15 November 2018
EMA/142348/2019
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

NovoRapid

insulin aspart

Procedure no: EMEA/H/C/000258/P46/048

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

Table of contents

1. Introduction

On 27th Aug 2018, the MAH submitted a completed paediatric study for NovoRapid, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH has stated that trial NN1218-4101: "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" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The formulations/products used in the current trial were suitable for paediatric subjects:

Fiasp

Faster aspart, 100 U/mL, 3 mL Penfill® (NovoPen Echo®).

NovoPen Echo® is approved for use in children and it delivers from 0.5 to 30 units of insulin in 0.5 unit increments.

The size of the needles was maximum 8 mm.

NovoRapid

Insulin aspart, 100 U/mL, 3 mL Penfill® (NovoPen Echo®).

NovoPen Echo® is approved for use in children and it delivers from 0.5 to 30 units of insulin in 0.5 unit increments.

The size of the needles was maximum 8 mm.

Tresiba

Insulin degludec, 100 U/mL, pre-filled 3 mL PDS290 pen-injector (FlexTouch®).

FlexTouch® is approved for use in children and it delivers from 1–80 units in steps of 1 unit.

The size of the needles was maximum 8 mm.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final study report for:

- Trial NN1218-4101: "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"

2.3.2. Clinical study

Description

The purpose of this trial was to evaluate the efficacy and safety profile of faster aspart (Fiasp) administered at mealtime and post-meal compared to NovoRapid/NovoLog in the paediatric population with T1DM with insulin degludec as basal insulin in all three treatment groups.

This trial included a post-meal faster aspart dosing group in order to assess whether post-meal administration could prove effective in achieving glucose control to offer a clinically acceptable treatment option. Together with the clinical pharmacology trial in children and adolescents, the current trial was conducted in order to fulfil the regulatory requirements for obtaining a paediatric indication for faster aspart.

Fiasp (faster aspart)

Fiasp is approved in all 28 EU countries and Iceland and Norway for treatment of diabetes mellitus in adults. As of 06 April 2018, Fiasp is launched in 13 out of these 30 countries.

NovoRapid (insulin aspart)

As of 06 April 2018, NovoRapid is approved and launched in all 28 EU countries and Norway and Iceland for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

*Tresiba (*insulin degludec)

Tresiba is approved in all 28 EU countries and Norway and Iceland for treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

Methods

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.

CHMP comments

The objectives are adequate.

Study 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/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 (for Serbia only: 2 years 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 1.

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/NovoLog. In this period, the investigator optimised the basal insulin on a weekly basis to individual FPG targets (Figure 1).

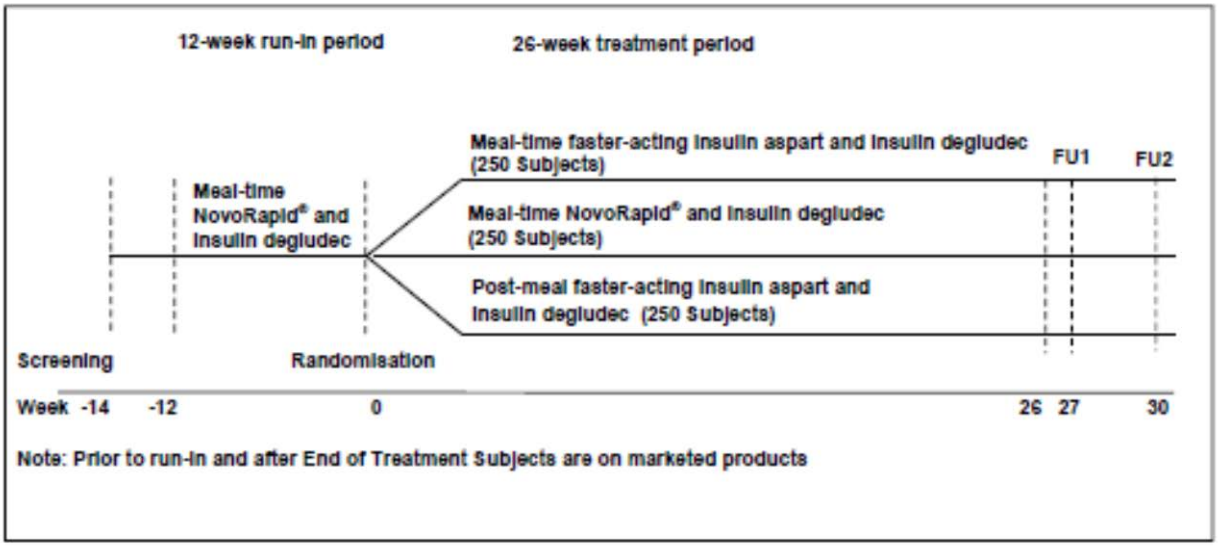
26-week treatment period

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/NovoLog, all in combination with insulin degludec (Figure 1).

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.

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 1 Trial design



CHMP comments

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.

Study population /Sample size

A total of 833 subjects were planned to enter the run-in period, and 750 subjects were planned for enrolment (enter randomised treatment). Subjects with T1DM aged 1 year to less than 18 years of age (for Serbia only: 2 years to less than 18 years of age) were enrolled.

Continuous glucose monitoring and meal test subgroup

A subgroup of approximately 150 subjects from selected sites aged ≥8 years of age at screening (visit 1) was planned to use a blinded device for CGM for at least 11 days in the periods up to 13 days before randomisation and up to 13 days before the end of the 26-week treatment period. This subgroup had 2 standardised meal tests in connection to these periods, a meal test at baseline (visit 14) and a meal test at the end-of-treatment (after 26 weeks, visit 40).

CHMP comments

The study population covers the paediatric population aged 1 year and above. A subgroup of children aged 8 years and above took part in a CGM substudy investigating the effects of Fiasp and NovoRapid in relation to a standardised meal test.

Treatments

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

- *Basal insulin*: Insulin degludec
- *Bolus insulin*: Faster aspart (test product) or NovoRapid/NovoLog (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.

CHMP comments

Insulin degludec (basal insulin) was administered according to label.

Bolus insulin

Timing of dosing: In the run-in period, all subjects received NovoRapid/NovoLog as bolus insulin. In the treatment period, subjects received mealtime faster aspart, post-meal faster aspart or mealtime NovoRapid/NovoLog 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/NovoLog) 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/NovoLog. Subjects received diabetes training including training in carbohydrate counting. NovoRapid/NovoLog 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/NovoLog.
- 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.

CHMP comments

NovoRapid was administered according to label (in close relation to the meal). Fiasp was also administered according to the recommendations approved for the adult population.

Dose titration recommendations were in place and are considered adequate.

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

CHMP comments

The endpoints are considered adequate. In addition, responder rates were provided.

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/NovoLog, 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/NovoLog, 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/NovoLog (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/NovoLog (step 2), respectively superiority of mealtime faster aspart vs mealtime NovoRapid/NovoLog (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.

CHMP comments

Statistical methods appear 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.

Results

Recruitment / Number analysed

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/NovoLog.

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/NovoLog (258 subjects). All 777 randomised subjects were exposed to trial product (Table 1).

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/NovoLog group.

A similar proportion of subjects completed both the trial and treatment period in each treatment group (Table 1).

Table 1 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 2).

Table 2 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/NovoLog group (Table 1).

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 1).

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/NovoLog group. No subjects withdrew from the trial due to an AE (Table 1).

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/NovoLog group. An overview of the reasons for withdrawal is shown in Table 1.

Screen failures

A total of 933 subjects were screened, of which 99 subjects were screening failures (Table 1). 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).

Data sets analysed

Table 3 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

CHMP comments

The recruitment targets were met. A high proportion of subjects completed the trial (98%), with no major imbalances between treatment groups. Due to the small number of subjects aged 1 to 3 years (n=4), only data for the larger subgroup (1 to 6 years of age, n=46) is presented. Premature discontinuations were few and evenly distributed between groups. No subjects discontinued due to AEs.

Baseline data

Demographics and baseline characteristics

Overall, the 3 treatment groups were similar with respect to demographics and baseline characteristics (Table 4, Table 5).

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/ (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/NovoLog 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 4 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 5 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

CHMP comments

The demographic and baseline characteristics were balanced between groups. European subjects were adequately represented.

Exposure

Run in

During the 12-week run-in, the patients were switched from their previous insulin treatment to insulin degludec once daily and mealtime NovoRapid/NovoLog. Exposure in the run-in period was 60.3 subject years for both the mealtime and post-meal faster aspart groups and 59.9 subject years for the

NovoRapid/NovoLog group. Thus, in total the exposure of NovoRapid during this period was 180.4 subject years.

In the treatment period, the total exposure was 128.4 subject years for the mealtime faster aspart group and 127.7 subject years for both the post-meal faster aspart and NovoRapid/NovoLog groups (Table 6).

Treatment period

The total observation time was 152.2 subject years for the mealtime faster aspart group, 151.0 subject years for the post-meal faster aspart group and 150.9 subject years for the NovoRapid/NovoLog group.

