the primary estimand addressed the effect of trial drug irrespective of whether randomised subjects were treated as directed or not. The secondary estimand addressed the effect of trial drug had all randomised subjects taken the treatment as directed. Results based on these two approaches were comparable due a high completion rate and a small difference between number of subjects who discontinued treatment and who withdrew from trial.			

Analysis description	**Analysis of the primary endpoint addressing the secondary estimand– on-treatment (FAS)** Change from baseline in HbA1c (%) week 26, estimated treatment difference (%-points); Faster aspart (meal) vs NovoRapid (meal) -0.17 (95% CI: -0.31; -0.04); p-value 0.012 Faster aspart (post) vs NovoRapid (meal) 0.12 (95% CI: -0.01; 0.26); p-value 0.069

2.4.2. Discussion on clinical efficacy

Assessment of paediatric data on clinical efficacy

The aim of the current submission is to provide data in support of a paediatric indication for faster aspart (Fiasp).

Design and conduct of clinical studies

Study 4101 data is a 26-week, randomised, partly double-blind, multicentre, multinational, active controlled, treat-to-target, 3-armed parallel-group trial with a 12-week run-in period, conducted to support the use of Fiasp for the treatment of children aged 1 year and above with diabetes mellitus. The trial compared effect and safety of mealtime faster aspart versus mealtime NovoRapid, 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 overall study design is in line with the Scientific advice given by the CHMP in 2013, with the exception that the basal insulin has been changed from insulin detemir to insulin degludec which was approved after the SA was given. The choice of basal insulin is acceptable as insulin degludec is approved in children from the age of 1 year. All insulins were administered according to label. Fiasp was administered according to the recommendations approved for the adult population. Titration algorithms were in place.

The trial also included a 26-week open-label post-meal faster aspart dosing group in combination with insulin degludec. Furthermore, a subgroup of children aged > 8 years took part in a CGM substudy investigating the effects of Fiasp and NovoRapid in relation to a standardised meal test. This is also in line with the SA (EMEA/H/SA/2136/1/FU/1/2013/III) as extrapolation from the data on post-meal dosing and effects on PPG after a standardised meal test in adults was not accepted by the CHMP.

The study design is considered adequate and the study duration, including the run-in period, is considered sufficient to evaluate the effect of Fiasp in comparison with NovoRapid in children aged 1 to 18 years of age.

Statistical methods are generally acceptable. The non-inferiority margin applied is not entirely endorsed as 0.4% is generally considered too wide, it may however be accepted for planning purposes. For control of the family-wise type I error rate a hierarchical (fixed sequence) testing procedure with three steps was used including in step 1) non-inferiority of meal-time fast-acting insulin aspart versus meal-time NovoRapid, in step 2) non-inferiority of post-meal fast-acting insulin aspart versus meal-time NovoRapid and in step 3) superiority of meal-time fast-acting insulin aspart versus meal-time NovoRapid. Rejection of a null hypothesis was only to be confirmed for analyses where all previous null hypotheses had been rejected in favour of fast-acting insulin aspart. This multiplicity approach is acceptable.

A primary and a secondary estimand was defined. The primary estimand used for confirmatory analyses was defined according to a "treatment-policy" strategy ignoring intercurrents events (treatment discontinuation and ancillary treatments). This can be criticized in the non-inferiority setting in that responses in both treatment groups will appear more similar following discontinuation of randomised treatment or use of another medication. A secondary estimand was defined according to a "hypothetical"-

strategy aiming at estimating treatment response week 26 if all subjects adhered. For a conclusion of superiority, the primary estimand is acceptable; considering that two of three primary hypotheses aimed at non-inferiority both estimands are of interest.

Overall, and having an impact on the analyses addressing the primary and secondary estimands, the majority of subjects, irrespective of randomised treatment arm, completed the 26-week treatment period; 254/260 (97.7%) of subjects on fast-acting insulin aspart (meal), 250/259 (96.5%) of subjects on fast-acting insulin aspart (post) and 252/258 (97.7%) of subjects on NovoRapid (meal).

Four amendments were made to the protocol. Two of the 4 protocol amendments were implemented after the first subject first visit. None of the changes is considered to have had any impact on the trial data. There was a rather high number of protocol deviations related to "informed consent". This was identified by the MAH and site personnel were retrained on the procedures, thus this issue was adequately handled.

Efficacy data and additional analyses

In total 777 subjects were included in the study. Recruitment in the lowest age group (1 to 3 years) was low and no children below the age of 2 years were included in the study. Only four children aged 2-3 years were included, all in the two faster aspart groups (2 in each groups).

Otherwise the recruitment targets were met. A high proportion of subjects completed the trial (98%), with no major imbalances between treatment groups. Premature discontinuations were few and evenly distributed between groups. No subjects discontinued due to AEs.

The demographic and baseline characteristics were balanced between groups. European subjects were adequately represented. A comparable exposure was observed for all treatment groups, with no apparent difference when analysed by age group.

HbA1c decreased slightly in the overall population and in all the three age groups during the 14 weeks run-in phase. During the randomised treatment period of the study, HbA1c remained stable in the Fiasp mealtime group, whereas HbA1c slightly increased in the post-meal group and in the NovoRapid group. The increase observed is in line with the outcome of previous paediatric studies.

When presented by age groups, it is observed that HbA1c remained stable in all treatment groups in the age group 6 to <12 years. The change in HbA1c observed in the overall population was driven by the changes in HbA1c observed in the two other age groups, i.e. children (1 - <6 years) and adolescents (12 - <18 years) respectively.

The study met its primary objective as both mealtime and post-meal Fiasp was found to be non-inferior to NovoRapid (ETD -0.17 [-0.30; -0.03]95%CI and 0.13 [-0.01; 0.26]95%CI for mealtime and post-meal dosing, respectively). In both analyses the upper limit of the 95%CI was below 0.3% which is considered an acceptable non-inferiority margin. Mealtime Fiasp was also shown to be superior to NovoRapid with regards to change from baseline in HbA1c 26 weeks after randomisation (ETD: -0.17 % [-0.30; -0.03]95% CI). The clinical relevance of this difference may be debated but considering that the mean HbA1c at baseline was rather low (7.56%) large improvements in HbA1c may be difficult to achieve. The responder rates decreased in all treatment groups over the treatment period, as expected since HbA1c increased during the treatment period. The outcome compares well with the data in adults presented in the Fiasp MAA, where both mealtime faster aspart and post-meal faster aspart was compared with mealtime NovoRapid (EPAR for Fiasp; Trial 3852).

FPG remained rather stable during the study in all treatment groups. No statistically significant differences were observed.

The 8-point SMBG profiles at week 26 differed somewhat between treatment groups. The observed mean 1-hour PPG and 1-hour PPG increment were lower for mealtime faster aspart compared to NovoRapid at all individual meals (breakfast, lunch and evening meal) and for "all meals", while the post-meal faster aspart group showed higher 1-hour PPGs and PPG increments compared to NovoRapid.

For mealtime faster aspart, a statistically significant difference in favour of mealtime faster aspart over NovoRapid was found for change from baseline to week 26 in 1-hour PPG after breakfast, lunch, and "all meals", but not for the main evening meal. The change from baseline to week 26 in 1-hour PPG increment was statistically significantly in favour of mealtime faster aspart after breakfast, main evening meal, and "all meals" but no for the lunch meal.

For post-meal faster aspart, a statistically significant difference in favour of NovoRapid was found for change from baseline to week 26 in 1-hour PPG after lunch, main evening meal, and "all meals", as well as for change from baseline to week 26 in 1-hour PPG increment after "all meals".

The data from the CGM subgroup largely confirms the data from the 8-point SMBG profiles.

The data from the meal test show that mealtime faster aspart was comparable to NovoRapid up to 1 hour after the meal after which the increment was actually higher with faster aspart. None of the differences observed in the meal test were statistically significant. Post-meal faster aspart showed less prandial glucose control at all time points. The prandial IG data confirms the data on PPG and PPG increment data.

There were no apparent differences in either daily mean bolus, basal or total insulin dose between treatment groups at week 26.

2.4.3. Conclusions on the clinical efficacy

The clinical data provided show that Fiasp is superior to NovoRapid when administered before the meal and non-inferior to NovoRapid when administered after the meal. The findings were consistent across age groups. Very few subjects below the age of 3 were included in the trial, but there is no concern that the efficacy would differ in children in this age group compared to older children, therefore the use of Fiasp from the age of 1 year is acceptable from an efficacy point of view.

2.5. Clinical safety

Introduction

Faster Insulin Aspart was approved for treatment of diabetes mellitus in adults, in the EU in January 2017. The active insulin component of FIASP, Insulin Aspart, has been on the market as NovoRapid worldwide for more 15 years for the treatment of diabetes mellitus and is approved for the treatment of diabetes mellitus in adults, adolescents and children aged 1 years (since 2016) and above. The safety profile is well known, with the major safety issue being hypoglycaemia. Medication errors, immunogenicity and lipodystrophy are also events of special interest.

To support the safety of an extension of the indication of faster aspart for use in children and adolescents, clinical safety results from trial NN1218-4101 was submitted. See section 2.4.1. Additionally, a pharmacology trial (4371) comparing the pharmacokinetic properties of Fiasp between children, adolescents and adults with T1DM and post marketing information from spontaneous reports of paediatric use post-marketing contribute with supportive safety data.

Patient exposure

In trial NN1218-4101, a total of 777 subjects were assigned to the 3 treatment groups (mealtime faster aspart, postmeal faster aspart and mealtime NovoRapid) in a 1:1:1 ratio. All 777 randomised subjects were exposed to trial product; 261 subjects to mealtime faster aspart, 258 subjects to postmeal faster aspart and 258 subjects to NovoRapid (Table 15). The trial population included the intended paediatric T1DM population to be treated with faster aspart with 32 children treated with faster aspart in the age group 1 to <6 years, 200 subjects in the age group 6 to <12 years and 287 subjects in the age group 12 to <18 years (Table 16).

The total exposure was 128.4 PYE for the mealtime faster aspart group and 127.7 PYE for both the post-meal faster aspart and NovoRapid groups (Table 15). Thus, there were no overall differences across the 3 treatment groups with regard to extent of exposure in PYE. There was neither any differences with regard to extent of exposure within each age group between the 3 treatment groups (

Table 17). However, the total exposure in PYE, of the respective treatment was notable lower in the 1-to < 6 years group (8 PYE), compared to the 6 to < 12 years (approx. 50 PYE) and 12 to < 18 years age groups (approx. 70 PYEs). See Table 17.

Thus, exposure in the youngest age group (1 -< 6 years) were lower compared to the other groups due to fewer subjects in this group.

The vast majority of subjects in all 3 treatment groups were exposed to trial products for ≥25 weeks. In total, 45.7% were exposed to trial products 25-26 weeks and 51.9% were exposed > 27 weeks.

Overall, the extent of exposure is considered acceptable for ages above 3 years. However, there was only four subjects treated with faster aspart in the ages below 3 years and at baseline the lowest age was 2 years (Table 16 and Table 7). Thus, no safety data is available for subjects between 1 and 2 years and very limited safety data in the ages between 2 and 3 years. Besides, none subjects with T2DM were exposed.

Table 15 Exposure - descriptive statistics - safety analysis set

	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	Total
Number of subjects	261	258	258	777
Total exposure, yrs	128.4	127.7	127.7	383.7
Exposure (yrs)				
N	261	258	258	777
Mean (SD)	0.49 (0.06)	0.49 (0.05)	0.49 (0.05)	0.49 (0.05)
Median	0.50	0.50	0.50	0.50
Min ; Max	0.02 ; 0.54	0.06 ; 0.55	0.04 ; 0.54	0.02 ; 0.55

N: Number of subjects, SD: Standard deviation, yrs: Years
Exposure in the treatment period is calculated as the last date on randomised treatment minus the first date on randomised treatment plus one day. The run-in period and the follow-up period are not included.

Table 16 Exposure - descriptive statistics

	Faster aspart (meal) N (%)	Faster aspart (post) N (%)	NovoRapid (meal) N (%)	Total N (%)
Number of subjects	260	259	258	777
Age group				
N	260 (100.0)	259 (100.0)	258 (100.0)	777 (100.0)
1 - <6 years	16 (6.2)	16 (6.2)	14 (5.4)	46 (5.9)
6 - <12 years	100 (38.5)	100 (38.6)	101 (39.1)	301 (38.7)
12 - <18 years	144 (55.4)	143 (55.2)	143 (55.4)	430 (55.3)
Division for 1 <6 years				
1 - <3 years	2 (0.8)	2 (0.8)	0	4 (0.5)
3 - <6 years	14 (5.4)	14 (5.4)	14 (5.4)	42 (5.4)

Table 17 Exposure by age group - summary - safety analysis set

	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	Total
Number of subjects	261	258	258	777
Exposure, years (%)				
Total	128.4 (100.0)	127.7 (100.0)	127.7 (100.0)	383.7 (100.0)
1 - <6 years	8.0 (6.2)	8.0 (6.3)	7.0 (5.5)	23.0 (6.0)
6 - <12 years	50.6 (39.4)	49.4 (38.7)	50.0 (39.2)	150.0 (39.1)
12 - <18 years	69.8 (54.3)	70.3 (55.1)	70.6 (55.3)	210.7 (54.9)

%: Percentage of subjects,
Exposure in the treatment period is calculated as the last date on randomised treatment minus the first date on randomised treatment plus one day. The run-in period and the follow-up period are not included.

Adverse events

Overall adverse events

The proportion of subjects with an AE during the study period was similar in the 3 treatment groups; 73.9%, 77.1% and 78.7% of subjects in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups respectively reported AEs. The AE rates were also similar in the different treatment groups (448.6, 531.1 and 464.5 per 100 PYE for mealtime faster aspart, post-meal faster aspart and NovoRapid respectively, Table 18).

