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SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support 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/P46/044

Note

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

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Rapporteur's assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

NovoRapid

International non-proprietary name: Insulin aspart

Procedure no.: EMA/H/C/258/P46 044

Marketing authorisation holder (MAH): Novo Nordisk A/S

Rapporteur:	Kristina Dunder
Start of the procedure:	22 February 2015
Date of this report:	24 March 2015
Deadline for Rapporteur's AR:	24 March 2015
Deadline for CHMP member's comments:	8 April 2015
Date of the Rapporteur's final report:	13 April 2015

Administrative information

Invented name of the medicinal product:	NovoRapid
INN (or common name) of the active substance(s):	Insulin aspart
MAH:	Novo Nordisk A/S
Currently approved Indication(s)	NovoRapid is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.
Pharmaco-therapeutic group (ATC Code):	Drugs used in diabetes. Insulins and analogues for injection, fast-acting. ATC code: A10AB05.
Pharmaceutical form(s) and strength(s):	
Rapporteur: Rapporteur's contact person: Name of the Assessor:	**Kristina Dunder** Tel: +46 18 17 46 69 Email: kristina.dunder@mpa.se **Carola Ryner** Tel: +46 18 18 36 64 Email: carola.ryner@mpa.se **Malin Filler (pharmacokinetics)** Tel: +46 18 17 47 04 Email: malin.filler@mpa.se **Annika Ekbom Schnell (clinical)** Tel: +46 18 17 42 29 Email: annika.ekbomschnell@mpa.se
Product PTL:	**Name: Antonio Cherchi** Email: antonio.cherchi@ema.europa.eu

1. Introduction

On 14 January 2015, 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 stated that the paediatric trial NN1218-3888 was conducted as part of the currently ongoing development programme for a new faster-acting insulin aspart formulation. In trial NN1218-3888, NovoRapid was selected as comparator.

NovoRapid (insulin aspart) is approved for the treatment of type 1 and 2 diabetes mellitus (T1DM and T2DM) in adults (including pregnant women), adolescents and children aged 2 and above. The first marketing authorisation was granted on 07 Sep 1999 in the European Union (EU), and for use in children aged 2 and above on 30 Mar 2005.

There is no paediatric investigational plan (PIP) for NovoRapid. The use of NovoRapid in children and adolescents has been studied in a number of clinical trials.

In this report, only data relevant for the assessment of efficacy and safety of NovoRapid in the paediatric population is discussed. Evaluation of the full clinical trial report will be conducted at submission of the marketing authorisation application for faster-acting insulin aspart.

2.2. Information on the pharmaceutical formulation used in the study

NovoRapid (insulin aspart), 100 U/mL solution provided in a 3 mL PDS290 pen-injector. The batch number was CP50922. The formulation includes glycerol, phenol, metacresol, zinc chloride, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide (for pH adjustment), and water for injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study NN1218-3888, a randomised, single-centre, double-blind, single-dose, two-period cross-over trial investigating the pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid in a meal-test setting, in children (6−11 years), adolescents (12−17 years) and adults (18−64 years) with T1DM.

2.3.2. Clinical study

NN1218-3888 - A Trial Investigating the Pharmacokinetic Properties of FIAsp (fast-acting insulin aspart) in Children, Adolescents and Adults with Type 1 Diabetes

Description

This was a randomised, single-centre, double-blind, single-dose, two-period cross-over trial investigating the pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid in a meal-test setting, in children (6−11 years), adolescents (12−17 years) and adults (18−64 years) with T1DM.

Methods

Objective(s)

Primary objective:

- To compare the total exposure of faster-acting insulin aspart between children, adolescents and adult subjects with type 1 diabetes.

Secondary objectives:

- To compare the maximum concentration of faster-acting insulin aspart between the three different age groups.
- To compare the pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid between the three different age groups.
- To compare the effects of age on faster-acting insulin aspart pharmacokinetic and pharmacodynamic properties with the effects of age on NovoRapid pharmacokinetic and pharmacodynamic properties.
- To compare the early pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart vs. NovoRapid in children and adolescents with type 1 diabetes.
- To assess the safety and tolerability of faster-acting insulin aspart in children, adolescents and adult subjects with type 1 diabetes.

Assessor's comment:

This assessment report focuses on the pharmacokinetic and pharmacodynamic properties of insulin aspart, administered as NovoRapid, in children and adolescents in comparison to previous data.

The MAH does not suggest any changes to the product information based on the results.

Study design

This was a randomised, single-centre, double-blind, single-dose, two-period, cross-over trial investigating the pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart and NovoRapid in children, adolescents and adults with type 1 diabetes. Each subject was randomly allocated to a treatment sequence consisting of two dosing visits during which the subject received a single subcutaneous injection of either faster-acting insulin aspart or NovoRapid at a predefined fixed dose level (0.2 U/kg bw) in connection to intake of a standardised meal (meal test).