In total, 45.7% were exposed to trial products 25-26 weeks and 51.9% were exposed > 27 weeks.

There were no notable differences across the 3 treatment groups with regard to extent of exposure.

Within each age group, no differences with regard to extent of exposure or the observation time were seen between the 3 treatment groups (Table 7).

Table 6 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 7 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.

CHMP comments

A comparable exposure was observed for all treatment groups, with no apparent difference when analysed by age group.

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 (Table 8).

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.

Table 8 Summary of important protocol deviations at subject level

PD category	Site level (number of PDs)	Subject level (number of PDs)					Total
		Screen and run-in failures	Mealtime faster aspart	Post-meal time faster aspart	Mealtime NovoRapid®/ NovoLog®	Total no of subject level PDs	
Informed consent	5	24	36	24	38	122	127
Inclusion/exclusion/randomisation criteria	-	7	5	4	7	23	23
Trial product handling	7	2	24	19	24	69	76
Treatment compliance	1	1	17	27	13	58	59
Assessment deviations	8	3	131	127	148	409	417
Other	53	10	62	65	57	194	267
Total	**94**	**47**	**275**	**266**	**287**	**875**	**969**

Abbreviations: PD = protocol deviation

CHMP comments

The protocol deviations have been accounted for. The number of PDs related to informed consent was rather high. According to the MAH, the site personnel were retrained on the informed consent procedure and missing or incorrect informed consent forms were corrected.

Efficacy results

Primary endpoint – change from baseline in HbA1c 26 weeks after randomisation

Run-in

During the run-in period, all subjects were treated with insulin degludec and NovoRapid/NovoLog. 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/NovoLog (Figure 2).

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.

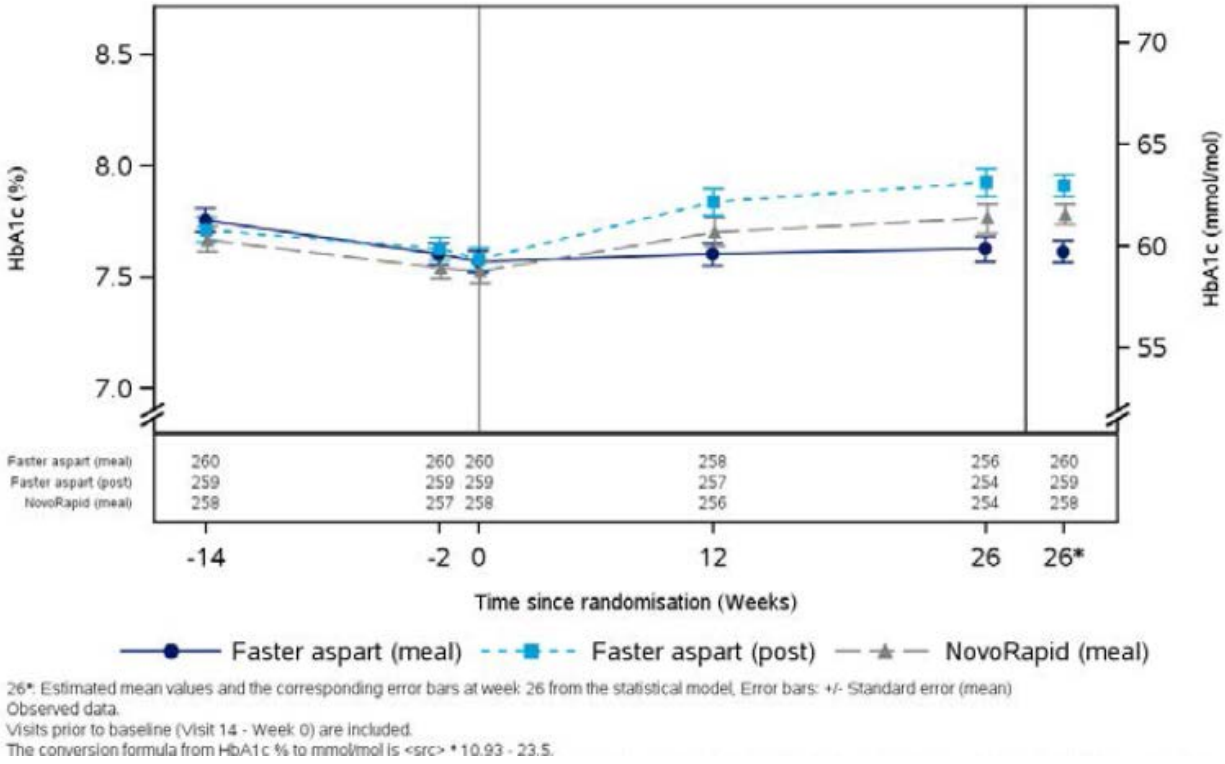
CHMP comments

HbA1c decreased slightly in all treatment groups and all ages during the 14 weeks run-in phase.

Week 26

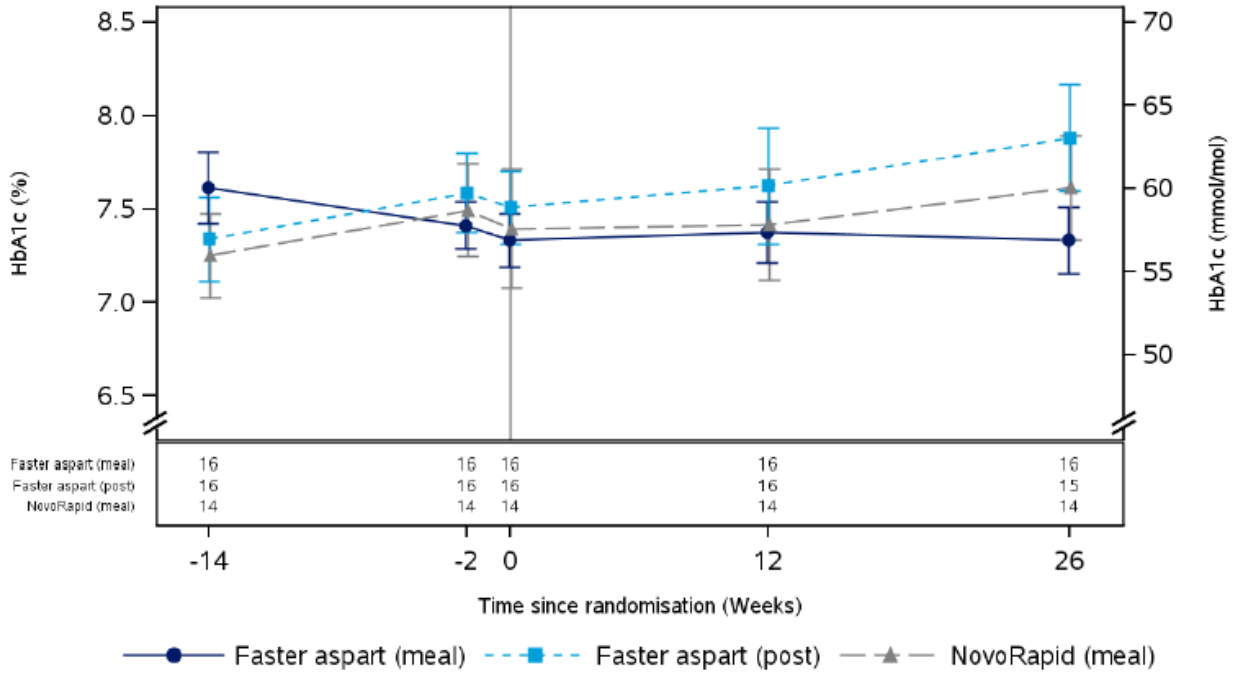
After 26 weeks of treatment, the observed mean HbA1c (at "last in-trial visit") in the mealtime faster aspart group remained stable compared to baseline (from 7.57% at randomisation to 7.63% [59.88 mmol/mol]), whereas the observed mean HbA1c increased slightly in the post-meal faster aspart (from 7.58% to 7.91% [62.97 mmol/mol]) and NovoRapid/NovoLog (from 7.53% to 7.76% [61.30 mmol/mol]) groups compared to baseline (Figure 2).