The majority of AEs in all 3 treatment groups were non-serious (98%) and of mild or moderate severity (99%). The proportion of subjects with severe AEs was comparable between the treatment groups (Table 18).

Across age groups, the frequency of subjects that reported an AE was slightly lower in the 1 to < 6 age group (58.7%) compared to the two older groups (77.4% in the 6 to<12 years group and 77.9% in the 12 to <18 years group respectively). No systematic unexpected differences were observed between the 3 treatment groups within each age group (Table 19)

Table 18 Adverse events - summary - on-treatment - safety analysis set

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R
Number of subjects	261				258				258			
Total exposure (yrs)	128.4				127.7				127.7			
Total events	193	(73.9)	576	448.6	199	(77.1)	678	531.1	203	(78.7)	593	464.5
Serious												
Yes	5	(1.9)	7	5.5	13	(5.0)	15	11.8	9	(3.5)	13	10.2
No	192	(73.6)	569	443.2	199	(77.1)	663	519.4	202	(78.3)	580	454.3
Severity												
Severe	3	(1.1)	4	3.1	7	(2.7)	9	7.1	3	(1.2)	4	3.1
Moderate	52	(19.9)	80	62.3	58	(22.5)	100	78.3	51	(19.8)	77	60.3
Mild	178	(68.2)	492	383.2	185	(71.7)	569	445.7	186	(72.1)	512	401.0
Related to randomised trial product												
Probable	10	(3.8)	12	9.3	13	(5.0)	16	12.5	11	(4.3)	12	9.4
Possible	3	(1.1)	3	2.3	6	(2.3)	7	5.5	9	(3.5)	12	9.4
Unlikely	192	(73.6)	547	426.0	196	(76.0)	647	506.8	200	(77.5)	559	437.9
Related to basal component												
Probable	4	(1.5)	6	4.7	15	(5.8)	19	14.9	15	(5.8)	15	11.7
Possible	10	(3.8)	12	9.3	9	(3.5)	9	7.1	11	(4.3)	13	10.2
Unlikely	193	(73.9)	558	434.6	199	(77.1)	650	509.2	201	(77.9)	564	441.8
Related to a technical complaint												
Yes	2	(0.8)	2	1.6	0				1	(0.4)	1	0.8
No	193	(73.9)	560	436.2	197	(76.4)	670	524.9	202	(78.3)	582	455.9
Outcome												
Recovered/resolve	187	(71.6)	538	419.0	196	(76.0)	647	506.8	202	(78.3)	573	448.8
Recovering/resolvin	12	(4.6)	14	10.9	8	(3.1)	8	6.3	9	(3.5)	10	7.8
Recovered/resolved with sequelae	0				1	(0.4)	1	0.8	3	(1.2)	3	2.3
Not recovered/not resolved	20	(7.7)	24	18.7	20	(7.8)	22	17.2	6	(2.3)	7	5.5
Fatal	0				0				0			
Unknown	0				0				0			

%: Percentage of subjects, E: Number of events, N: Number of subjects, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Relationship is based on investigators assessment.
MedDRA version 20.0.
Technical complaint is related to randomised trial product.

Table 19 Adverse events – age groups – safety analysis set

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subject exposed			
1 to < 6 years	16	16	14
6 to < 12 years	101	99	101
12 to < 18 years	144	143	143
Total events			
1 to < 6 years	9 (56.3) 33 411.7	10 (62.5) 46 575.6	8 (57.1) 22 314.6
6 to < 12 years	77 (76.2) 234 462.3	75 (75.8) 283 573.2	81 (80.2) 262 523.7
12 to < 18 years	107 (74.3) 309 443.0	114 (79.7) 349 496.5	114 (79.7) 309 437.4
Serious events			
1 to < 6 years	0	1 (6.3) 1 12.5	0
6 to < 12 years	4 (4.0) 5 9.9	5 (5.1) 7 14.2	4 (4.0) 6 12.0
12 to < 18 years	1 (0.7) 2 2.9	7 (4.9) 7 10.0	5 (3.5) 7 9.9
Severe events			
1 to < 6 years	0	1 (6.3) 1 12.5	0
6 to < 12 years	2 (2.0) 3 5.9	3 (3.0) 5 10.1	3 (3.0) 4 8.0
12 to < 18 years	1 (0.7) 1 1.4	3 (2.1) 3 4.3	0
Related to randomised trial product			
1 to < 6 years	0	0	0
6 to < 12 years	6 (5.9) 7 13.8	8 (8.1) 13 26.3	9 (8.9) 10 20.0
12 to < 18 years	7 (4.9) 8 11.5	9 (6.3) 10 14.2	10 (7.0) 14 19.8

Abbreviations: %: percentage of subjects within age group; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure within age group

Most common adverse events

The three most frequent AEs (by SOC) in all treatment groups were 'infections and infestations (57.3% of all subjects), 'gastrointestinal disorders' (17.9% of all subjects) 'respiratory, thoracic and mediastinal disorders (14.8% of all subjects).

Overall, no differences in frequency and rate were seen between the treatment groups; however, the proportion of subjects reporting AEs and the rate in the SOC 'gastrointestinal disorders' were higher in the post-meal faster aspart group (22.9%) compared with the mealtime faster aspart (14.2%) and NovoRapid groups (16.7%). This was mainly due to a higher frequency of '*vomiting*' reported in the post-meal faster aspart group (8.1% compared to 3.4% in the mealtime faster aspart group and 2.7% in the NovoRapid group).

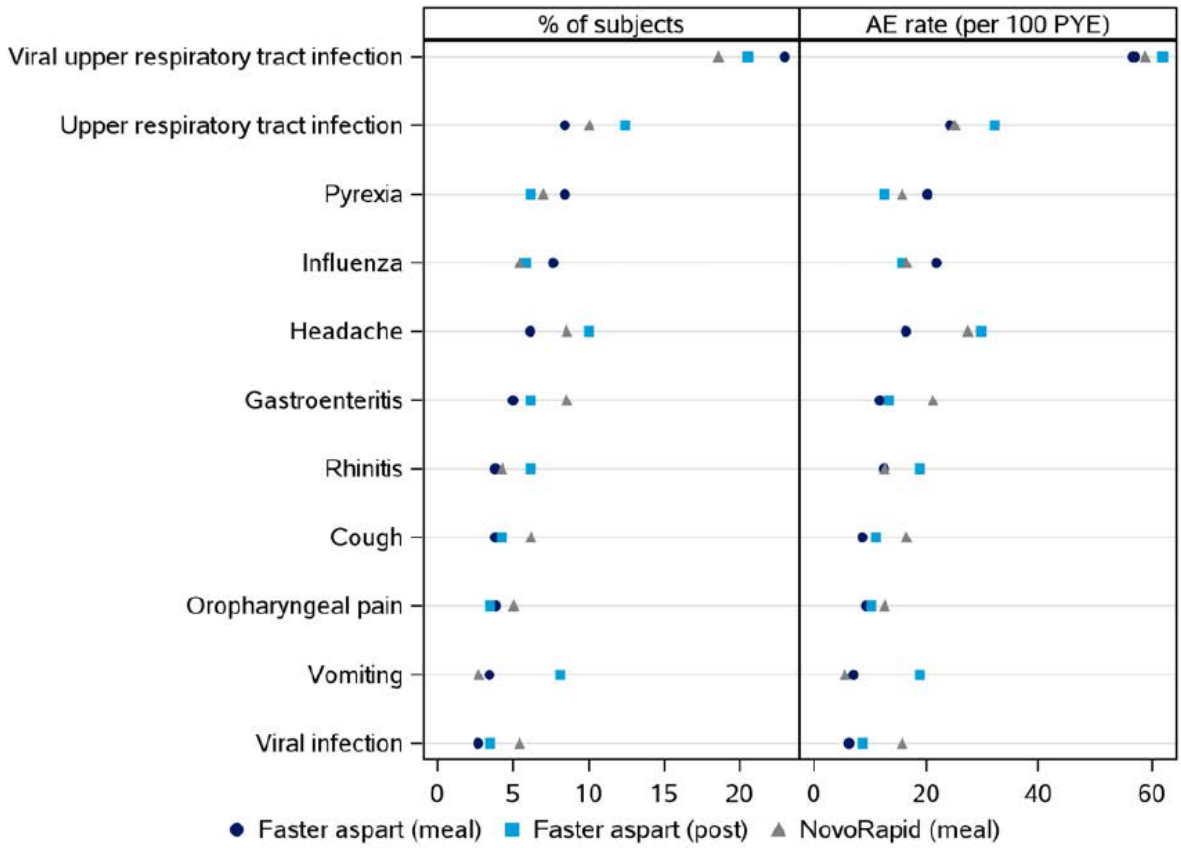
All subjects: The most frequently reported preferred terms in all 3 treatment groups was '*viral upper respiratory tract infection*'; reported by 23.0%, 20.5% and 18.6% of subjects in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups respectively. Other frequently reported AEs were '*upper respiratory tract infection*' and '*headache*'; these AEs were reported by 8.4%, 12.4% and 10.1%; and by 6.1%, 10.1% and 8.5% of subjects in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups, respectively (Figure 15). There were no clinically relevant differences across the treatment groups with respect to the most frequently reported AEs.

Age groups: The most frequently reported preferred terms within the SOC 'Infections and infestations' were in the age group 1 to < 6 years: *pharyngitis* (10.9%) and *influenza/upper respiratory tract infection/nasopharyngitis/ear infection* (all 6.5% each), in the age group 6 to < 12 years: *upper respiratory tract infection* (10.6%) and *rhinitis/influenza/gastroenteritis* (7.3% each), in the age group 12 to < 18 years: *upper respiratory tract infection* (10.5%) *and gastroenteritis* (6.3%). The most frequently reported preferred terms within the SOC 'Gastrointestinal disorders' were in the age group 1 to < 6 year: *diarrhea* and *vomiting* (8.7% each), in the age group 6 to < 12 years: *abdominal pain* (5.6%) and *vomiting* (3.3%) and in the age group 12 to < 18 years: *abdominal pain* and *vomiting* (3.7% each). Further, '*headache*' within the SOC 'nervous system disorders' was frequently reported in the age groups 6 to <12 years and 12 to <18 years.

Overall, as expected the AE profile differed slightly between the different age groups regarding PT within the most common SOCs ("Infections and infestations" and "Gastrointestinal disorders"). These differences reflected more the normal background differences of disease in these age groups.

In all age groups, frequency of *vomiting* was higher among subjects treated with post meal faster aspart (8.1%, compared to 3.4% in the mealtime faster aspart group and 2.7% in the mealtime NovoRapid group). This difference was more pronounced in the two older age groups (9.1% (n=9) of subjects aged 6 to < 12 years reported AEs of *vomiting* in the post meal faster aspart group compared to 5% and 3% in the faster aspart meal group and NovoRapid group respectively and in 7% (n=10) of the subjects in the post meal faster aspart group in the oldest age group [12 - <18 years] compared with 2.1% in both faster aspart meal group and NovoRapid group. This phenomenon has not been noticed in the development program for adult and there are no clear explanations for this increased incidence. However, vomiting is general considered more frequently occurring in children than adults. Further, none of the events was reported as serious, severe or related to study drug and that almost all subjects reporting vomiting (n=37/777) reported this only once (total number of events were 40).

Figure 15 Adverse events by preferred term - treatment emergent - most frequent (≥ 5%) - on-treatment - safety analysis set



%: Percentage of subjects, AE: Adverse event, PYE: Patient years of exposure
Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period.
MedDRA version 20.0.

Table 20 Adverse events in the system organ classes 'infections and infestations' and 'gastrointestinal disorders' by age groups – summary - on-treatment – safety analysis set

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Infections and infestations			
1 to < 6 years	8 (50.0) 21 262.0	9 (56.3) 22 275.3	6 (42.9) 15 214.5
6 to < 12 years	68 (67.3) 131 258.8	54 (54.5) 122 247.1	64 (63.4) 128 255.8
12 to < 18 years	75 (52.1) 135 193.5	89 (62.2) 157 223.4	72 (50.3) 130 184.0
Gastrointestinal disorders			
1 to < 6 years	3 (18.8) 4 49.9	5 (31.3) 11 137.6	1 (7.1) 2 28.6
6 to < 12 years	15 (14.9) 18 35.6	24 (24.2) 42 85.1	21 (20.8) 31 62.0
12 to < 18 years	19 (13.2) 24 34.4	30 (21.0) 41 58.3	21 (14.7) 25 35.4

Abbreviations: % = percentage of subjects; E = number of events; N = number of subjects; R: event rate per 100 patient years of exposure

Adverse events by relation to trial products

In total 62 AEs (of 1847) were reported as possibly and/or probably related to randomised trial drug in 49 subjects (6.3%; 34 subjects reported any event judged as probably and 18 subject any event as possible related to randomised trial drug). The distribution between the three treatment groups was 5.0% (n=13 subjects), 6.6% (n=17 subjects) and 7.4% (n=19 subjects) in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups respectively. None of the preferred terms were reported with a

frequency ≥ 2% and no marked differences were seen between the 3 treatment groups with respect to frequency or type of possibly or probably related AEs.

Possibly or probably related AEs reported with a frequency ≥ 1% in any group were 'injection site reaction (n=4), 'hypoglycaemia' (n=10), 'lipohypertrophy' (n=7) and 'blood glucose decreased' (n=4) (Table 21)

In total, 7 of the 62 possibly or probably related AEs were classified as serious (2, 4 and 1 event in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups). These events ('accidental overdose' [n=3], 'hypoglycaemia' [n=2] and 'hypoglycaemia unconsciousness' [n=2]).