Immediately after (as soon as possible and no later than 2 minutes after) trial product administration, a standardised liquid meal (BOOST® Nestlé/Novartis Medical Nutrition; macronutrient distribution: 68% carbohydrates, 17% protein, 15% fat) was given to the subject and consumed within 8 minutes after dosing. The amount of BOOST® given was adjusted to the subject's weight. The subject then refrained from eating until 6 hours after dosing (end of the meal test).

Blood samples for determination of blood-glucose were collected during the meal test until 6 h post-administration. Blood-samples for determination of insulin in serum were taken up to 12 hours after drug-administration.

Free (PEG-precipitated) serum insulin aspart was measured using a validated insulin aspart specific enzyme-linked immunosorbent assay (ELISA).

Assessor's comment:

In general the study design appears acceptable.

The bioanalytical report or validation reports could not be found in the dossier. This may be overlooked for this application.

Sample size

The trial was a descriptive one, and, thus, the number of subjects needed to complete the trial was set to 12 in each of the three age groups without any formal sample size calculation, in accordance with current guidelines.

Treatments

Each subject received a single subcutaneous dose of either fast-acting insulin aspart or NovoRapid in a randomised, double-blinded manner at a dose-level of 0.2 U/kg bw.

The subjects were instructed to comply with the requirements for their diabetes treatment prior to each of the dosing visits (visit 2–3). Three days (72 hours) prior to trial product administration, subjects using insulin degludec were switched to NPH insulin, and 2 days (48 hours) prior to trial product administration, subjects using insulin detemir or insulin glargine were switched to NPH insulin, according to individual dosing instructions provided by the investigator. The last injection of NPH insulin or other intermediate-acting insulin products was to take place at least 22 hours prior to trial product administration.

At the dosing visits, the subjects were to meet at the site the evening before dosing, in order to receive an overnight infusion of human soluble insulin (Actrapid) until the morning of the dosing day in order to achieve stable plasma glucose concentration.

Outcomes/endpoints

Pharmacokinetics

The pharmacokinetic parameters included $AUC_{IAsp,0-12\ h}$, $AUC_{IAsp,0-15min}$, $AUC_{IAsp,0-30min}$, $AUC_{IAsp,0-1h}$, $AUC_{IAsp,0-90min}$, $AUC_{IAsp,0-2h}$, $C_{max,IAsp}$, onset of appearance$_{IAsp}$, time to 50 % $C_{max,Iasp}$.

Pharmacodynamics

The pharmacodynamic parameters included $\Delta PG_{av,0-1h}$, $\Delta PG_{av,0-2h}$, $\Delta PG_{av,0-6h}$, PG_{1h}, PG_{2h}, ΔPG_{max} (0–6 hours), PG_{max} (0–6 hours), tPG_{max} (0–6 hours), PG_{min} (0–6 hours).

Statistical Methods

The primary endpoint as well as the secondary PK/PD endpoints were each analysed by means of a linear mixed model with treatment and period as fixed effects and subjects as random effect. For all the PD endpoints, $PG_{Pre\text{-}dose}$ was added as a covariate. For the two PK endpoints onset of $appearance_{IAsp}$ and time to 50% $C_{max,Iasp}$, and for all PD endpoints the model was chosen to be additive whereas it was multiplicative for all other endpoints. When the PK endpoints were derived, compartmental modelling was used as an aid wherever applicable. All safety endpoints were listed and summarized using descriptive statistics.

Results

Recruitment / Number analysed

A total of 55 subjects were screened, of whom 41 were randomised. The most common reasons for screening failure were not having a total daily insulin treatment of < 1.2 (I)U/kg/day (inclusion criterion 5) and not having a total daily bolus insulin treatment of ≥ 0.3 and < 0.7 (I)U/kg/day (inclusion criterion 6).

All but one of the randomised subjects were exposed to trial products; this unexposed subject was withdrawn from the trial prior to visit 2, day 1 due to violation of dosing day exclusion criterion 13. Two further subjects were withdrawn from the trial after visit 2, following exposure to trial product (faster-acting insulin aspart in both cases): one subject was withdrawn due to there being difficulties in taking blood samples on a rescheduled dosing visit, whilst the other subject withdrew as it was not possible for him to attend a rescheduled dosing visit 3 necessitated by a deviation in the storage temperature affecting the trial product on the original date. The remaining 38 subjects were exposed to both faster-acting insulin aspart and NovoRapid and completed the trial.