Figure 2 HbA1c by treatment week - observed mean and lsmean plot - in-trial (FAS)



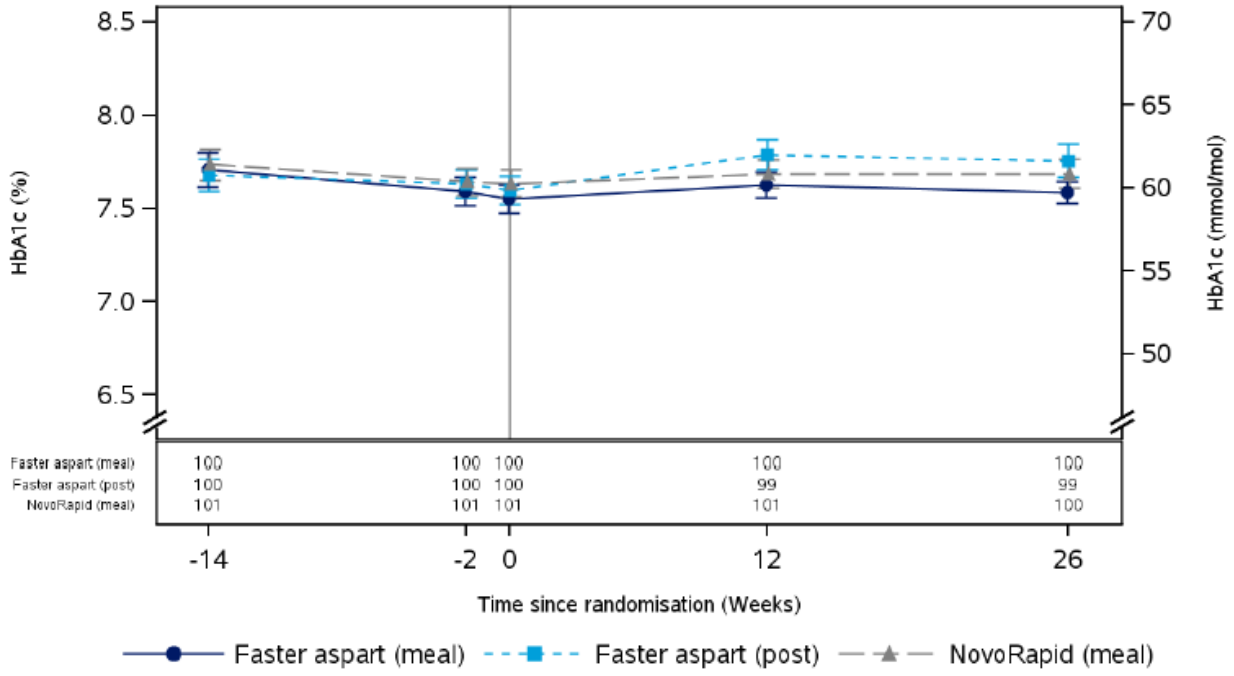
In the age group 6 to <12 years, all 3 treatment groups appeared stable in observed mean HbA1c from baseline to week 26 with no other differences between age groups observed (Figure 3, Figure 4 and Figure 5).

Figure 3 HbA1c by treatment week - mean plot - in-trial - children (1 - <6 years) - full analysis set



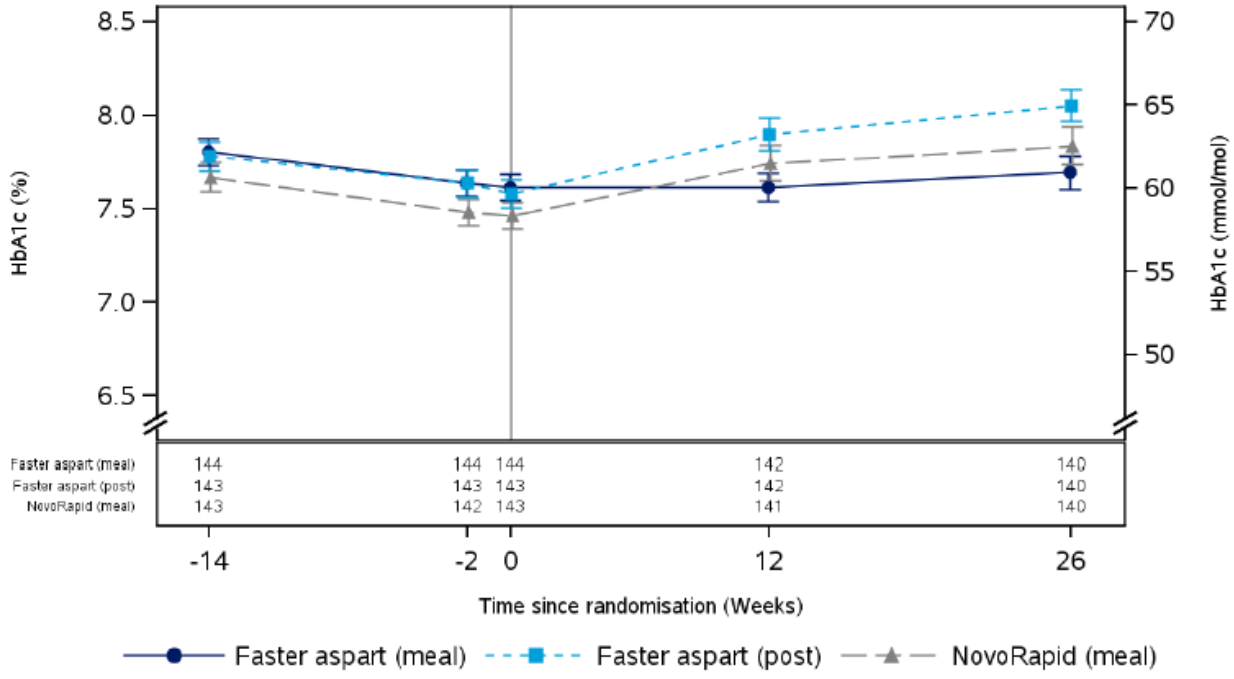
Error bars: +/- Standard error (mean)
Observed data.
Visits prior to baseline (Visit 14 - Week 0) are included.
The conversion formula from HbA1c % to mmol/mol is <src> * 10.93 - 23.5.

Figure 4 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 5 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.

CHMP comments

In the overall population HbA1c remained stable in the Fiasp mealtime group, whereas HbA1c 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. Differences in change in HbA1c was more apparent between the three treatment groups in the two other age group i.e. children (1 - <6 years) and adolescents (12 - <18 years) respectively.

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/NovoLog (Table 9 and Figure 2).

The estimated treatment difference 26 weeks after randomisation was -0.17 %-points (-1.82 mmol/mol) between mealtime faster aspart and NovoRapid/NovoLog and 0.13 %-points (1.40 mmol/mol) between post-meal faster aspart and NovoRapid/NovoLog (Table 9).

Table 9 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/NovoLog and unconditional switch to NovoRapid/NovoLog). 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/NovoLog.

A tipping point analysis were also performed for step three in the hierachical testing procedure, superiority of meal time faster aspart compared to NovoRapid/NovoLog, 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 10).

Table 10 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.

CHMP comments

The study met its primary objective as both mealtime and post-meal Fiasp was found to be non-inferior to NovoRapid. 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).

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 11). 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/NovoLog (OR: 1.33 [0.87; 2.01]) or between post-meal faster aspart and NovoRapid/NovoLog (OR: 0.66 0.43; 1.02]).

There was also no statistically significant difference between faster aspart and NovoRapid/NovoLog 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 11 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.

CHMP comments

The responder rates decreased in all treatment groups over the treatment period.

Supportive secondary efficacy endpoints

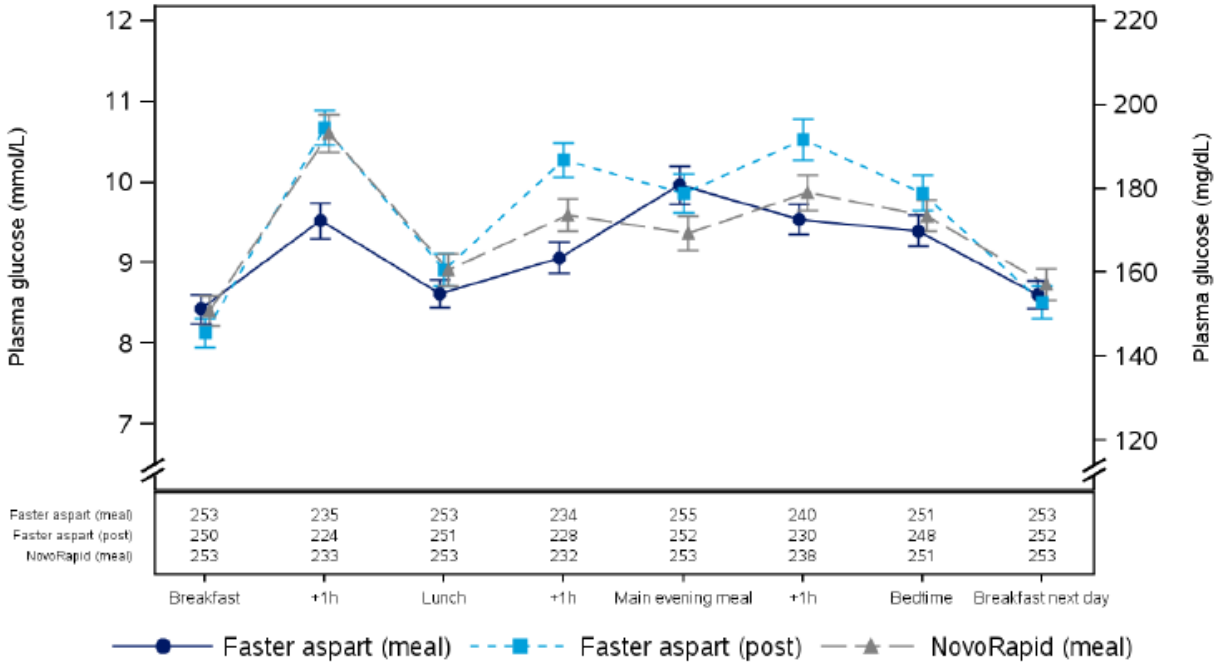
8-point self-measured plasma glucose profiles including postprandial glucose and postprandial glucose increment

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/NovoLog (Figure 6). With post-meal faster aspart, the observed mean SMPG was higher at 1 hour after lunch and main evening meal compared to NovoRapid/NovoLog at 26 weeks after randomisation.