In the age group 1 to < 6 years, none of the reported AEs was possibly or probably related to randomised trial product. In the age groups 6 to < 12 years and 12 to < 18 years, the AEs possibly or probably related to randomised trial product were infrequently reported in all 3 treatment groups and no marked differences were seen between treatment or age groups with respect to frequency or type of AEs.

The most frequent PTs reported as possible or probably related to faster aspart are adequately reflected in the SmPC.

Table 21 Adverse events possibly or probably related to faster aspart or NovoRapid

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	261	258	258
Total events possibly or probably related[a]	13 (5.0) 15 11.7	17 (6.6) 23 18.0	19 (7.4) 24 18.8
Most frequent preferred terms (≥1%)			
Injection site reaction	0	3 (1.2) 3 2.4	1 (0.4) 1 0.8
Hypoglycaemia	3 (1.1) 3 2.3	2 (0.8) 2 1.6	5 (1.9) 5 3.9
Lipohypertrophy	3 (1.1) 4 3.1	1 (0.4) 1 0.8	3 (1.2) 3 2.3
Blood glucose decreased	1 (0.4) 1 0.8	3 (1.2) 3 2.4	0

[a] Related to randomised trial product.

Adverse event by severity

The majority of AEs in all 3 treatment groups were of mild (85% [1573/1847] of all AEs) or moderate severity (14% [257/1847] of all AEs]). Only four of the 17 severe AEs were considered possible or probably related. A summary of AEs in relation to severity and relation to trial products is shown in Table 22.

Table 22 Severe, moderate and mild adverse events – all subjects

	Faster aspart (meal) N (%)	E	R	Faster aspart (post) N (%)	E	R	NovoRapid (meal) N (%)	E	R
Number of subjects	261			258			258		
Total events	193 (73.9)	576	448.6	199 (77.1)	678	531.1	203 (78.7)	593	464.5
Severe	3 (1.1)	4	3.1	7 (2.7)	9	7.1	3 (1.2)	4	3.1
Possibly/probably related[a]	1 (0.4)	2	1.6	1 (0.4)	2	1.6	0		
Moderate	52 (19.9)	80	62.3	58 (22.5)	100	78.3	51 (19.8)	77	60.3
Possibly/probably related[a]	0			1 (0.4)	2	1.6	5 (1.9)	6	4.7
Mild	178 (68.2)	492	383.2	185 (71.7)	569	445.7	186 (72.1)	512	401.0
Possibly/probably related[a]	12 (4.6)	13	10.1	16 (6.2)	19	14.9	14 (5.4)	18	14.1

[a] Related to randomised trial product.

Serious adverse event/deaths/other significant events

Death

No deaths were reported in the FIASP group, while one non-treatment emergent death was reported in the NovoRapid group. A subject in the group 6 to < 12 years died in an accident 11 days after the last dose of randomised treatment. The relation to trial products was considered unlikely by both the investigator and MAH.

Serious adverse events

All subject: In study 4101, a total of 35 SAEs were reported by 27 (3.5%) subjects; 7 SAEs were reported by 5 (1.9%) subjects in the mealtime faster aspart group, 15 SAEs were reported by 13 (5.0%) subjects in the post-meal faster aspart group and 13 SAEs were reported by 9 (3.5%) in the NovoRapid group (Table 23).

The majority of SAEs were reported in the SOCs 'infections and infestations' and 'metabolism and nutrition disorders'. Overall, none of the SAEs were reported by ≥ 1% of subjects, except '*gastroenteritis*' that was reported by 3 (1.2%) subjects in the NovoRapid group

In total, 7 SAEs were considered probably related to randomised trial product (2 events in the mealtime faster aspart group, 4 events in the post-meal faster aspart group and one event in the NovoRapid group), these events were all related to events in association to hypoglycaemia.

None of the SAEs was reported as possible related to study drug.

Overall the frequency of SAEs was reported in slightly higher frequency in subjects treated with meal faster aspart (1.9%) meal compared to treatment with post meal faster aspart (5%). This difference was driven by more reported diabetes related PTs such as DKA and hypoglycaemia. However, the number of subjects in each group was few and conclusions should carefully be drawn.

Age groups: In the age group 1 to < 6 years, 1 SAE was reported in the post-meal faster aspart group ('influenza'). In all, 18 SAEs were reported in the age group 6 to < 12 years and 16 SAEs were reported in the age group 12 to < 18 years. In both age groups no SAEs were reported by more than 1 subject, except 'accidental overdose' and 'hypoglycaemic unconsciousness' (reported by 2 subjects with post-meal faster aspart in the age group 6 to < 12 years) and 'gastroenteritis' (reported by 2 subjects with NovoRapid in the age group 12 to < 18 years).

Table 23 Serious adverse events – age groups – safety analysis set

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
1 to < 6 years	0	1 (6.3) 1 12.5	0
6 to < 12 years	4 (4.0) 5 9.9	5 (5.1) 7 14.2	4 (4.0) 6 12.0
12 to < 18 years	1 (0.7) 2 2.9	7 (4.9) 7 10.0	5 (3.5) 7 9.9

Abbreviations: %: percentage of subjects within age group; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure within age group

Adverse event of special interest

- **Medication errors**

Very few probably related medication errors were reported (3, 2 and 1 event in the mealtime Fiasp, post meal Fiasp and NovoRapid groups). Table 24. The available data did not suggest an increased risk of medications errors for Fiasp compared to NovoRapid.

None of the medication errors led to withdrawal or premature discontinuation of trial product.

Table 24 Medication errors

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	261	258	258
Total events	3 (1.1) 3 2.3	2 (0.8) 2 1.6	1 (0.4) 1 0.8
Serious events	1 (0.4) 1 0.8	2 (0.8) 2 1.6	0
Probably related[a]	3 (1.1) 3 2.3	2 (0.8) 2 1.6	1 (0.4) 1 0.8
Preferred terms			
Accidental overdose	2 (0.8) 2 1.6	2 (0.8) 2 1.6	1 (0.4) 1 0.8
Incorrect dose administered	1 (0.4) 1 0.8	0	0

[a] Related to randomised trial product.
Abbreviations: %: percentage of subjects; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure

Cross-reference: Modified from Trial 4101 (M 5.3.5.1), EOT Table 14.3.1.51

- **Injection site reactions**

Injections site reaction is a known risk for both faster aspart and NovoRapid and labelled in the SmPC for FIASP.

In total, 59 injection site reactions were reported by 33 (4.2%) subjects; 11 events were reported by 8 (3.1%) subjects in the mealtime faster aspart group, 31 events were reported by 14 (5.4%) subjects in the post-meal faster aspart group and 17 events were reported by 11 (4.3%) subjects in the NovoRapid group. All AEs related to injection site reactions were non-serious and of mild severity. The majority of AEs related to injection site reactions were unlikely related to randomised trial product (Table 25).

Additionally, 15 AEs (5 in the mealtime faster aspart group, 4 in the post-meal faster aspart group and 6 in the NovoRapid) were reported by the investigator as injection site reactions, but were not caught in the NNMQ search.

Thus, overall there was no difference in frequency of ISR between the three treatment groups.

As seen in

Table 26, the events of injection site reaction were evenly distributed between the two oldest age groups (6 to <12 years and 12 to <18 years). No events occurred in the youngest age group (1 to < 6 years). Three subjects randomised to the postmeal faster aspart group reported 19 'injection site haemorrhage' events.

None of the 'injection site haemorrhage' events were considered possibly or probably related to randomised trial product.

Table 25 Injection site reactions – all subjects – safety analysis set

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	261	258	258
Total events	8 (3.1) 11 8.6	14 (5.4) 31 24.3	11 (4.3) 17 13.3
Serious events	0	0	0
Probably or possibly related[a]	3 (1.1) 3 2.3	6 (2.3) 6 4.7	4 (1.6) 5 3.9
Most frequent preferred terms (≥1%)			
Injection site haemorrhage	1 (0.4) 4 3.1	4 (1.6) 20 15.7	1 (0.4) 2 1.6
Injection site bruising	0	3 (1.2) 4 3.1	2 (0.8) 2 1.6
Injection site pain	3 (1.1) 3 2.3	0	2 (0.8) 3 2.3
Injection site reaction	0	5 (1.9) 5 3.9	1 (0.4) 1 0.8

[a] Related to randomised trial product.

Table 26 Injection site reactions - age groups –safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Novo Rapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Total events	8 (3.1)	11	8.6	14 (5.4)	31	24.3	11 (4.3)	17	13.3
1 to < 6 years	0			0			0		
6 to < 12 years	3 (3.0)	6	11.9	8 (8.1)	25	50.6	3 (3.0)	4	8.0
12 to < 18 years	5 (3.5)	5	7.2	6 (4.2)	6	8.5	8 (5.6)	13	18.4

%: percentage of subjects; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure.

- **Lipodystrophy**

Lipodystrophy is a known risk for both faster aspart and NovoRapid and labelled in SmPC for FIASP.

In total, 17 events of lipodystrophy were reported by 15 (1.9%) subjects; 8 events reported by 7 (2.7%) subjects in the mealtime faster aspart group, 5 events reported by 4 (1.6%) subjects in the post-meal faster aspart and 4 events reported by 4 (1.6%) subjects in the NovoRapid group (Table 27). The majority (15 of 17) of the lipodystrophy events were reported as 'lipohypertrophy', while the remaining 2 events were reported as 'lipodystrophy acquired'; both with post-meal faster aspart

Overall, there was no difference in frequency of lipodystrophy between the three treatment groups.

As seen in Table 28, the events of lipodystrophy were evenly distributed between the two oldest age groups (6 to <12 years and 12 to <18 years). No events occurred in the youngest age group (1 to < 6 years).

Table 27 Lipodystrophy -all subjects -safety analysis set

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	261	258	258
Total events	7 (2.7) 8 6.2	4 (1.6) 5 3.9	4 (1.6) 4 3.1
Serious events	0	0	0
Possibly or probably related[a]	3 (1.1) 4 3.1	(0.4) 1 0.8	3 (1.2) 3 2.3
Preferred terms			
Lipohypertrophy	7 (2.7) 8 6.2	3 (1.2) 3 2.4	4 (1.6) 4 3.1
Lipodystrophy acquired	0	1 (0.4) 2 1.6	0

[a] Related to randomised trial product.
Abbreviations: %: percentage of subjects; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure

Cross-reference: Modified from Trial 4101 (M 5.3.5.1), EOT Tables 14.3.1.45, 14.3.1.20 and 14.3.1.25

Table 28 Lipodystrophy - age groups – safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Novo Rapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Total events	7 (2.7)	8	6.2	4 (1.6)	5	3.9	4 (1.6)	4	3.1
1 to < 6 years	0			0			0		
6 to < 12 years	3 (3.0)	3	5.9	2 (2.0)	3	6.1	2 (2.0)	2	4.0
12 to < 18 years	4 (2.8)	5	7.2	2 (1.4)	2	2.8	2 (1.4)	2	2.8

%: percentage of subjects; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure.

- **Allergic reactions**

Hypersensitivity and *allergic skin manifestations* is labelled in the SmPC for FIASP.

In total, 38 allergic reactions were reported by 30 (3.9%) subjects. There were no differences across treatment groups with respect to the type of allergic reactions or the proportion of subjects experiencing the reactions Table 29. The most frequently reported allergic reactions (≥ 1% of subjects in any treatment group) were 'rash' (in all n=7) and 'rhinitis allergic' (n=6). Table 29

None of the allergic reactions were serious. One reaction was considered possibly or probably related to randomised trial product ('urticaria' in the NovoRapid group).

Overall, there was no difference in frequency of allergic reactions between the three treatment groups.

As seen in

Table 30, the events of allergic reaction were evenly distributed between the two oldest age groups (6 to <12 years and 12 to <18 years). One event occurred in the youngest age group (1 to < 6 years).

Table 29 Allergic reactions – all subjects – safety analysis set

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	261	258	258
Total events	13 (5.0) 17 13.2	8 (3.1) 8 6.3	9 (3.5) 13 10.2
Serious events	0	0	0
Possibly or probably related[a]	0	0	1 (0.4) 1 0.8
Most frequent preferred terms (≥1%)			
Rash	4 (1.5) 4 3.1	1 (0.4) 1 0.8	2 (0.8) 2 1.6
Rhinitis allergic	2 (0.8) 5 3.9	0	4 (1.6) 4 3.1

[a] Related to randomised trial product.

Table 30 Allergic reactions – age groups – safety analysis set

	Faster aspart (meal)			Faster aspart (post)			Novo Rapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Total events	13 (5.0)	17	13.2	8 (3.1)	8	6.3	9 (3.5)	13	10.2
1 to < 6 years	0			1 (6.3)	1	12.5	0		
6 to < 12 years	4 (4.0)	7	13.8	4 (4.0)	4	8.1	5 (5.0)	7	14.0
12 to < 18 years	9 (6.3)	10	14.3	3 (2.1)	3	4.3	4 (2.8)	6	8.5

%: percentage of subjects; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure.

- **Hypoglycaemia**

Novo Nordisk classified all hypoglycaemic episodes into the following categories: 'severe hypoglycaemia' (according to ISPAD classification) 'BG confirmed hypoglycaemia', 'severe or BG confirmed symptomatic hypoglycaemia' and 'severe or BG confirmed hypoglycaemia' (Figure 16). All hypoglycaemic episodes were also classified according to ADA classification (Figure 17).