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

Figure 6 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.

CHMP comments

The 8-point SMBG profiles at week 26 differed somewhat between treatment groups. Mealtime Fiasp showed lower BG-levels after meals compared to NovoRapid, whereas higher BG-levels after lunch and main evening meal was observed with post-meal Fiasp compared to NovoRapid.

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/NovoLog 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/NovoLog.

- 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/NovoLog.
- 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/NovoLog.

For mealtime faster aspart, a statistically significant difference in favour of mealtime faster aspart over NovoRapid/NovoLog 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/NovoLog 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).

CHMP comments

Analyses of the postprandial glucose and postprandial glucose increment confirm the pattern observed in the 8-point profiles.

Fluctuation in the 8-point profile

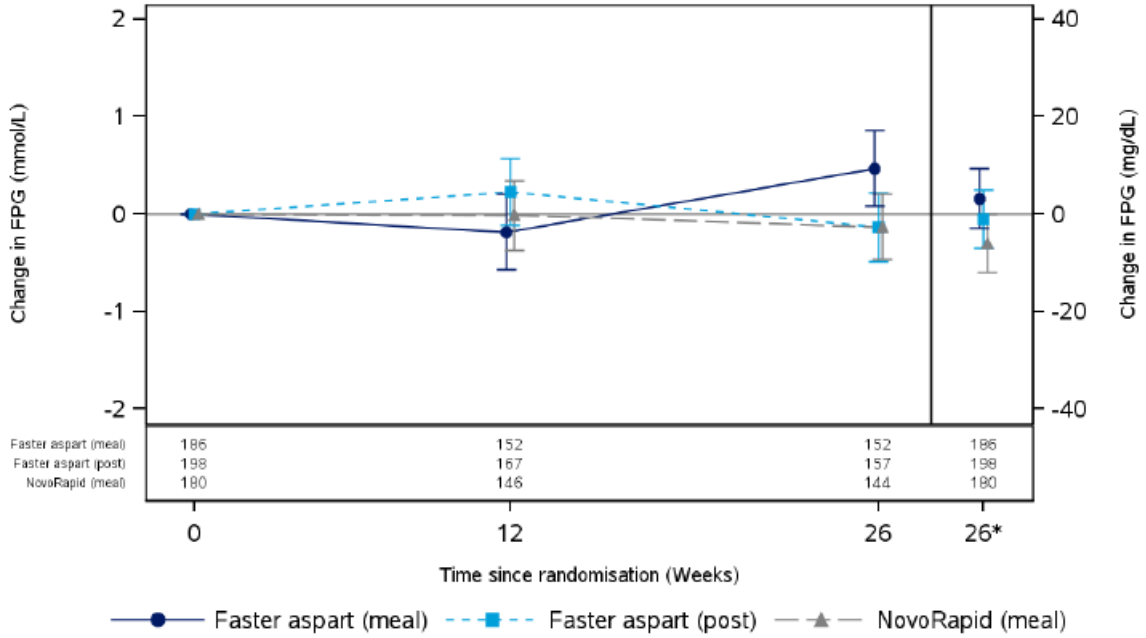
At week 26, there were no statistically significant differences in the fluctuation in the 8-point profile (SMPG) for mealtime faster aspart versus NovoRapid/NovoLog or for post-meal faster aspart versus NovoRapid/NovoLog.

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/NovoLog. 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/NovoLog (Figure 7). There was no statistically significant difference between mealtime faster aspart and NovoRapid/NovoLog or post-meal faster aspart and NovoRapid/NovoLog 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 7 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.

CHMP comments

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

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/NovoLog (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/NovoLog, respectively. The change from baseline to week 26 in 1.5-anhydroglucitol with mealtime faster aspart was statistically significantly different from that with NovoRapid/NovoLog (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/NovoLog (ETD: -0.29 µg/mL [-0.73; 0.14]95% CI).

CHMP comments

The largest increase in 1,5-anhydroglucitol was observed in the post-meal Fiasp treated group, however no statistically significant difference versus NovoRapid was observed. The increase in 1,5-anhydroglucitol was significantly lower in the mealtime Fiasp treated group compared to NovoRapid.

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/NovoLog. No apparent differences between treatment groups were identified among the observed doses at each main meal.
- The mean daily basal insulin dose at week 26 was 21.6 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/NovoLog.
- 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/NovoLog.

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/NovoLog).

CHMP comments

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

- 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/NovoLog.

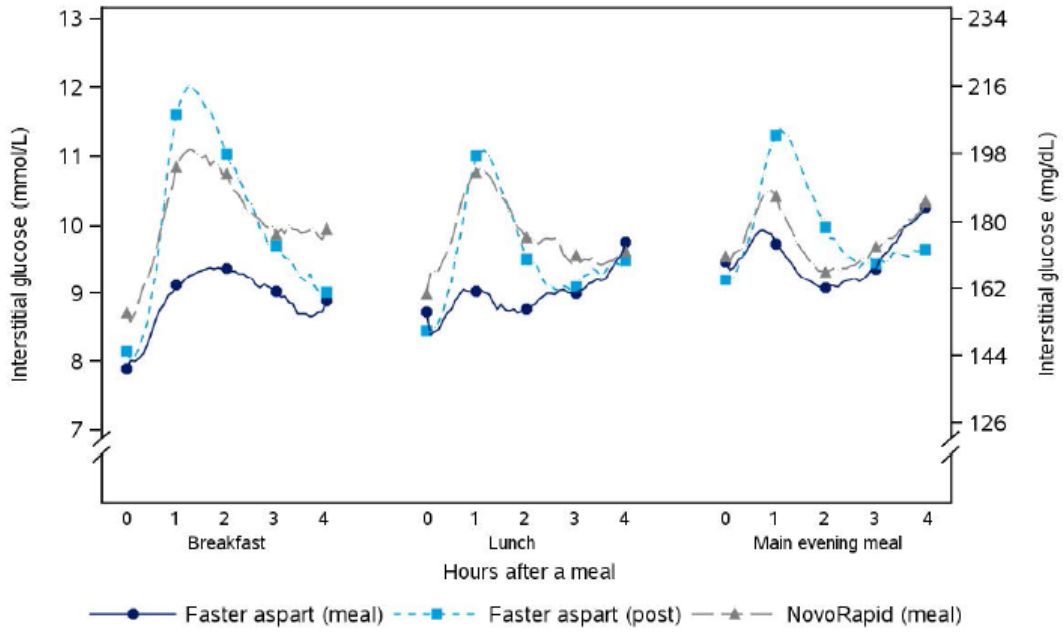
There were no observed differences in incidence of episodes or percentage of time spend with low IG (IG ≤2.5, 3.0, 3.9 mmol/l [45, 54, 70 mg/dL]) and high IG (IG >10.0, 12.0, 13.9 mmol/l [180, 216, 250 mg/dL]) between the 3 treatment groups at week 26, or in change from baseline to week 26 in mean of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

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/NovoLog 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/NovoLog at week 26.

Figure 8 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.

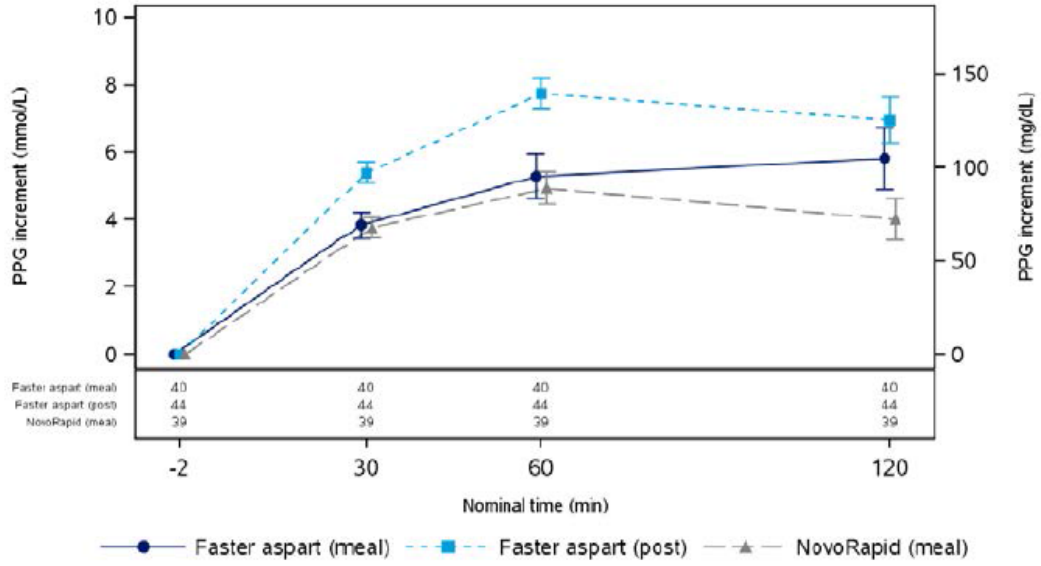
CHMP comments

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

Postprandial glucose and postprandial glucose increment (meal-test)

At week 26, the observed mean PPG profiles were similar for mealtime faster aspart and NovoRapid/NovoLog, whereas the post-meal faster aspart profile was higher at all time points (30-min, 60-min and 120-min) when compared with NovoRapid/NovoLog. A similar profile was seen for the mean PPG increment (Figure 9).

Figure 9 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/NovoLog 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/NovoLog at all 3 time points for both PPG and PPG increment (meal test).

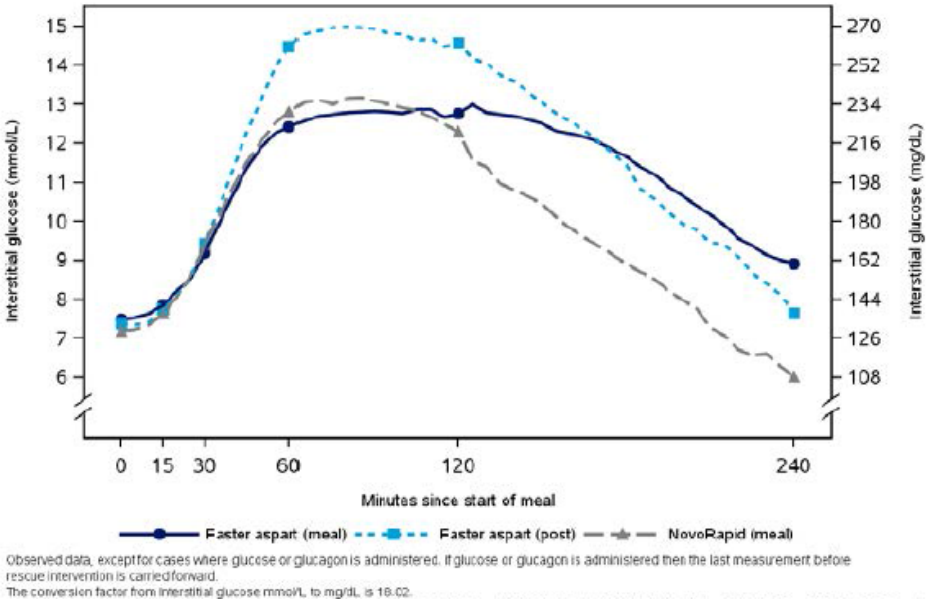
CHMP comments

The data from the meal test show that mealtime Fiasp was comparable to NovoRapid up to 1 hour after which the increment was higher with Fiasp. Post-meal Fiasp showed less prandial glucose control at all time points.

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

There were no statistically significant differences between mealtime faster aspart and NovoRapid/NovoLog 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/NovoLog 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 10).

Figure 10 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/NovoLog, was statistically significantly different in favour of NovoRapid/NovoLog, whereas no difference was seen between post-meal faster aspart and NovoRapid/NovoLog.

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

CHMP comments

The prandial IG data confirms the data on PPG and PPG increment.

Safety results

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/NovoLog groups respectively reported AEs. The AE rate with mealtime faster aspart, post-meal faster aspart and NovoRapid/NovoLog was 448.6, 531.1 and 464.5 per 100 PYE (Table 12).

The majority of AEs in all 3 treatment groups were non-serious (1812 of 1847 events [98%]) and of mild or moderate severity (1830 of 1847 events [99%]). The proportion of subjects with severe AEs was comparable between the treatment groups 1.1% (n=4), 2.7% (n=7) and 1.2% (n=3) of subjects in the mealtime faster aspart, post-meal faster aspart and NovoRapid/NovoLog groups (Table 12).

The majority of AEs were assessed by the investigator as unlikely related to randomised trial product (1753 of 1847 events [95%]) or basal component (1772 of 1847 events [96%]).

Table 12 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.

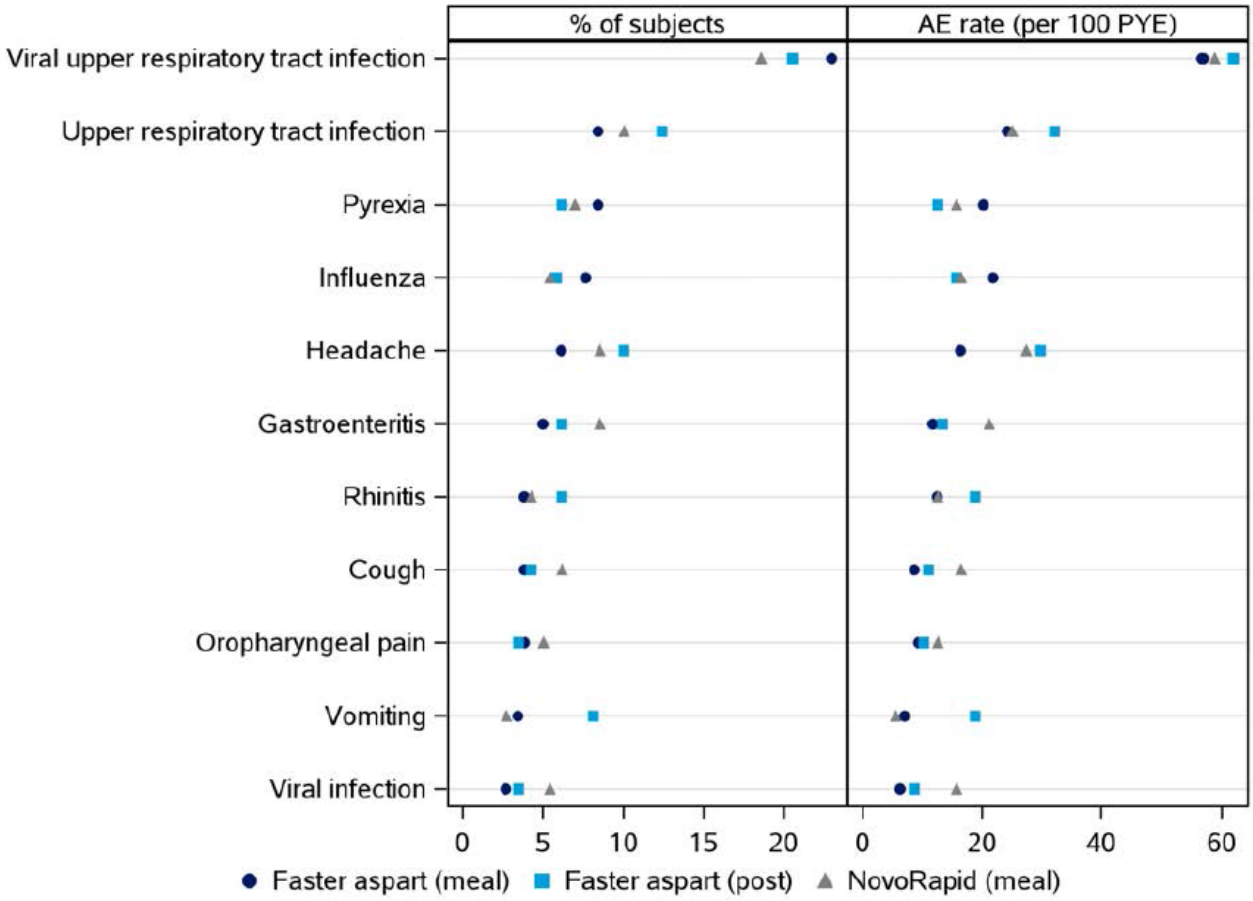
Most common adverse events

The most frequent AEs (by SOC) in all treatment groups were 'infections and infestations', 'gastrointestinal disorders', 'respiratory, thoracic and mediastinal disorders', 'general disorders', 'administration site conditions' and 'nervous system disorders' .

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/NovoLog 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/NovoLog groups, respectively (Figure 11). There were no clinically relevant differences across the treatment groups with respect to the most frequently reported AEs.

In each of the 3 age groups, the majority of AEs were reported within the SOCs 'infections and infestations' and 'gastrointestinal disorders' (Table 13). 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).

Figure 11 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 13 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

CHMP comments

Overall, there were no differences regarding most common AEs of clinical significance between the three treatment groups. 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.