Figure 16 Novo Nordisk classification of hypoglycaemia in paediatrics

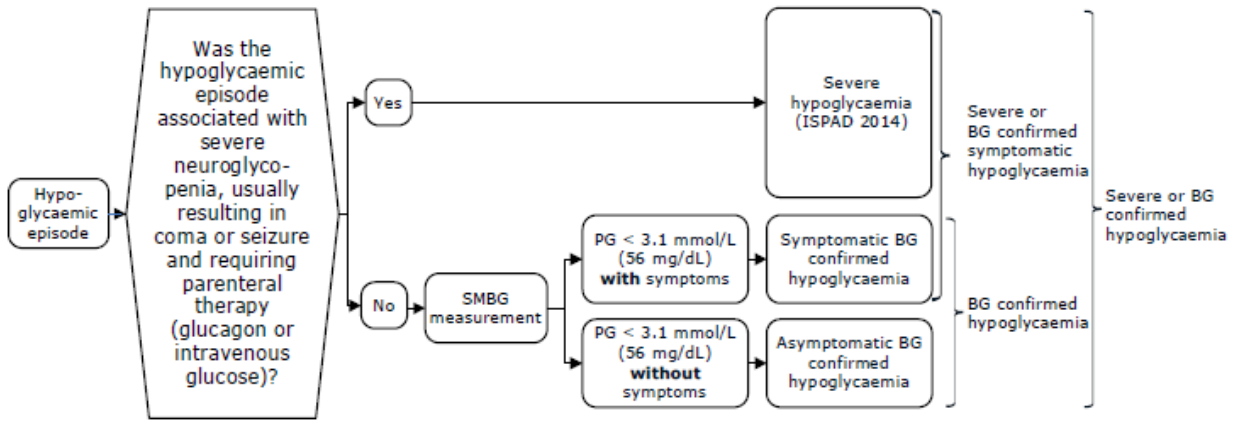
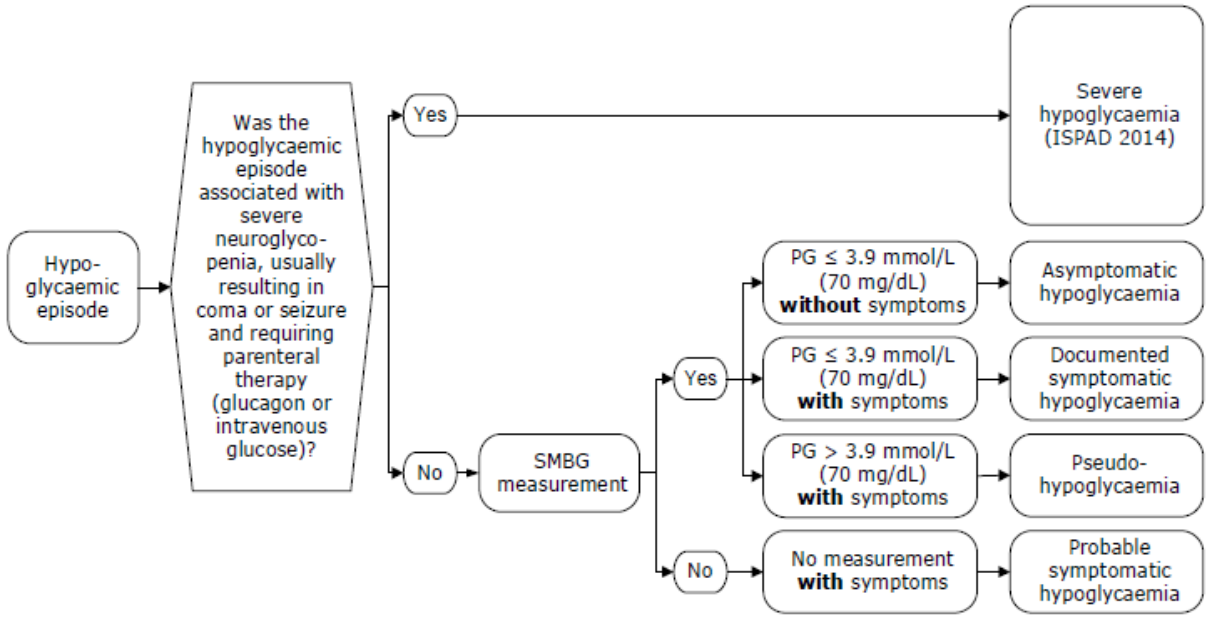


Figure 17 American Diabetes Association classification of hypoglycaemia in paediatrics



Overall hypoglycaemic episodes

The proportion of subjects with hypoglycaemic episodes was similar for mealtime faster aspart, post-meal faster aspart and NovoRapid (96.2%, 96.9% and 96.5% of subjects). The observed rate was slightly lower for NovoRapid (6973 episodes per 100 PYE) compared to mealtime faster aspart and post-meal faster aspart (7556 and 7481 episodes per 100 PYE) (Table 31).

Table 31 Hypoglycaemic episodes by classification - treatment emergent - summary - on-treatment - safety analysis set

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	261			258			258			777		
Total exposure (yrs)	128.4			127.7			127.7			383.7		
Total events	251 (96.2)	9701	7556	250 (96.9)	9550	7481	249 (96.5)	8902	6973	750 (96.5)	28153	7337
BG confirmed	228 (87.4)	3580	2788	227 (88.0)	3586	2809	217 (84.1)	3272	2563	672 (86.5)	10438	2720
Severe or BG confirmed symptomatic	192 (73.6)	2242	1746	194 (75.2)	2427	1901	185 (71.7)	2194	1719	571 (73.5)	6863	1789
Severe or BG confirmed	228 (87.4)	3583	2791	227 (88.0)	3594	2815	217 (84.1)	3276	2566	672 (86.5)	10453	2724
NN unclassifiable	251 (96.2)	6118	4765	244 (94.6)	5956	4666	245 (95.0)	5626	4407	740 (95.2)	17700	4613
ADA/ISPAD												
Severe (ISPAD 2014)	3 (1.1)	3	2	8 (3.1)	8	6	4 (1.6)	4	3	15 (1.9)	15	4
Documented symptomatic	210 (80.5)	5391	4199	213 (82.6)	5712	4475	207 (80.2)	5170	4050	630 (81.1)	16273	4241
Asymptomatic	215 (82.4)	4255	3314	214 (82.9)	3781	2962	211 (81.8)	3656	2864	640 (82.4)	11692	3047
Probable symptomatic	8 (3.1)	12	9	6 (2.3)	10	8	9 (3.5)	24	19	23 (3.0)	46	12
Pseudo-hypoglycaemia	19 (7.3)	35	27	9 (3.5)	37	29	13 (5.0)	47	37	41 (5.3)	119	31
ADA unclassifiable	5 (1.9)	5	4	1 (0.4)	2	2	1 (0.4)	1	1	7 (0.9)	8	2

%: Percentage of subjects, ADA: American Diabetes Association, BG: Blood glucose, E: Number of events, ISPAD: International Society for Pediatric and Adolescent Diabetes, N: Number of subjects, NN: Novo Nordisk, PG: Plasma glucose, R: Event rate per 100 patient years of exposure, yrs: Years
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ISPAD 2014 classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).
NN unclassifiable: Includes non-severe episodes (ISPAD 2014) that are not BG confirmed (PG <3.1 mmol/L (56 mg/dL)) as well as non-severe episodes (ISPAD 2014) that cannot be classified due to missing data.

Severe hypoglycaemic episodes

All subjects: Overall, in all 3 treatment groups the number of severe hypoglycaemic episodes (ADA definition) was comparable 3 (1.1%), 8 (3.1%) and 4 (1.6%) between the mealtime faster aspart, post-meal faster aspart and NovoRapid groups respectively (Table 31).

The majority of severe hypoglycaemic episodes (11 of 15 [73%]) were reported during daytime. Three of the four nocturnal severe hypoglycaemic episodes were reported in the post-meal faster aspart treatment group.

Age groups: None of the severe hypoglycaemic episodes were reported in the age group 1 to < 6 years, 9 episodes were reported in the age group 6 to < 12 years (2, 4 and 3 episodes in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups) and 6 episodes were reported in the age group 12 to < 18 years (1, 4 and 1 episodes in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups) (Table 21)

Severe or blood glucose confirmed hypoglycaemic episodes

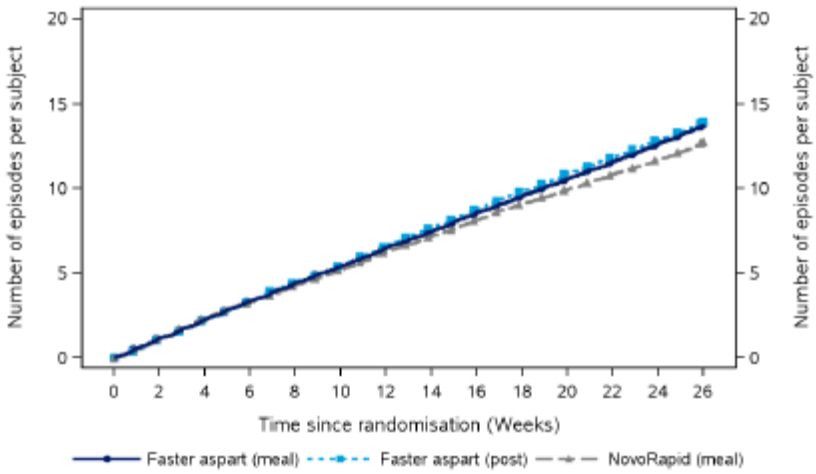
All ages: In total, 10453 severe or blood glucose confirmed hypoglycaemic episodes (Figure 16) were reported in 672 (86.5%) of the subjects. The proportion of subjects reported severe or BG confirmed hypoglycaemic episodes were similar between the three treatment groups: 87.4% of subjects, in the post-meal faster aspart group 88.0% of subjects and in the NovoRapid group 84.1% of the subjects (Table 31). The estimated rate ratios for severe or BG confirmed hypoglycaemic episodes were 1.11 [0.90; 1.37] 95%CI for mealtime faster aspart versus NovoRapid and also 1.11 [0.90; 1.37] 95%CI for post-meal faster aspart versus NovoRapid.

Thus, no statistically significant differences were seen between mealtime faster aspart and NovoRapid or between post-meal faster aspart and NovoRapid.

Severe or BG confirmed hypoglycaemic episodes were evenly distributed throughout the 26-week treatment period with no differences between treatment groups Figure 18. The distribution of the number of severe or BG confirmed hypoglycaemic episodes were similar across the 3 treatment groups.

In total, 66% of all "severe or BG confirmed hypoglycaemic episodes" were symptomatic and 89% occurred in the daytime.

Figure 18 Severe or blood glucose confirmed hypoglycaemic episodes – all subjects – mean cumulative function



Age groups: The frequency of subjects with severe or blood glucose confirmed hypoglycaemic episodes was highest in the youngest age group (91.3%) compared to the 6 - <12 years age group (87.7%) and the 12 - <18 years age-group (85.1%). When comparing the treatment groups within the age groups, a slightly higher incidence of severe or blood-glucose confirmed hypoglycaemic episodes was noted in the faster aspart treatment groups compared to NovoRapid treatment groups in the ages below 12 (Table 32). The clinical relevance of this finding is considered low.

Table 32 Severe or blood glucose confirmed hypoglycaemic episodes by age group

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
1 to < 6 years			
Number of subjects	16	16	14
Total exposure (years)	8.0	8.0	7.0
Severe or BG confirmed[a]	15 (93.8) 243 3031	15 (93.8) 289 3616	12 (85.7) 163 2331
6 to < 12 years			
Number of subjects	101	99	101
Total exposure (years)	50.6	49.4	50.0
Severe or BG confirmed[a]	88 (87.1) 1540 3042	93 (93.9) 1490 3018	83 (82.2) 1472 2942
12 to < 18 years			
Number of subjects	144	143	143
Total exposure (years)	69.8	70.3	70.6
Severe or BG confirmed[a]	125 (86.8) 1800 2580	119 (83.2) 1815 2582	122 (85.3) 1641 2323

[a] Severe according to the ISPAD 2014 classification and/or have a recorded plasma glucose <56 mg/dL.
Abbreviations: %: percentage of subjects within age group; BG: blood glucose; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure within age group

Daytime episodes

A similar proportion of subjects reported daytime "severe or BG confirmed hypoglycaemic episodes" in the three treatment groups (86.6%, 86.8% and 84.1% in the mealtime faster aspart, post-meal faster aspart and NovoRapid group respectively). Table 33

Table 33 Severe or blood glucose confirmed daytime and nocturnal hypoglycaemic episodes – summary – on-treatment – safety analysis set

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	261	258	258
Severe[a] or BG confirmed			
Daytime	226 (86.6) 3187 2482	224 (86.8) 3117 2442	217 (84.1) 2963 2321
Nocturnal[b]	112 (42.9) 396 308	125 (48.4) 477 374	104 (40.3) 313 245
Severe[a] or BG confirmed symptomatic			
Daytime	189 (72.4) 2062 1606	192 (74.4) 2167 1698	182 (70.5) 2035 1594
Nocturnal[b]	71 (27.2) 180 140	88 (34.1) 260 204	71 (27.5) 159 125

[a] Severe according to the ISPAD 2014 classification and/or have a recorded plasma glucose <3.1 mmol/L (56 mg/dL).
[b] The period between 23:00 and 07:00 (both included).
Abbreviations: % = percentage of subjects; BG = blood glucose; E = number of events; N = number of subjects; R: event rate per 100 patient years of exposure

Nocturnal episodes

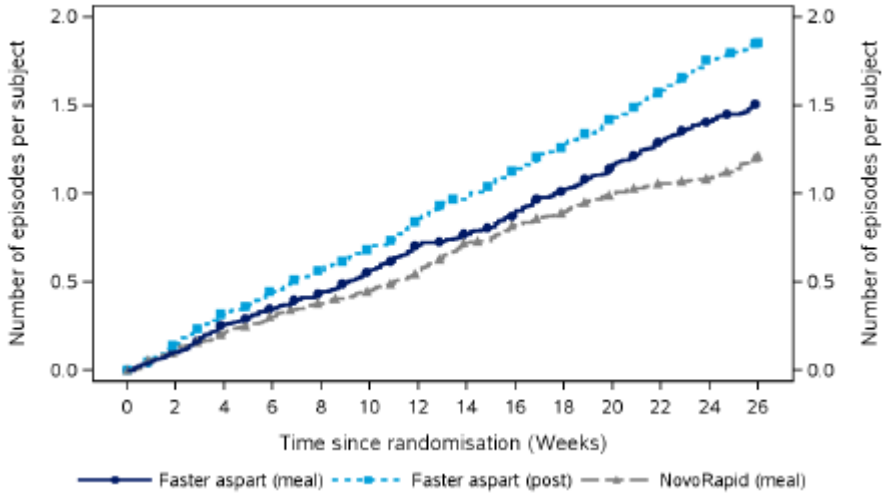
All subjects: A higher proportion of subjects in the post-meal faster aspart group (48.4%) reported nocturnal severe or BG confirmed hypoglycaemic episodes compared with the mealtime faster aspart and NovoRapid groups (42.9% and 40.3%) (Table 33). The estimated rate ratio for mealtime faster aspart versus NovoRapid was 1.29 [0.93; 1.79] 95%CI and 1.50 [1.09; 2.08] 95%CI for postmeal faster aspart versus NovoRapid; the latter being statistically significant.

An explanation by the Applicant that may explain the higher rate of nocturnal severe or BG confirmed hypoglycaemic episodes in the postmeal faster aspart group (204 per 100 PY) compared to NovoRapid (125 100 PY) is that one subject (12 ≤ age < 18 years) in the postmeal faster aspart group contributed with a high number of nocturnal severe or BG confirmed hypoglycaemic episodes (the subject had 45 episodes during the treatment period and also had a high number of episodes during run-in period).

The higher number of nocturnal severe or BG confirmed hypoglycaemic episodes in the post-meal faster aspart group were mainly seen in the evening from 22:00 to 01:00 and in the morning from 6:00 to 7:00. To note is that in trial 4101 with children and adolescents, a hypoglycaemic episode was defined as nocturnal if it occurred from 23:00–07:00 (inclusive).

The cumulative number of nocturnal severe or BG confirmed hypoglycaemic episodes per subject is shown in Figure 19.

Figure 19 Nocturnal severe or blood glucose confirmed hypoglycaemic episodes – mean cumulative function



Age groups: Nocturnal severe or blood glucose confirmed hypoglycaemic episodes by age groups are presented in Table 34.

In the age group 1 to <6 years, both the proportion of subjects with nocturnal severe or BG confirmed hypoglycaemic episodes and rate of episodes per 100 PY were numerically higher in the both groups with FIASP (62.5% and 412 in mealtime FIASP group respectively 56.3% and 363 in postmeal FIASP group) compared to the NovoRapid group (21.4% and 114 events per 100 PY). See Table 34. According to the Applicant, the higher number of episodes in the mealtime faster aspart group compared to the NovoRapid group can to some extent be explained by one subject in the mealtime faster aspart group who had 15 episodes during the treatment period; that subject also had a high number of episodes during the during run-in period.

In the age group 6 to <12 years both the proportion of subjects and the rate were higher in the postmeal FIASP group (50.5% and 326 events per 100 PY) than in the NovoRapid group and the mealtime FISAP group (37.6% in both and 224 respectively 306 events per 100 PY in the NovoRapid and mealtime FIASP group).

For the age group 12 to <18 years treated with postmeal faster aspart group, the proportion of subjects with these episodes was similar to NovoRapid but the rate was numerically higher with postmeal faster aspart than with NovoRapid (Table 34). The higher rate of nocturnal hypoglycaemic episodes in the post-meal faster aspart treatment group ages 12 to < 18 years could possibly be explained by one subject in the age group reporting 45 nocturnal severe or blood glucose confirmed hypoglycaemic episodes.

Thus, overall it could not be excluded that subjects using a postmeal faster aspart regime might have a greater risk to more often develop nocturnal hypoglycaemia compared to subjects using meal-time NovoRapid. However, considering that, in clinical practice, postmeal dosing will only be an administration option and not a regime to use on a regular basis together with the inserted warning in SmPC section 4.4 the risk for nocturnal hypoglycaemia is considered manageable.

Table 34 Nocturnal severe or blood glucose confirmed hypoglycaemic episodes – age groups

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects			
1 to < 6 years	16	16	14
6 to < 12 years	101	99	101
12 to < 18 years	144	143	143
Nocturnal severe hypoglycaemic episodes			
1 to < 6 years	0	0	0
6 to < 12 years	0	1 (1.0) 1 2	0
12 to < 18 years	0	2 (1.4) 2 3	1 (0.7) 1 1
Nocturnal severe or BG confirmed hypoglycaemic episodes			
1 to < 6 years	10 (62.5) 33 412	9 (56.3) 29 363	3 (21.4) 8 114
6 to < 12 years	38 (37.6) 155 306	50 (50.5) 161 326	38 (37.6) 112 224
12 to < 18 years	64 (44.4) 208 298	66 (46.2) 287 408	63 (44.1) 193 273

Abbreviations: %: percentage of subjects within age groups; BG: blood glucose; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure within age groups

Mealtime episodes

Within the first hour after the start of the meal, the rate of severe or BG confirmed hypoglycaemic episodes was low in all 3 treatment groups; however, lower in the post-meal faster aspart group (52 episodes per 100 PYE) compared with the mealtime faster aspart and NovoRapid groups (93 and 82 episodes per 100 PYE) (Table 35).

For each of the time intervals 1–2 hours and 2–3 hours after the start of a meal, the rate was higher than the preceding time interval in all 3 treatment groups. For the 3–4 hour time interval, however, the rate of hypoglycaemia declined and was lower than for the 2–3 hour interval in all treatment groups (Table 35 and Figure 20).

No statistically significant difference was seen between mealtime faster aspart and NovoRapid in the rate of severe or BG confirmed hypoglycaemia within 1, 2, or 4 hours after start of a meal, or between 1–2, 2–3, 2–4 or 3–4 hours after the start of a meal.

However, the rate of severe or BG confirmed hypoglycaemia within 1 hour after start of a meal was statistically significantly lower for post-meal faster aspart compared to NovoRapid; the estimated rate ratio was 0.64 [0.42; 0.96]95% CI) (Figure 21).

No statistically significant differences were seen between post-meal faster aspart and NovoRapid within 2 or 4 hours after start of a meal, or between 1–2, 2–3, 2–4 hours or 3–4 hours after the start of a meal.

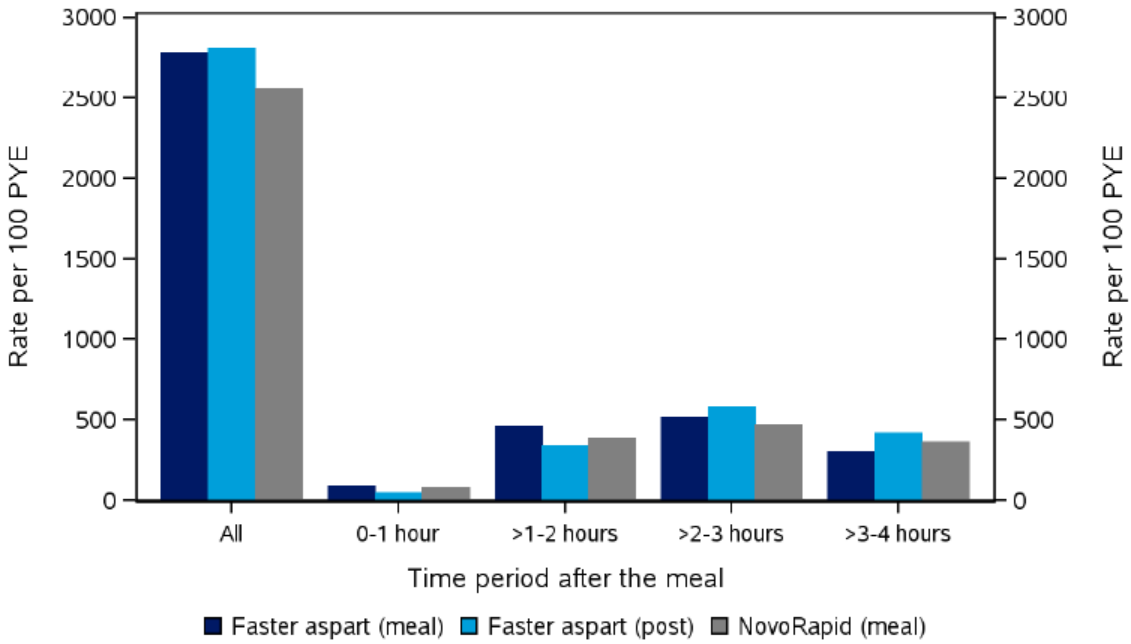
Thus, overall there was no difference between the two mealtime treatment groups (faster aspart vs NovoRapid) in the aspect of hypoglycaemic episodes 1-4 hours after mealtime.

Table 35 Severe or blood glucose confirmed hypoglycaemic episodes related to meals – treatment emergent – summary – on-treatment – safety analysis set

	Faster aspart (meal)				Faster aspart (post)				NovoRapid (meal)			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	261				258				258			
Severe or BG confirmed												
Within 1 hour after meal	64	(24.5)	119	93	46	(17.8)	66	52	62	(24.0)	105	82
Between 1-2 hours after meal	151	(57.9)	598	466	124	(48.1)	439	344	136	(52.7)	496	389
Between 2-3 hours after meal	151	(57.9)	666	519	157	(60.9)	742	581	145	(56.2)	601	471
Between 3-4 hours after meal	135	(51.7)	394	307	150	(58.1)	535	419	132	(51.2)	466	365
Within 2 hours after meal	161	(61.7)	717	558	136	(52.7)	505	396	147	(57.0)	601	471
Within 4 hours after meal	200	(76.6)	1777	1384	201	(77.9)	1782	1396	191	(74.0)	1668	1307
Between 2-4 hours after meal	179	(68.6)	1060	826	190	(73.6)	1277	1000	169	(65.5)	1067	836
Total	228	(87.4)	3583	2791	227	(88.0)	3594	2815	217	(84.1)	3276	2566
Severe or BG confirmed symptomatic												
Within 1 hour after meal	53	(20.3)	94	73	34	(13.2)	49	38	47	(18.2)	85	67
Between 1-2 hours after meal	122	(46.7)	478	372	103	(39.9)	365	286	111	(43.0)	410	321
Between 2-3 hours after meal	127	(48.7)	514	400	133	(51.6)	568	445	117	(45.3)	458	359
Between 3-4 hours after meal	103	(39.5)	279	217	113	(43.8)	393	308	102	(39.5)	324	254
Within 2 hours after meal	134	(51.3)	572	446	110	(42.6)	414	324	118	(45.7)	495	388
Within 4 hours after meal	167	(64.0)	1365	1063	167	(64.7)	1375	1077	159	(61.6)	1277	1000
Between 2-4 hours after meal	144	(55.2)	793	618	156	(60.5)	961	753	140	(54.3)	782	613
Total	192	(73.6)	2242	1746	194	(75.2)	2427	1901	185	(71.7)	2194	1719

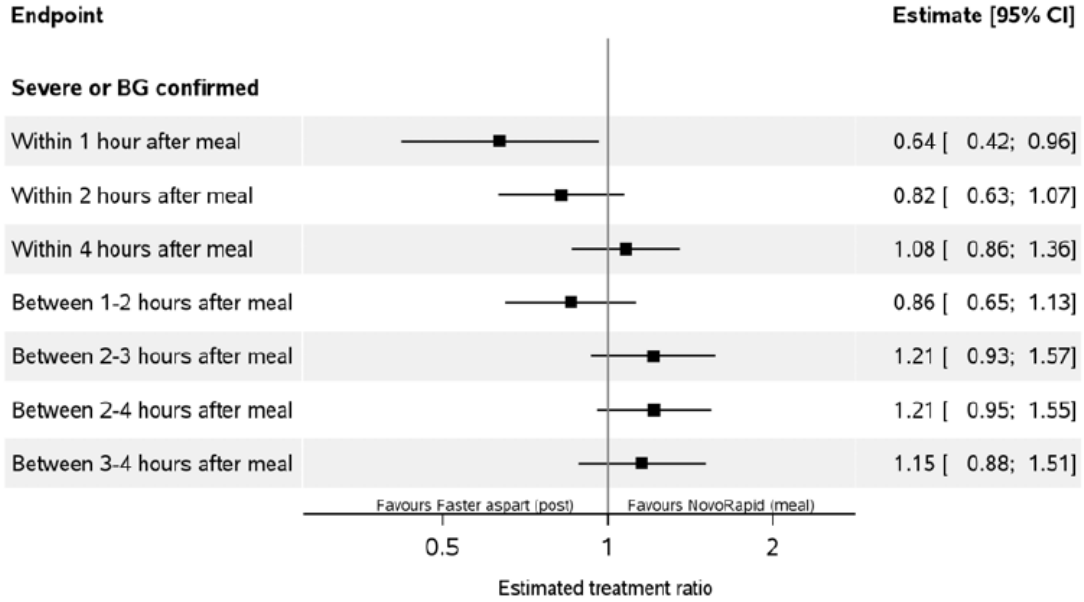
%: Percentage of subjects, BG: Blood glucose, E: Number of events, N: Number of subjects, PG: Plasma glucose, R: Event rate per 100 patient years of exposure
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Severe or BG confirmed: Severe according to the ADA classification and/or have a recorded PG <3.1 mmol/L (56 mg/dL).

Figure 20 Severe or blood glucose confirmed hypoglycaemic episodes distribution of meal related rates



All: Total amount of severe or bg confirmed hypoglycaemic episodes, BG: Blood glucose
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Episodes with missing time stamps or with missing main meal time are not included.