Adverse events by relation to trial products

Faster aspart or NovoRapid/NovoLog (bolus insulin)

In total 62 AEs (of1847) were reported as possibly or probably related to randomised trial in 49 subjects (6.3%). 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/NovoLog 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).

In all, 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/NovoLog 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 were considered to be 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.

Basal insulin (insulin degludec)

In all, 40 AEs reported by 34 (4.4%) subjects and with a rate of 10.4 events per 100 PYE were assessed as probably related to basal insulin and 34 AEs reported by 30 (3.9%) subjects with a rate of 8.9 events per 100 PYE were assessed as possibly related to basal insulin.

Deaths and other serious adverse events

Death

One non-treatment emergent death (drowning) was reported in the trial. A patient drowned during the second follow-up period (study day 195).

The subject was randomised to NovoRapid/NovoLog treatment. The death occurred 11 days after the last dose of randomised treatment. The relation to trial products was considered unlikely by both the investigator and NovoNordisk A/S.

Serious adverse events

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/NovoLog group.

The majority of SAEs were reported in the SOCs 'infections and infestations' and 'metabolism and nutrition disorders'. However, the number of events within these SOCs was infrequently reported with a total of 10 events in 9 (1.2%) subjects in each of the SOCs. None of the SAEs were reported by ≥ 1% of subjects, except 'gastroenteritis' that was reported by 3 (1.2%) subjects in the NovoRapid/NovoLog group

In total, 7 SAEs were considered probably related to randomised trial product; 2 events in the mealtime faster aspart group ('accidental overdose' and 'hypoglycaemia'), 4 events in the post-meal faster aspart group ('accidental overdose' [2 events] and 'hypoglycaemic unconsciousness' [2 events] and 1 event in the NovoRapid/NovoLog group ('hypoglycaemia'). None of the SAEs was reported as possible related to study drug.

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/NovoLog in the age group 12 to < 18 years).

CHMP comments

The SAEs reported as probably related to study drug (n=7) were all related to events in association with hypoglycaemia.

Adverse events leading to withdrawal from the trial

No subjects withdrew from the trial due to an AE.

Adverse events leading to permanent discontinuation of trial product

No subjects discontinued trial product prematurely due to an AE

Adverse events leading to dose reduction

In total 46 events were leading to dose reduction. 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 14).

Table 14 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.

Adverse event of special interest

Injection site reactions

In all, 59 injection site reactions reported by 33 (4.2%) subjects were identified by the NNMQ search; 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/NovoLog group. The majority of AEs related to injection site reactions were unlikely related to randomised trial product and all were non-serious and of mild severity. Additionally, 15 AEs (5 in the mealtime faster aspart group, 4 in the post-meal faster aspart group and 6 in the NovoRapid/NovoLog) were reported by the investigator as injection site reactions, but were not caught in the NNMQ search.

CHMP comments

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

Lipodystrophy

The NNMQ search identified 17 events of lipodystrophy 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/NovoLog group. 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

CHMP comments

Lipodystrophy is a known risk for both faster aspart and NovoRapid and labelled in the current SmPCs.

Allergic reactions

The NNMQ search identified 38 allergic reactions reported by 30 (3.9%) subjects. In all, 17 reactions were reported by 13 (5.0%) subjects in the mealtime faster aspart group, 8 reactions by 8 (3.1%) subjects in the post-meal faster aspart group and 13 reactions by 9 (3.5%) subjects in the NovoRapid/NovoLog group.

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

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

CHMP comments

Urticaria is labelled in the current SmPC.

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 12). All hypoglycaemic episodes were also classified according to ADA classification (Figure 13).

Figure 12 Novo Nordisk classification of hypoglycaemia in paediatrics

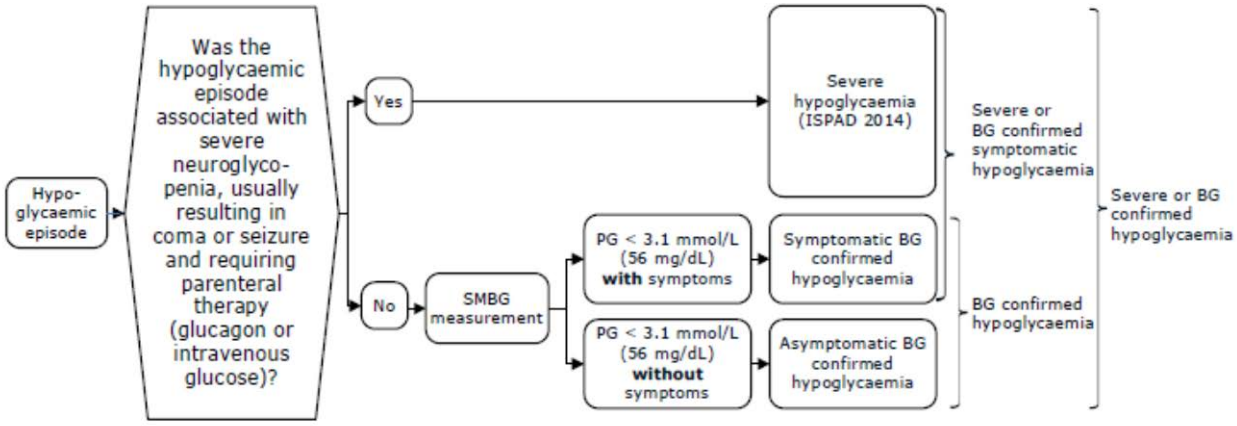
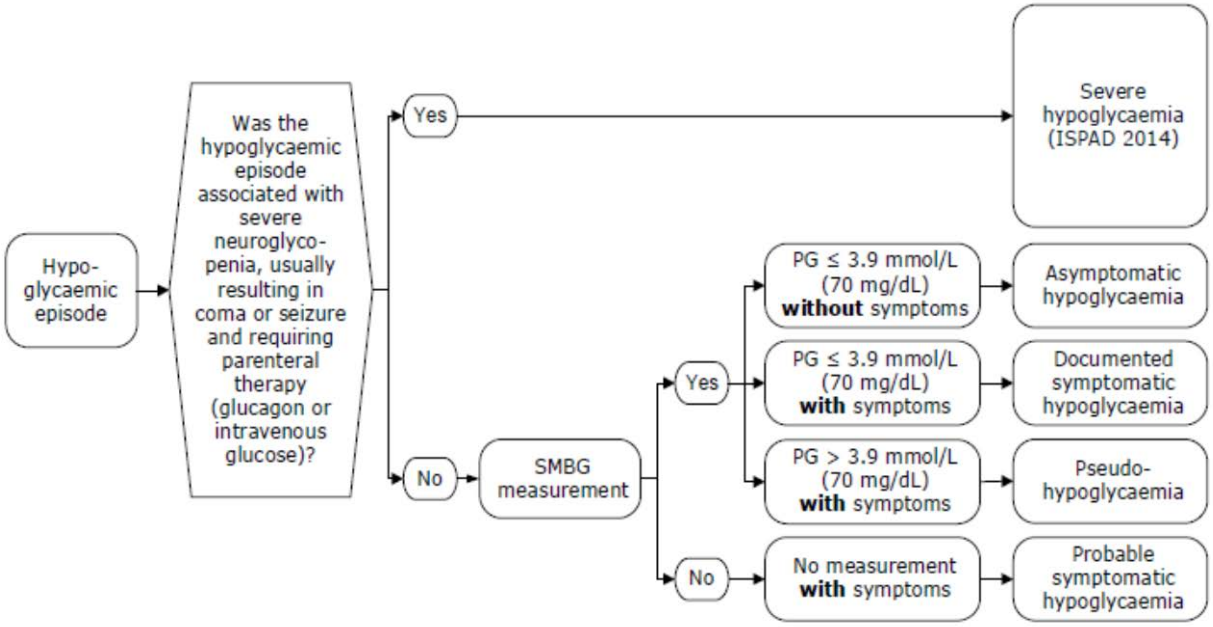


Figure 13 American Diabetes Association classification of hypoglycaemia in paediatrics



Run in period

The overall proportion of subjects reporting non-treatment emergent hypoglycaemic episodes during the 12-week run-in period was 96.9% (753 events), with an event rate of 8791 episodes per 100 PYE.

The overall number of *severe hypoglycaemic episodes* (ADA/ISPAD) was 14 (1.8%) and similar for subjects later randomised to mealtime faster aspart (6 episodes reported by 6 [2.3%] subjects), post-meal faster aspart (5 episodes reported by 4 [1.6%] subjects) and NovoRapid/NovoLog (5 episodes reported by 4 [1.6%] subjects.

A similar proportion of subjects in the 3 age groups had non-treatment emergent hypoglycaemic episodes; however, the event rate was slightly higher for subjects in the age groups 1 to < 6 years (100.0%; 9381 episodes per 100 PYE) and 6 to < 12 years (97.7%; 9682 episodes per 100 PYE) compared to the age group 12 to < 18 years (96.0%; 8107 episodes per 100 PYE).

26 week treatment period

- Overall hypoglycaemic episodes

The proportion of subjects with hypoglycaemic episodes was similar for mealtime faster aspart, post-meal faster aspart and NovoRapid/NovoLog (96.2%, 96.9% and 96.5% of subjects). The observed rate was slightly lower for NovoRapid/NovoLog (6973 episodes per 100 PYE) compared to mealtime faster aspart and post-meal faster aspart (7556 and 7481 episodes per 100 PYE) (Table 15).

Table 15 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

Overall, in all 3 treatment groups the number of severe hypoglycaemic episodes was comparable 3 (1.1%), 8 (3.1%) and 4 (1.6%) between the mealtime faster aspart, post-meal faster aspart and NovoRapid/NovoLog groups respectively (Table 15).

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.

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/NovoLog 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/NovoLog groups).

- Severe or blood glucose confirmed hypoglycaemic episodes

Incidence of events

In total, 10543 severe or blood glucose confirmed hypoglycaemic episodes (episodes that is severe according to the ISPAD classification or BG confirmed by a PG value <3.1 mmol/L [56 mg/dL] with symptoms consistent with hypoglycaemia) were reported in 672 (86.5%) of the subjects. The proportion of subjects reported severe or BG confirmed hypoglycaemic episodes in the mealtime faster aspart group was 87.4% of subjects, in the post-meal faster aspart group 88.0% of subjects and in the NovoRapid/NovoLog group 84.1% of the subjects (Table 15).

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/NovoLog and also 1.11 [0.90; 1.37]95%CI for post-meal faster aspart versus NovoRapid/NovoLog.

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

Number of episodes

The distribution of the number of severe or BG confirmed hypoglycaemic episodes was similar across the 3 treatment groups; approximately half (50%) of the subjects experienced 10 or less severe or BG confirmed hypoglycaemic episodes.

Age groups

Across age groups and in each treatment group, no pronounced differences in proportion of subjects with severe or BG confirmed hypoglycaemic episodes were seen, whereas the rate was higher in the age groups 1 to < 6 years and 6 to < 12 years than in the age group 12 to < 18 years in the faster aspart groups. In the NovoRapid/NovoLog group, the rate was higher in the age group 6 to < 12 years compared to the other age groups (Table 16).

Table 16 Severe or blood glucose confirmed hypoglycaemic episodes by age group

	Faster aspart (meal)			Faster aspart (post)			NovoRapid (meal)		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Severe or BG confirmed hypoglycaemic episodes[a]									
1 to < 6 years	15 (93.8)	243	3031	15 (93.8)	289	3616	12 (85.7)	163	2331
6 to < 12 years	88 (87.1)	1540	3042	93 (93.9)	1490	3018	83 (82.2)	1472	2942
12 to < 18 years	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 <3.1 mmol/L (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

CHMP comments

Overall a slightly higher incidence of severe or blood-glucose confirmed hypoglycaemic episodes were noted in the faster aspart treatment groups compared to NovoRapid treatment groups in the ages below 12 and especially below 6 years.

Symptomatic episodes

The majority (6863 of 10453 episodes [66%]) of all "severe or BG confirmed hypoglycaemic episodes" were symptomatic and the majority (9267 of 10453 episodes [89%]) of all severe or BG confirmed hypoglycaemic episodes occurred in the daytime.

Daytime episodes

A similar proportion of subjects reported daytime "severe or BG confirmed hypoglycaemic episodes" in the mealtime faster aspart, post-meal faster aspart and NovoRapid/NovoLog groups (86.6%, 86.8% and 84.1%) (Table 17).

Table 17 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

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/NovoLog groups (42.9% and 40.3%) (Table 17). 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.

The number of severe or BG confirmed hypoglycaemic episodes per subject accumulated at a similar rate in the 3 treatment groups.

CHMP comments

A higher proportion of subjects experienced nocturnal severe or BG confirmed hypoglycaemic episodes in the faster aspart post-meal treatment group compared to the meal time dosing 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/NovoLog groups (93 and 82 episodes per 100 PYE) (Table 18).

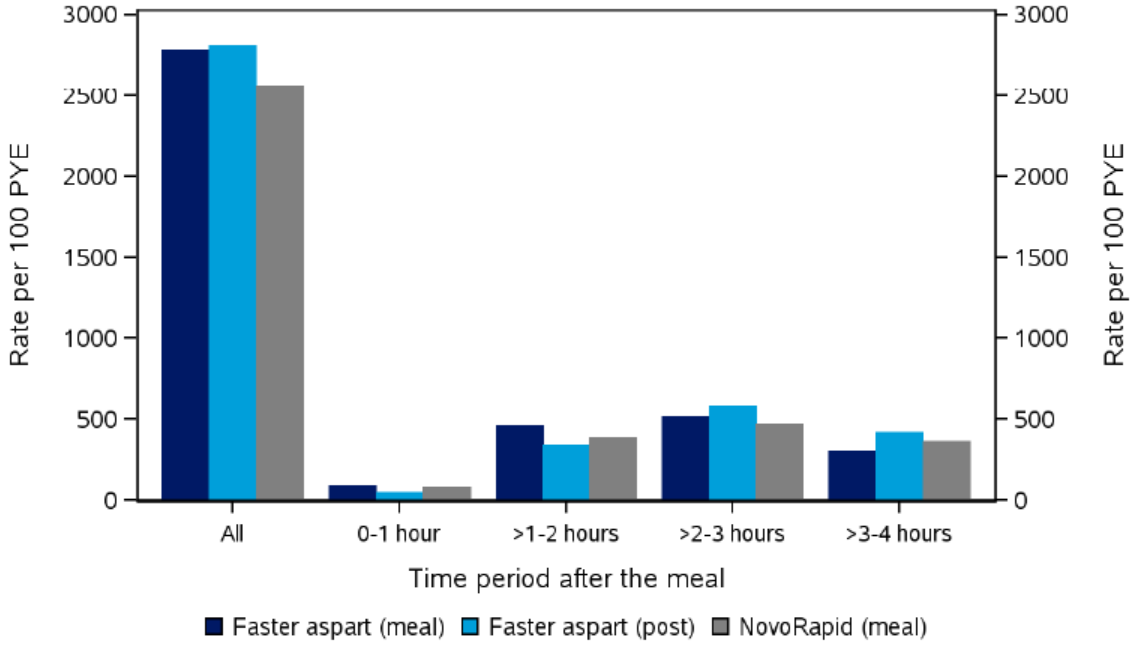
Table 18 Severe or blood glucose confirmed hypoglycaemic episodes related to meals – treatment emergent – summary – on-treatment – safety analysis set

	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).

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 was lower than for the 2–3 hour interval in all treatment groups (Table 18 and Figure 14).

Figure 14 Severe or blood glucose confirmed hypoglycaemic episodes distribution of meal related rates



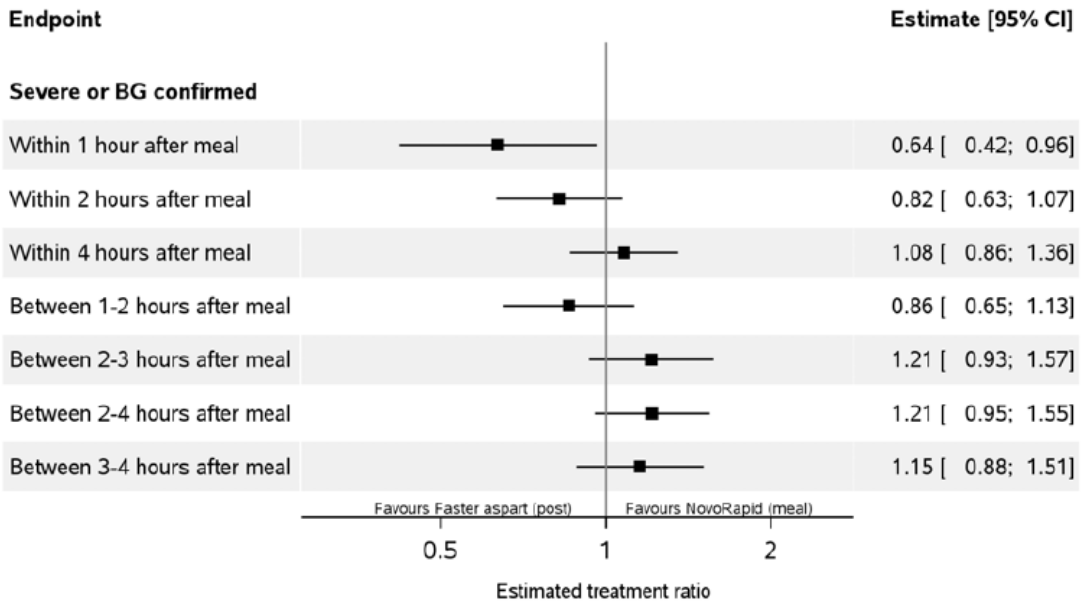
All: Total amount of severe or bg confirmed hypoglycaemic episodes, BG: Blood glucose
Treatment emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period.
Episodes with missing time stamps or with missing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

No statistically significant difference was seen between mealtime faster aspart and NovoRapid/NovoLog 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/NovoLog; the estimated rate ratio was 0.64 [0.42; 0.96]95% CI) (Figure 15).