Figure 21 Severe or blood glucose confirmed hypoglycaemic episodes related to meals - Faster aspart (post)/NovoRapid (meal) - forest plot - on-treatment - full analysis set (post-hoc analysis)



BG: Blood glucose, CI: Confidence interval
Estimate: Estimated treatment ratio

Severe or blood glucose confirmed hypoglycaemic episodes by time

All subjects: No pronounced differences were seen between mealtime faster aspart, postmeal faster aspart and NovoRapid in rate of or proportion of subjects reporting severe or BG confirmed hypoglycaemic episodes.

Table 36 Severe or BG confirmed hypoglycaemic episodes by time - treatment emergent - summary – trial 4101 - on-treatment - safety analysis set

	Faster aspart (meal) N	(%)	E	R	Faster aspart (post) N	(%)	E	R	NovoRapid (meal) N	(%)	E	R	Total N	(%)	E	R
Number of subjects	261				258				258				777			
Total treatment emergent time (yrs)	129.1				128.4				128.4				385.8			
Severe or BG confirmed	228	(87.4)	3583	2775	227	(88.0)	3594	2800	217	(84.1)	3276	2552	672	(86.5)	10453	2709
1st week	90	(34.5)	158	3159	82	(31.8)	122	2467	84	(32.6)	142	2872	256	(32.9)	422	2834
2nd week	94	(36.0)	151	3032	87	(33.7)	174	3519	84	(32.6)	158	3195	265	(34.1)	483	3248
3rd week	87	(33.6)	142	2861	72	(27.9)	145	2933	94	(36.6)	163	3309	253	(32.7)	450	3034
4th week	93	(35.9)	150	3022	86	(33.3)	154	3123	88	(34.2)	150	3045	267	(34.5)	454	3063
5 - 8 Weeks	159	(61.4)	556	2812	161	(62.6)	564	2863	153	(59.5)	500	2546	473	(61.2)	1620	2740
9 - 12 Weeks	149	(58.0)	520	2646	147	(57.2)	548	2791	140	(54.7)	500	2548	436	(56.6)	1568	2662
13 - 16 Weeks	150	(58.6)	534	2731	153	(59.8)	557	2863	139	(54.3)	478	2450	442	(57.6)	1569	2681
17 - 20 Weeks	141	(55.3)	514	2629	154	(60.9)	528	2727	137	(53.9)	452	2329	432	(56.7)	1494	2562
21 - 24 Weeks	143	(56.1)	527	2696	132	(52.6)	496	2578	124	(49.0)	442	2281	399	(52.6)	1465	2519
>= 25 Weeks	125	(49.0)	331	2976	116	(46.2)	306	2731	111	(44.0)	291	2628	352	(46.4)	928	2778

Hypoglycaemic episodes reported as serious adverse events

In all, 6 hypoglycaemic episodes were reported as SAEs ('hypoglycaemia' and 'hypoglycaemic unconsciousness'). None of the hypoglycaemic episodes reported as SAEs were reported in the age group 1 to <6 years, 4 were reported in the age group 6 to <12 years and 2 were reported in the age group 12 to <18 years.

- **Hyperglycaemic episodes**

A hyperglycaemic episode was defined as: if a subject looked/felt ill and had either a SMPG > 14.0 mmol/L (250 mg/dL) and blood ketones > 1.5 mmol/L or SMPG > 14.0 mmol/L (250 mg/dL) and urine ketones above moderate.

In all, 12 hyperglycaemic episodes were reported by 12 (1.5%) subjects (4 in the meal faster aspart group, 1 in the post-meal faster aspart group and 7 in the NovoRapid group). One episode was reported

in the age group 1 to <6 years, 3 in the age group 6 to <12 years and 8 in the age group 12 to <18 years. The number of subjects with hyperglycaemic episodes and the number of the episodes were too low to see a pattern in relation to treatment.

In total 5 events of DKA was reported (2 in the postmeal faster aspart group and 3 in the Novorapid treatment group). All 5 events of DKA were reported in the age group 12 to <18 years.

- **Insulin Antibodies**

Samples for antibodies were collected at baseline (week 0) at week 12 and at the end-of-trial visit (week 26). The subjects attended these visits without taking any kind of insulin in the morning to minimise potential assay interference.

The presence of antibodies (insulin aspart specific antibodies and antibodies cross-reacting with human insulin as well as the total level of antibodies [comprised of the 2 types of antibodies]) is presented as the percentage of bound radioactivity (B) out of the total amount of radioactivity (T) (% B/T) on the 3 sampling days during the span of the on-treatment period.

Cut-point values for each antibody measurement are listed below:

- Anti-insulin aspart specific antibodies: >1.9% B/T
- Antibodies cross-reacting between insulin aspart and human insulin: >0.7% B/T
- Total insulin aspart antibodies: >1.9% B/T

The percentage of subjects categorised as positive for specific antibodies (13.6–20.5%), respectively positive for cross-reacting antibodies (93.0–96.2%) was similar between the 3 treatment groups, irrespective of the timing of the sample or whether the response was sustained or a single occurrence (Table 37).

Across all 3 treatment groups, only minor changes in mean level of anti-insulin aspart specific antibodies were seen from baseline to week 12, hereafter a slight decrease between week 12 and week 26 was seen (Figure 22).

There did not appear to be any correlation between allergic reactions or injection site reactions and an increase in antibody levels from baseline to end-of-trial, or with high antibody levels, for any of the treatment groups.

The percentage of subjects categorised as positive for specific antibodies was similar between the 3 age groups (1-6 years: 6.3 – 14.3%; 6-12 years: 10.1 – 19.8%; 12-18 years: 14.7 – 16.7%), irrespective of the timing of the sample or whether the response was sustained or a single occurrence.

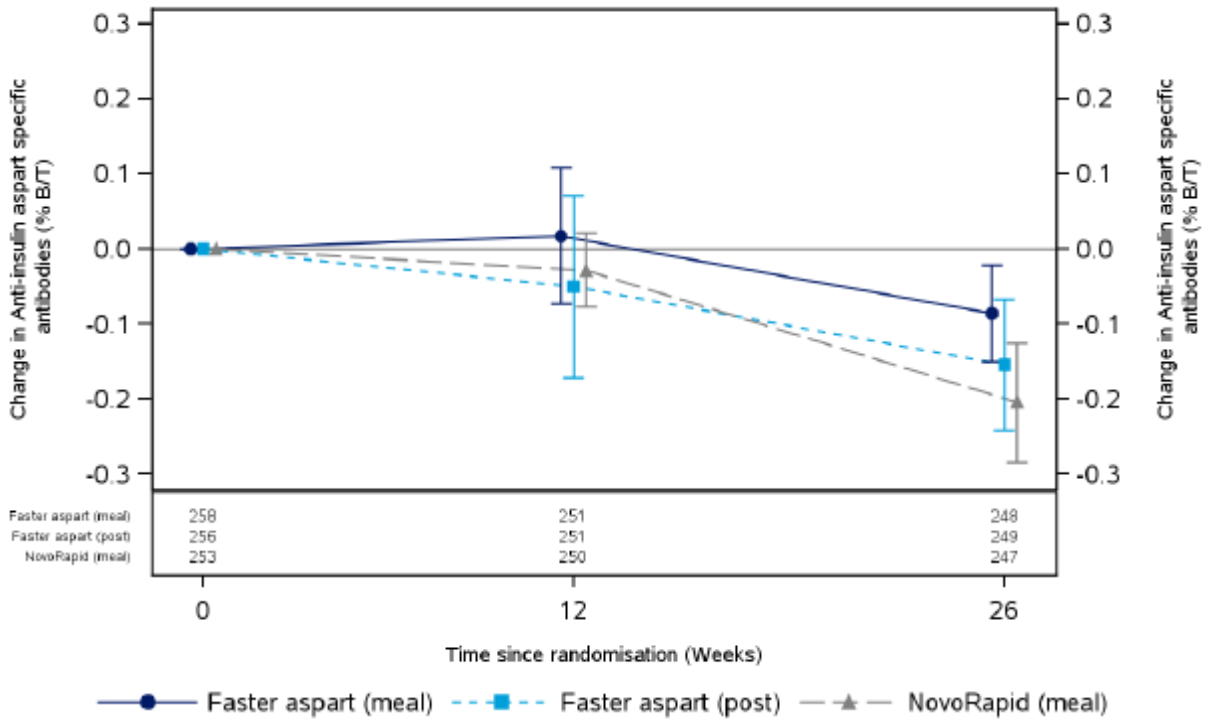
In line with the results for specific antibodies, the percentage of subjects categorised as positive for cross-reacting antibodies was similar between the 3 age groups. At baseline, the percentage of subjects categorised as positive for cross-reacting antibodies was 85.7–98.0%, and 92.9-100% of the subjects were categorised as positive at any time during the treatment period. The percentage of subjects with a sustained positive response was slightly lower than the percentage of subjects with positive response at any time during the treatment period and comparable to the percentage of subjects categorised as positive for cross-reacting antibodies at baseline.

Table 37 Incidence of anti-insulin aspart antibody positive subjects

		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.
Baseline: antibody sample above limit at baseline.
Anytime: at least one antibody sample above limit during the on-treatment period including the baseline visit.
Sustained: More than one antibody sample above limit during the on-treatment period including the baseline visit or above at last on-treatment observation.

Figure 22 Anti-insulin aspart specific antibodies by treatment week - change from baseline - mean plot - on-treatment



- **Medication errors**

During the on-treatment period, 6 medication errors were reported by 6 subjects; 3 in the mealtime faster aspart group, 2 events in the post-meal faster aspart group and 1 in the NovoRapid group. All the medication errors were considered probably related to randomised trial product.

Five of the medication errors were reported as 'accidental overdose' (4 were associated with hypoglycaemia and three were serious) and 1 event as 'incorrect dose administered'.

- **Technical complaints**

In all, 3 technical complaints related to AEs were reported. The AEs were non-serious and of mild severity. Two AEs ('injection site pain' and 'incorrect dose administered') were reported by 2 subjects in the mealtime faster apart group. The AE 'injection site pain' was considered unlikely related to randomised trial product, while the AE 'incorrect dose administered' was considered probably related to randomised trial product. One AE ('injection site pain') was reported in the NovoRapid group. The AE was considered unlikely related to randomised trial product. Following visual and functional investigations of the returned devices by Novo Nordisk, it was concluded that the trial product was normal.

Laboratory findings and vital signs

Biochemistry and haematology

Mean values for biochemistry and haematology remained stable during the trial, and there were no apparent differences across the treatment groups in mean values or mean change in values during the trial

Lipids

The treatment ratios in total cholesterol and LDL were statistically significantly lower for mealtime faster aspart compared to NovoRapid. Although statistically significant, the small difference is not considered clinically relevant (total cholesterol: estimated rate ratio 0.97 [0.95; 0.99]95% CI; LDL: estimated rate

ratio 0.97 [0.94; 1.00]95% CI). No statistically significant difference in treatment ratios in HDL was observed between mealtime faster aspart and NovoRapid.

The treatment ratios in total cholesterol, LDL and HDL showed no statistically significant differences between postmeal faster aspart and NovoRapid.

Vital signs

Mean blood pressure (systolic and diastolic) and pulse remained stable within each treatment group during the trial. No noticeable differences were seen across the 3 treatment groups in the parameters at baseline and after 26 weeks of treatment.

Body weight and body mass index (SD-score)

The estimated changes from baseline in body weight SD-score (and BMI SD-score) 26 weeks after randomisation were +0.03 (+0.02) in the mealtime faster aspart group, +0.01 (+0.00) in the post-meal faster aspart group and +0.03 (+0.01) in the NovoRapid group.

No statistically significant differences between either the faster aspart group or NovoRapid were shown.

Safety in special populations

Safety in clinical pharmacology study 4371 (see Efficacy section for further description of the trial) did not reveal any new safety issues.

Intrinsic factors

The only intrinsic factor investigated in trial 4101 was age. Other intrinsic factors were investigated in the original application submitted in 2015.

Discontinuation due to adverse events

No subjects withdrew from the trial due to an AE and no subjects discontinued trial product prematurely due to an AE.

Adverse events leading to dose reduction

In total 62 events were leading to dose reduction. The reporting-rate of these events was slightly lower in mealtime Fiasp (9.3 per100 PY) compared to NovoRapid (20.4 per 100 PY) as well as postmeal Fiasp (18.8 per 100 PY) (Table 38).The most frequent (≥ 1%) preferred terms leading to dose reduction were 'gastroenteritis, 'vomiting', 'hypoglycaemia' and 'blood glucose decreased'; however, these were infrequently reported in all 3 treatment groups (Table 38).

Table 38 Adverse events leading to dose reduction

	Faster aspart (meal) N (%) E R	Faster aspart (post) N (%) E R	NovoRapid (meal) N (%) E R
Number of subjects	261	258	258
Total events	11 (4.2) 12 9.3	16 (6.2) 24 18.8	19 (7.4) 26 20.4
Serious events	0	4 (1.6) 5 3.9	4 (1.6) 4 3.1
Probably related[a]	0	1 (0.4) 2 1.6	2 (0.8) 2 1.6
Possibly related[a]	0	0	1 (0.4) 2 1.6
Most frequent preferred terms (≥1%)			
Gastroenteritis	2 (0.8) 2 1.6	3 (1.2) 3 2.4	9 (3.5) 10 7.8
Vomiting	3 (1.1) 3 2.3	2 (0.8) 2 1.6	1 (0.4) 1 0.8
Hypoglycaemia	0	3 (1.2) 3 2.4	4 (1.6) 4 3.1
Blood glucose decreased	1 (0.4) 1 0.8	3 (1.2) 3 2.4	1 (0.4) 1 0.8

[a] Related to randomised trial product.
Abbreviations: %: percentage of subjects; E: number of events; N: number of subjects; R: event rate per 100 patient years of exposure

Post marketing experience

Novo Nordisk received the marketing authorisation of faster aspart with the trade name Fiasp during 2017 in Canada (on 06 January), in the EU (on 09 January) 2017 and in the US (on 29 September) 2017. Fiasp was approved for treatment of diabetes mellitus in adults. According to the approved label, use of Fiasp in paediatric population is considered as off-label use and as such is addressed in other safety documentation including the periodic safety update reports (PSURs).

As with all post-marketing reports, it is voluntary to report off-label use to the marketing authorisation holder.

As of 30 September 2018, the MAH has received 94 spontaneous case reports of paediatric use with Fiasp. The majority of cases were reported from EU and 6 cases originated from US. In all, 50 of the spontaneous case reports included an AE and in 4 of the cases, the patients experienced SAEs: 2 serious cases of ketoacidosis, 1 serious case of lipoatrophy, and 1 serious case with events pertaining to aggression and other behaviour disturbances.

Based on above data, no safety concerns have been raised in the paediatric population when treated with Fiasp.

2.5.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

To support safety in the paediatric population results from trial 4101 was submitted.

Exposure

The trial population included the intended paediatric T1DM population with 46 subjects in the age group 1 to <6 years, 301 subjects in the age group 6 to <12 years and 430 subjects in the age group 12 to <18 years. Within the age groups the subjects were assigned to the 3 treatment groups, mealtime faster aspart, postmeal faster aspart and mealtime NovoRapid, in a 1:1:1 ratio.

Overall, the extent of exposure of faster aspart in the paediatric population is considered acceptable. However, the total exposure (number of subjects and subject years), of the respective treatment was notable lower in the 1- to < 6 years group (n=32; 8 PYE), compared to the 6 to < 12 years (n=200; approx. 50 PYE) and 12 to < 18 years age groups (n=287; approx. 70 PYE). According to the data presented, there were only four subjects randomised to treatment with faster aspart in the ages below 3 years and at baseline the lowest age was 2 years. Thus, no safety data is available for subjects between 1 and 2 years and very limited safety data in the ages between 2 and 3 years. Further discussion regarding this issue is reflected below.

Adverse events

Common adverse events: Overall the safety profile was in accordance with the SmPC for Fiasp (and NovoRapid). Across all treatment groups the most frequently reported preferred term was '*viral upper respiratory tract infection*' (20.7%). Other frequently reported PTs were *upper respiratory tract infection*' (10.3%) and '*headache*' (8.2%). To note in this context is that "Hypoglycaemic episodes" were only to be reported as AEs if they met the definitions of SAE. The overall risk for hypoglycaemia is discussed below. As expected the AE profile differed slightly between the different age groups regarding PT within the most common SOCs and PTs. These differences reflected more the normal background differences of disease repertoires in these age groups.

In all age groups, frequency of *vomiting* was higher among subjects treated with post meal faster aspart (8.1%) compared to the mealtime faster aspart group (3.4%) and the mealtime NovoRapid group (2.7% in). The difference was higher in the two older age groups (children and adolescents above 12 years). This phenomenon has not been noticed in the development program for adult and there are no clear explanations for this increased incidence. However, vomiting is general considered more frequently occurring in children than adults. Further, none of the events was reported as serious, severe or related to study drug and that almost all subjects reporting vomiting (n=37/777) reported this only once (total number of events were 40). Thus, this finding does not warrant any further action.

Related adverse events: In total 62 AEs (of 1847) were reported as possible and/or probably related to randomised trial drug in 49 subjects. The distribution between the three treatment groups was similar 5.0%, 6.6% and 7.4% in the mealtime faster aspart, post-meal faster aspart and NovoRapid groups respectively. No marked differences were seen between the 3 treatment groups with respect to frequency or type of possibly or probably related AEs. Possibly or probably related AEs reported with a frequency ≥ 1% in any group were 'injection site reaction (n=4), 'hypoglycaemia' (n=10), 'lipohypertrophy' (n=8) and 'blood glucose decreased' (n=4). No AE was reported in a frequency > 2%.

SAEs, Death

The frequency of SAEs was reported in slightly lower frequency in subjects treated with meal faster aspart (1.9%) compared to treatment with post meal faster aspart (5%). This difference was driven by more reported diabetes related PTs such as DKA and hypoglycaemia. However, the number of subjects in each group was few and conclusions should be drawn with caution. Overall, none of the SAEs were reported by ≥ 1% of subjects, except '*gastroenteritis*' that was reported by 3 (1.2%) subjects in the NovoRapid group.

One non-treatment emergent death (drowning) was reported in the trial 11 days after last dose of NovoRapid. No death occurred in any of the two groups with faster aspart.

Hypoglycaemia

"*Severe or blood-glucose hypoglycaemic episodes*" were reported in 86.5% of the subjects with a similar distribution between the three treatment groups. However, these events were reported in a higher proportion in the youngest age group (91.3%) compared to the 6 - <12 years age group (87.7%) and the

12 - <18 years age-group (85.1%). When comparing the treatment groups within the age groups, a slightly higher rate of severe or blood-glucose confirmed hypoglycaemic episodes was noted in the two faster aspart treatment groups compared to NovoRapid treatment groups in the ages below 12. The clinical relevance of this finding is considered low.

As expected, the rate of severe or BG confirmed hypoglycaemic episodes were lower in the post-meal faster aspart group compared with the mealtime faster aspart and NovoRapid groups one and 1-2 hours after meal. However, after 2-3 and 3-4 hours after meal the rate was higher in the postmeal faster aspart group.

Overall, the rate of severe or BG confirmed nocturnal hypoglycaemic episodes was slightly higher in the postmeal faster aspart group (374 per 100 PY [48.4%]) compared to the mealtime treatment groups (308 per PYE in the mealtime faster aspart group [42.9%] and 245 per PYE with NovoRapid [40.3%]). According to the Applicant the higher rate in the post-meal faster aspart group could to some extent be explained by one subject (belonging to the 12 to <18 years age group) that reported with a high number (n=45) of nocturnal severe or BG confirmed hypoglycaemic episodes in this group.

The higher incidences of nocturnal hypoglycaemic episodes in the postmeal treatment groups in the late evening might reflect the administration of dosing after the evening meal. This is considered to be of clinical relevance and something to be cautioned about when administering faster aspart post-meal to children close to bed-time. However, the incidence of severe nocturnal hypoglycaemia was low and this risk is overall considered manageable but post-meal treatment with FIASP in the evenings should be handled special awareness due to the risk for nocturnal hypoglycaemia especially in the younger children. In addition, in clinical practice, postmeal dosing will only be an administration option and not a regime to use on a regular basis. The risk for nocturnal hypoglycaemia should be is reflected in the SmPC section 4.4.

Allergic reactions, Injection site reactions and Lipodystrophy

Overall, there was no difference in frequency of allergic reactions (in total 4%), Injection site reactions (in total 4%) and lipodystrophy (in total 2%) between the three treatment groups. These events have not been analysed across age groups. The AEs related to lipodystrophy, injections site reactions and allergic reactions were evenly distributed between the two oldest age groups (6-< 12 years and 12 to < 18 years). No or few events were reported in the youngest age group.

Antibodies

Across all 3 treatment groups, only minor changes in mean level of anti-insulin aspart specific antibodies were seen from baseline to week 12, hereafter a slight decrease between week 12 and week 26 was seen. The antibody development by age group were aligned with the results seen in the total population.

Children below 1 and 3 years

There are limited safety data of faster aspart in the ages between 2 and 3 years. However, when comparing the using of faster aspart in the youngest age group with the older ones, no new pronounced differences were noted besides a higher proportion and rate of hypoglycaemic episode in the youngest age group. Thus, albeit limited, these data indicate that the treatment with faster insulin aspart in children aged 2-3 years old also is tolerated to the same extent as the older children and adolescents.

No children in the ages 1 to < 2 years was included in the study. However, NovoRapid has the same active component as Fiasp (insulin aspart) and is since 2016 authorised, in the EU, in children above 1 year. Limited safety data is also available for NovoRapid (insulin aspart) in children aged 1-2 years, which does not indicate any differences in the safety profile in this subgroup. These data supported the extension of the indication for NovoRapid to include children from 1 year of age (EMEA/H/C/000258/II/0112). Evaluation of the present data did not identify any differences in the safety

profile of clinical significance between faster aspart and NovoRapid. Thus, there are no suspicions that safety should differ in subjects between 1 to 2 years using faster aspart compared to use of NovoRapid in this age group. However, as for all subjects and especially the youngest children, care should be taken when faster aspart is administered postmeal in evenings due to the risk for nocturnal hypoglycaemic episodes.

2.5.2. Conclusions on clinical safety

The safety profile of faster aspart in the paediatric population was in accordance with the know safety profile of Fiasp in adults and NovoRapid in adults and children above 1 year. As expected, the major risk with both treatments across all age groups was hypoglycaemia. With post-meal faster aspart treatment the risk for nocturnal hypoglycaemia tended to be higher. This is reflected in the SmPC. In addition, in clinical practice, postmeal dosing will only be an administration option and not a regime to use on a regular basis. Albeit, limited data in subjects between 2 and 3 years, the data presented indicate that the treatment with faster insulin aspart in these ages was tolerated to the same extent as the older children and adolescents. No subjects between 1 to > 2 year were included in the study. However, since no difference of clinical significance in the overall safety profile was noted between faster aspart and NovoRapid, there are no suspicions that safety should differ in subjects between 1 to 2 years using faster aspart compared to use of NovoRapid in these ages. However, as for all subjects and especially the youngest children, care should be taken if faster aspart is administered postmeal in evenings due to the possible increased risk for nocturnal hypoglycaemic episodes.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 3.1 for Fiasp is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 3.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Medication errors (mainly wrong drug administered)
Important potential risks	None
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance activities. Routine pharmacovigilance is considered sufficient to identify, characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Risk minimisation measures
Important identified risk: Medication errors (mainly wrong drug administered)	***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Product differentiation strategy: Coloured cartons, labels and plastic components of primary packaging to prevent wrong drug administration due to mix-up of different insulin products Text in SmPC, PL and IFU 1 SmPC Section 4.2 where information is given on posology and method of administration. 2 SmPC Section 4.2 where passive discouragement for withdrawing insulin with a syringe from cartridges and prefilled pens is included. It is further specified that if administration by a syringe, intravenous injection or infusion pump is necessary, a vial should be used. 3 Section 4.4 Special warnings and precautions for use where information on avoidance of accidental mix-ups is given. Additionally, advice on practical actions to minimise the risk is given, for example for patients to check the insulin label before each injection and that a syringe should never be used to draw the medicinal product from the cartridge of a pre-filled pen. 4 SmPC Section 6.6 where special precautions are given for disposal and other handling. Text/wording allowing the possibility to withdraw insulin from cartridges and prefilled pens with a syringe in case of emergency has been deleted from this section. 5 PL Section 2 with information on when the medicine should not be used, and also to check the label before use to ensure the right type of medicine is used. 6 PL Section 3 with information on how to use the product correctly. In addition, text on correct usage of Fiasp® patients with poor eyesight is also included. 7 IFU where information is given on how to handle the product including instruction to check the label to ensure the right type of insulin is used and instruction on how to avoid injection of air to ensure proper dosing and to carry a spare prefilled pen in case it is lost or damaged ***Additional risk minimisation measures:*** To increase awareness of differences between Fiasp® and Tresiba® products, a communication plan regarding the risk of mix-up between Fiasp® and Tresiba® has been prepared. The communication plan includes a direct healthcare professional communication (DHPC) addressing pharmacies and dispensing clinics. This risk minimisation is intended to be used until there are no longer any Fiasp® products on the market with only yellow colour plastic components

2.7. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated to include information on the use of Fiasp in children. The Package Leaflet (PL) is updated accordingly.

In addition, minor editorial changes are made to the PI.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fiasp (insulin aspart) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Type 1 diabetes mellitus (T1DM) is among the most common chronic diseases in children and adolescents. T1DM accounts for over 90% of all childhood and adolescent diabetes. Subjects with T1DM require lifelong treatment with insulin. Type 2 diabetes mellitus (T2DM) is becoming increasingly common in adolescents, particularly in the peripubertal period although the disease remains relatively rare apart from in minority populations. Available data suggest that preadolescent children are unlikely to have T2DM even if obese. Both T1DM and T2DM are associated with acute and chronic complications.

With this application the MAH seek to extend the indication for Fiasp to include children and adolescents from the age of 1 year.

3.1.2. Available therapies and unmet medical need

A basal-bolus insulin regimen is generally recommended for paediatric T1DM subjects aiming at resembling physiological insulin secretion. The challenge to obtain good glycaemic control in the absence of hypoglycaemia is greater in a paediatric population compared to an adult population due to growth, more variable lifestyle, need of assistance with insulin injection and hormonal changes.

Preferable, rapid-acting insulin analogues like faster aspart should be given immediately before meals. However, a significant proportion of people with diabetes regularly need to take (or be given) their dose of bolus insulin either during or after a meal, e.g. toddlers and infants where the size and composition of a meal cannot be accurately predicted in advance. This despite glycaemic control having a positive association with administration before the meal. There is a need for better documentation on the efficacy and safety when a bolus insulin is given post-meal.

3.1.3. Main clinical studies

Study 4101 data is a 26-week, randomised, partly double-blind, multicentre, multinational, active controlled, treat-to-target, 3-armed parallel-group trial with a 12-week run-in period. The trial compared effect and safety of mealtime faster aspart versus mealtime NovoRapid, 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 trial also included a 26-week open-label post-meal faster aspart dosing group in combination

with insulin degludec. Furthermore, a subgroup of children aged > 8 years took part in a CGM substudy investigating the effects of Fiasp and NovoRapid in relation to a standardised meal test.