No statistically significant differences were seen between post-meal faster aspart and NovoRapid/NovoLog 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.

Figure 15 Severe of blood glucose confirmed hypoglycaemic episodes related to meals - Faster aspart (post) / NovoRapid (meal) - forest plot - on-treatment - full analysis set (post-hoc analysis)

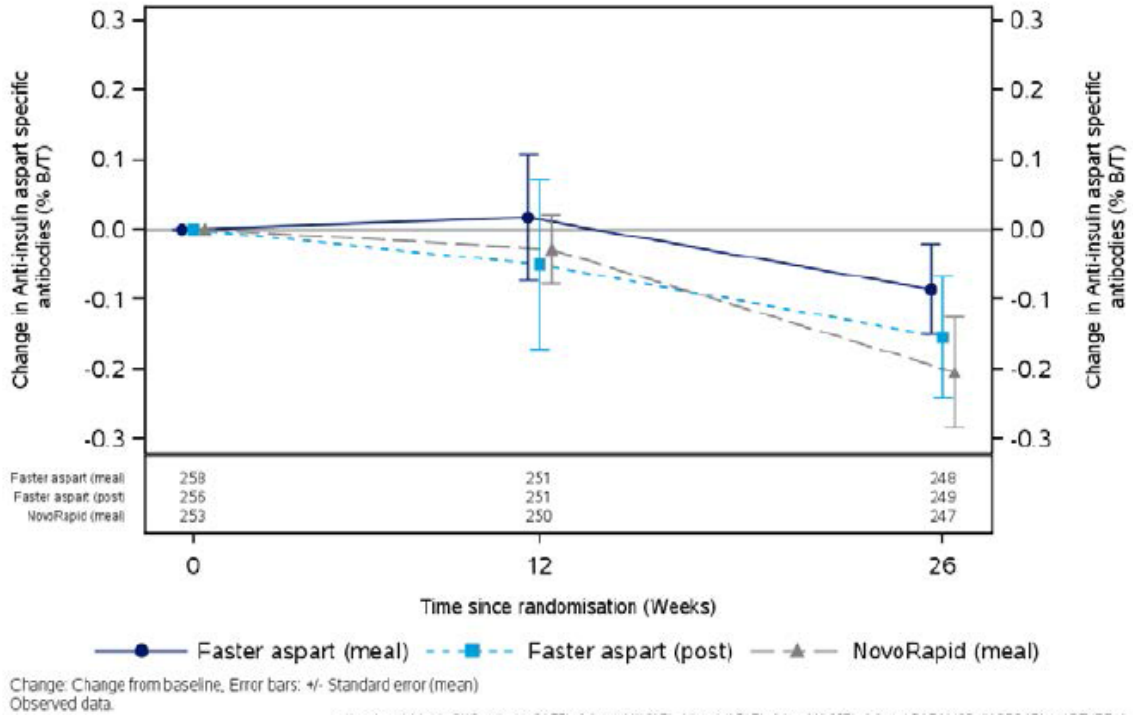


BG: Blood glucose, CI: Confidence interval
Estimate: Estimated treatment ratio

Antibodies

Overall, there were no differences in mean anti-insulin aspart specific antibodies, mean anti-insulin aspart antibodies cross-reacting to human insulin, and mean total anti-insulin aspart antibodies (specific and cross-reacting with human insulin) across the 3 treatment groups at baseline and after 12 and 26 weeks of treatment.

Figure 16 Anti-insulin aspart specific antibodies by treatment week - change from baseline



CHMP comments

The anti-insulin aspart antibodies decreased in all treatment groups over time.

Medication errors

During the on-treatment period, 6 medication errors were reported by 6 (0.8%) subjects; 3 events were reported by 3 (1.1%) subjects in the mealtime faster aspart group, 2 events were reported by 2 (0.8%) subjects in the post-meal faster aspart group and 1 event was reported by 1 (0.4%) subject in the NovoRapid/NovoLog 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'.

Physical examination, vital signs and laboratory assessments

There were no clinically relevant differences from baseline to week 26 across treatment groups in physical examination, vital signs or other laboratory assessments.

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/NovoLog group.

No statistically significant differences between either the faster aspart group and NovoRapid/NovoLog were shown.

2.3.3. Discussion on clinical aspects

The MAH has submitted a completed paediatric study for faster aspart (Fiasp) including treatment with NovoRapid as comparator. The purpose of this trial was to evaluate the efficacy and safety profile of faster aspart (Fiasp) administered at mealtime and post-meal compared to NovoRapid/NovoLog in the paediatric population with T1DM with insulin degludec as basal insulin in all three treatment groups. NovoRapid is currently approved for children aged 1 year and above.

Together with the clinical pharmacology trial in children and adolescents, the current trial was conducted in order to fulfil the regulatory requirements for obtaining a paediatric indication for faster aspart (Fiasp). A thorough assessment of the study will be made within the upcoming procedure. This report mainly focuses on the additional paediatric data provided for NovoRapid and the potential implications for the product information.

The data submitted concerns 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/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 (for Serbia only: 2 years 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. 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. 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 total 777 subjects were included in the study. The study population covers the paediatric population aged 1 year and above. All insulins were administered according to label. Fiasp was administered according to the recommendations approved for the adult population.

Statistical methods appear 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.

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 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. 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). The responder rates decreased in all treatment groups over the treatment period, as expected since HbA1c increased during the treatment period.

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. Mealtime Fiasp showed lower BG-levels after meals compared to NovoRapid, whereas higher BG-levels after lunch and main evening meal was observed with post-meal Fiasp compared to NovoRapid. Analyses of the postprandial glucose and postprandial glucose increment confirm the pattern observed in the 8-point profiles. 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 Fiasp was comparable to NovoRapid up to 1 hour after which the increment was higher with Fiasp. Post-meal Fiasp showed less prandial glucose control at all time points. The prandial IG data confirms the data on PPG and PPG increment.

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

Safety

All subjects (n=777) later randomised to the treatment period were exposed to NovoRapid (as bolus insulin) during the 12 week run-in period (in total 160 subject years). During the treatment period 258 subjects were exposed to mealtime NovoRapid with an exposure rate of 150.9 subject years.

Overall the safety profile was in accordance with the SmPC for Fiasp, NovoRapid and Tresiba and there were no differences of clinical importance between the three treatment groups (faster aspart meal-dosing, faster aspart post-meal and NovoRapid). 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 repertoires in these age groups.

In total, AEs were reported as possibly or probably related to NovoRapid in 19 subjects (7.4%) including one SAE. 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. One non-treatment emergent death (drowning) was reported in a subject randomised to NovoRapid treatment.

In total, the proportion of subjects with hypoglycaemic episodes was 96.5% and similar for mealtime faster aspart, post-meal faster aspart and NovoRapid/NovoLog. Severe or blood-glucose hypoglycaemic episodes were reported in 86.5% of the subjects with a similar distribution between the three treatment groups. However, in the ages below 12 and especially below 6 years a slightly higher incidence of severe or blood-glucose hypoglycaemic episodes were noted in the faster aspart treatment groups compared to NovoRapid treatment groups. This pattern was also noted for severe hypoglycaemia which was reported in total in 1.9%.

Hypoglycaemic episodes in relation to meals showed a similar pattern for mealtime Fiasp and NovoRapid, with a slightly lower rate observed with NovoRapid except for 3-4 hours after the meal. With post-meal Fiasp a somewhat different pattern was observed, with a higher rate of hypoglycaemias 2-3 hours and 3-4 hours after the meal.

A similar proportion of subjects reported daytime “severe or BG confirmed hypoglycaemic episodes” in the mealtime faster aspart, post-meal faster aspart and NovoRapid/NovoLog groups (84-87%). However, 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/NovoLog groups (42.9% and 40.3%). This was mainly seen in the evening from 22:00 to 01:00 and in the morning from 6:00 to 7:00. The higher incidences in the late evening might reflect the administration of dosing after the meal. This might be of clinical relevance and something to be cautioned about when administered post-meal to children close to bed-time.

Overall, no new safety issues were identified for use of NovoRapid in the paediatric population and the AE profile for the study was in accordance with the SmPC for insulin aspart.

The results of the current trial do not change the benefit risk profile of NovoRapid in the paediatric population.

3. Rapporteur’s overall conclusion and recommendation

The safety and efficacy in the paediatric population for NovoRapid is already established. The results of the current trial did not identify any change in efficacy or new safety issues. The benefit risk profile of the product remains unchanged.

☒ **Fulfilled:**

No regulatory action required.