Data is presented for the overall population (777 subjects) and for the three age groups: 1-6 years (46 subjects), 6-12 years (301 subjects) and 12-18 years (430 subjects). No children below the age of 2 years were actually included in the study. Four children aged 2-3 years were included, all in the two faster aspart groups (2 in each groups). The demographic and baseline characteristics were balanced between groups. A high proportion of subjects completed the trial (98%).

3.2. Favourable effects

The study met its primary objective as both mealtime and post-meal Fiasp was found to be non-inferior to NovoRapid (ETD -0.17 [-0.30; -0.03]95%CI and 0.13 [-0.01; 0.26]95%CI for mealtime and post-meal dosing, respectively). In both analyses the upper limit of the 95%CI was below 0.3% which is considered an acceptable non-inferiority margin. Mealtime Fiasp was also shown to be superior to NovoRapid with regards to change from baseline in HbA1c 26 weeks after randomisation (estimated treatment difference: -0.17 % [-0.30; -0.03]95% CI).

During the randomised treatment period of the study, HbA1c remained stable in the Fiasp mealtime group, whereas HbA1c slightly increased in the post-meal group and in the NovoRapid group.

The responder rates decreased in all treatment groups over the treatment period, as expected since HbA1c increased during the treatment period. No statistically significant differences were observed between the treatment groups.

When presented by age groups, it is observed that HbA1c remained stable in all treatment groups in the age group 6 to <12 years. The change in HbA1c observed in the overall population was driven by the changes in HbA1c observed in the two other age groups, i.e. children (1 - <6 years) and adolescents (12 - <18 years) respectively.

FPG remained rather stable during the study in all treatment groups. No statistically significant differences were observed.

The 8-point SMBG profiles at week 26 differed somewhat between treatment groups. The observed mean 1-hour PPG and 1-hour PPG increment were lower for mealtime faster aspart compared to NovoRapid at all individual meals (breakfast, lunch and evening meal) and for "all meals", while the post-meal faster aspart group showed higher 1-hour PPGs and PPG increments compared to NovoRapid.

For mealtime faster aspart, a statistically significant difference in favour of mealtime faster aspart over NovoRapid was found for change from baseline to week 26 in 1-hour PPG after breakfast, lunch, and "all meals" (ETD: -0.70 mmol/L [-1.14; -0.27]95% CI), but not for the main evening meal. The change from baseline to week 26 in 1-hour PPG increment was statistically significantly in favour of mealtime faster aspart after breakfast, main evening meal, and "all meals" (ETD: -0.93 mmol/L [-1.35; -0.52]95% CI) but no for the lunch meal.

For post-meal faster aspart, a statistically significant difference in favour of NovoRapid was found for change from baseline to week 26 in 1-hour PPG after lunch, main evening meal, and "all meals", as well as for change from baseline to week 26 in 1-hour PPG increment after "all meals".

The data from the CGM subgroup largely confirms the data from the 8-point SMBG profiles.

The data from the meal test show that mealtime faster aspart was comparable to NovoRapid up to 1 hour after the meal after which plasma glucose increment was higher with faster aspart. None of the differences observed in the meal test were statistically significant. Post-meal faster aspart showed less post prandial glucose control at all time points.

There were no apparent differences in either daily mean bolus, basal or total insulin dose between treatment groups at week 26.

3.3. Uncertainties and limitations about favourable effects

No children in the age group 1-2 years were included in the trial and only 4 children aged 2-3 years were included, all in the two faster aspart groups (two in each group). Thus, the efficacy data in the youngest age group is very limited but as there is no reason to believe that the PD effect is different in the youngest children, extrapolation of efficacy data from older children is acceptable.

3.4. Unfavourable effects

The total exposure (number of subjects and subject years), of the respective treatment was notable lower in the 1- to < 6 years group (n=32; 8 PYE), compared to the 6 to < 12 years (n=200; approx. 50 PYE) and 12 to < 18 years age groups (n=287; approx. 70 PYE). According to the data presented, there were only four subjects randomised to treatment with faster aspart in the ages below 3 years and at baseline the lowest age was 2 years.

The overall proportion of subjects with an AE during the study period was 76.5% and similar across the 3 treatment groups (74% -79%). Across all treatment groups the most frequently reported preferred term was '*viral upper respiratory tract infection*' (20.7%), other frequently reported PTs were *upper respiratory tract infection*' (10.3%) and '*headache*' (8.2%). "*Hypoglycaemic episodes*" were only to be reported as AEs if they met the definitions of SAE. The majority of AEs in all 3 treatment groups were non-serious (98%) and of mild or moderate severity (99%). As expected the AE profile differed slightly between the different age groups regarding PT within the most common SOCs and PTs. These differences reflected more the normal background differences of disease repertoires in these age groups.

The majority of the SAEs (in total n=18 in the two faster aspart groups) reported in the SOCs 'infections and infestations' and 'metabolism and nutrition disorders. Overall, none of the SAEs were reported by ≥ 1% of subjects in any of the two faster aspart groups.

Overall the AE profile was in accordance with the SmPC for Fiasp (and NovoRapid) without any difference of clinical significance between the three treatment groups.

"*Severe or blood-glucose hypoglycaemic episodes*" were reported in 86% of the subjects with almost a similar distribution between the three treatment groups. However, overall these events were reported in a slightly higher proportion in the youngest age group (91%) compared to the two older age groups (88% in the 6 - <12 years age group and 85% in the 12 - <18 years age-group). This difference was driven by slightly higher frequencies of subjects reporting severe or blood-glucose confirmed hypoglycaemic episodes in the two faster aspart treatment groups in the ages below 12 years (94% reported these events in subjects treated with faster aspart in the ages 1 to < 6 years and 90% in the ages 6 to < 12 years) compared to NovoRapid treatment groups in these age-groups (86% reported *Severe or blood-glucose hypoglycaemic episodes in the ages* 1 to < 6 years and 82% in the ages 6 to < 12 years).

In study NN1218-4101, a higher incidence and rate of nocturnal hypoglycaemia defined as severe or blood-glucose confirmed hypoglycaemia was reported among subjects treated with post-meal faster aspart (48.4%; 374 events per 100 PY) compared with NovoRapid (40.3%; 245 events per 100 PY) and mealtime faster aspart (42.9%; 308 events per 100 PY). However, in clinical practice, postmeal dosing will only be an administration option and not a regime to use on a regular basis. A recommendation how to handle the risk for nocturnal hypoglycaemia with postmeal dosing in the paediatric population has been inserted SmPC section 4.4.

Reassuringly, the incidence of severe nocturnal hypoglycaemic episodes was low (in total 4 events in four subjects).

ADRs related to allergic reaction, ISR, lipodystrophies and medication errors were reported in 4%, 4%, 2% and 0.7% respectively of the subject without any difference of clinical relevance between treatment or age groups.

3.5. Uncertainties and limitations about unfavourable effects

Even though, the inclusion criteria in study NN1218-4101 allowed subjects from one year to participate in the study, the minimum age at baseline across all treatment groups was 2 years. Thus, no subjects were below two years and only four children between 2 and 3 years was included. Thus, there is a limitation in exposure of Fiasp in the age span 1-3 years, which is covered in the proposed indication.

3.6. Effects Table

Table 39 Effects Table for Fiasp in the treatment of diabetes in children (data cut-off: 06 April 2018)

Effect	Short description	Unit	Fiasp meal-time	Fiasp post-meal	Novo Rapid	Uncertainties / Strength of evidence	References
Favourable Effects							
HbA1c	Change in HbA1c from baseline to week 26	%	0.05	0.35	0.23	**Treatment difference at week 26:** Faster aspart (meal) - NovoRapid (meal): -0.17 [-0.30; -0.03], p=0.014 Faster aspart (post) - NovoRapid (meal): 0.13 [-0.01; 0.26], p=0.061	Study NN1218-4101
1-h PPG	Postprandial (1-hour) glucose (SMPG) after 26 weeks	mmol/L	9.26	10.50	9.98	Change from baseline in 1-hour PPG was statistically significantly different in favour of mealtime faster aspart for 'all meals' (ETD: -0.70 mmol/L $[-1.14; -0.27]_{95\% CI}$) and for the individual meals breakfast and lunch, whereas there was no difference for the main evening meal.	Study NN1218-4101
Unfavourable Effects							
Exposure	All subjects Median (min-max)	Years	12.00 (2.0-17.0)	12.00 (2.0-17.0)	12.00 (4.0-17.0)		
Exposure	Number of subjects 1 to < 3 years	N	2	2	0	All 4 subjects completed the treatment period	Study NN1218-4101
Severe or b-glucose confirmed hypo-glycaemia	Incidence and event rate per 100 PY	% (per 100 PY)	87.4% (2791)	88.0% (2815)	84.1% (2566)	The estimated rate ratios for severe or BG confirmed hypoglycaemic episodes were 1.11 [0.90; 1.37] 95%CI for mealtime faster aspart versus NovoRapid and also 1.11 [0.90; 1.37] 95%CI for post-meal faster aspart versus NovoRapid.	Study NN1218-4101
Severe or b-glucose confirmed nocturnal hypo-glycaemia	Incidence and event rate per 100 PY	% (per 100 PY)	42.9% (308)	48,4% (477)	40.3% (313)	The estimated rate ratio for mealtime faster aspart versus NovoRapid was 1.29 [0.93; 1.79] 95%CI (p=0.13) and 1.50 [1.09; 2.08] 95% CI for postmeal faster aspart versus NovoRapid (p=0.14)	Study NN1218-4101

Abbreviations: N=number of subjects

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Subjects with T1DM require life-long insulin treatment for survival. In order to allow individualised treatment, with the aim of achieving good metabolic control, insulins with different PD profiles are needed. T1DM is rare in very young children but insulin treatment is mandatory to prevent death, irrespective of age. With the current submission, data to support the use of Fiasp in children and adolescents aged 1 year and above have been submitted.

It is well recognized that insulin treatment in diabetic subjects should, as much as possible, mimic the physiological feedback system that regulates insulin secretion by way of circulating levels of glucose. It is also known that the insulin response to glucose is normally very swift and that insulin release from the pancreas reaches a prime target of insulin action, namely the liver, within minutes by way of the portal circulation. It is therefore, theoretically at least, advantageous for patients, including children, to receive very fast acting insulin treatment which, albeit given by necessity subcutaneously (thereby bypassing the portal circulation), will as much as possible mimic physiological conditions.

Fiasp, given either before or after the meal was compared with NovoRapid given before meals and was shown superior to NovoRapid when given before meals. The clinical relevance of the treatment difference of -0.17 observed between mealtime Fiasp and NovoRapid may be debated but, considering that the mean HbA1c at baseline was rather low (7.56%), large improvements in HbA1c may be difficult to achieve, especially as the bolus insulin will mostly affect the postprandial glucose excursion. The comparison between Fiasp given after the meal with NovoRapid given before the meal, showed that post-meal dosing when used on a regular basis, is suboptimal as reflected by a numerically higher HbA1c. These data are of importance since many patients (especially young children) already take their bolus dose after the meal out of fear of hypoglycaemia. Post-meal dosing is however not to be used on a regular basis but is an option in certain situations and the SmPC has been amended to more clearly reflect this.

The study aimed at including children aged 1 to 18 years, but no children in the age group 1-2 years were included in the trial. Thus, the efficacy data in the youngest age group is very limited but as there is no reason to believe that the PD effect is different in the youngest children, extrapolation of efficacy data is acceptable.

Although only limited safety data in children aged 2 to 3 years is available, the data indicate that treatment with insulin aspart in Fiasp is comparable to that of older children and adolescents. Limited safety data is also available for NovoRapid (insulin aspart) in children aged 1-2 years, which does not indicate any differences in the safety profile in this subgroup. These data supported the extension of the indication for NovoRapid to include children from 1 year of age (EMEA/H/C/000258/II/0112).

The risk for nocturnal hypoglycaemia is always an issue for subject treated with insulin and special attention with regards to carbohydrate intake and insulin dosing in the evenings. The slightly higher risk for nocturnal hypoglycaemias with post-meal insulin aspart is considered manageable with the proposed warning in the SmPC section 4.4.

3.7.2. Balance of benefits and risks

The beneficial effects of Fiasp in the paediatric population, aged 1 to 18 years, is considered to outweigh the risks, thus the benefit risk balance is positive. The data in the youngest children is limited. Data on NovoRapid, which is already approved for use in this population provide further support for the safe use also in children from 1 year of age, as the only difference between the two products, i.e. the faster onset of action with Fiasp, has been shown to result in better glycaemic control without undue increase in the

risk of hypoglycaemias. Notably, all 46 children in the age group 1-6 years of age completed the trial on study drug, indicating that Fiasp (and NovoRapid) was well tolerated also in the youngest age groups.

3.7.3. Additional considerations on the benefit-risk balance

The indication proposed by the MAH does not specify the type of diabetes. According to the EMA "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (CPMP/EWP/1080/00 Rev. 1), extrapolation of data from adults with T2DM to children with T2DM is acceptable if efficacy and safety has been demonstrated in adults with T2DM and in children with T1DM. This issue was discussed in the SA given by CHMP in 2013. The condition of demonstrating efficacy and safety in adults with T2DM and in children with T1DM is considered fulfilled and therefore extrapolation to the paediatric T2DM population is acceptable.

3.8. Conclusions

The overall B/R of Fiasp in the treatment of children with diabetes mellitus aged 1 year and above is positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include treatment of children and adolescents aged 1 year and above based on data from the phase 3b clinical trial NN1218-4101, supported by data from the Clinical Pharmacology trials NN1218-4371 and clinical study NN1218-3888 which was included in the initial MAA.
As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC and the corresponding sections of the Package Leaflet are updated accordingly.
In addition, the Marketing authorisation holder (MAH) took the opportunity to make other non-related minor or editorial changes were implemented throughout the EU PI to increase readability/consistency.
An updated RMP version 3.1 was agreed during the procedure.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Fiasp is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1