Table 1 Subject disposition

	Children N (%)	Adolescents N (%)	Adults N (%)	Total N (%)
Screened				55
Screening failures				14
Randomised	13 (100.0)	13 (100.0)	15 (100.0)	41 (100.0)
Exposed	12 (92.3)	13 (100.0)	15 (100.0)	40 (97.6)
Withdrawals	1 (7.7)	0 (00.0)	2 (13.3)	3 (7.3)
Protocol violation	0 (00.0)	0 (00.0)	1 (6.7)	1 (2.4)
Other	1 (7.7)	0 (00.0)	1 (6.7)	2 (4.9)
Completed trial	12 (92.3)	13 (100.0)	13 (86.7)	38 (92.7)
Safety analysis set	12 (92.3)	13 (100.0)	15 (100.0)	40 (97.6)
Full analysis set	12 (92.3)	13 (100.0)	15 (100.0)	40 (97.6)

N: Number of subjects, %: Percentage of subjects
One subject who completed the trial was randomised in error. All data for this subject was used.

Baseline data

All randomised and exposed subjects were of race group White. There were more females (n=8) than males (n=4) in the children age group, whilst this was reversed in the adult group (4 females and 11 males). The distribution in the adolescent group was more equal, with 6 females and 7 males. The mean age was 10.4 years in the children age group (age range 9−11 years), 15.1 in the adolescent group (age range 13−17 years), and 20.2 in the adult group (age range 18−25 years). Ten of the

children were assessed as prepubertal (Tanner stage 1) and 2 as pubertal (Tanner stage 2 or above), and in the adolescent group, 1 was assessed as prepubertal and 12 as pubertal. The mean body weight was 40.7 kg (range 32.8-57.0 kg) in children, 62.4 kg (range 44.1-87.8 kg) in adolescents and 74.6 kg (range 54.4-105.7 kg) in adults.

The mean duration of diabetes was 6.1, 6.9 and 8.9 years for the children, adolescent and adult groups, respectively, reflecting the young mean age of the adult group. Mean observed HbA1c values were lowest in children (7.7%), with the adult group having a mean value of 7.9%, and adolescents having the highest mean of 8.1%.

Assessor's comment:

The age range in the paediatric patient group was very narrow, only including children aged 9-11. The adult patient group was relatively young with an age range of 18-25 years.

Efficacy results

Pharmacokinetic results

Mean profiles for serum insulin aspart concentration after administration of NovoRapid is presented in Figure 1 and Figure 2 below.

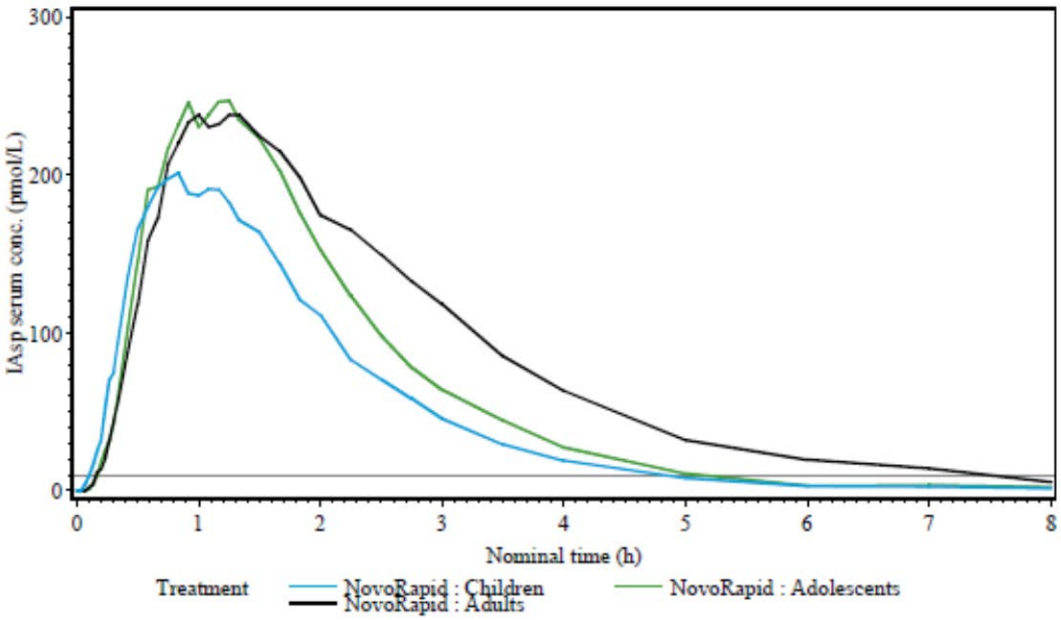

Figure 1 Mean serum insulin aspart profiles (NovoRapid) 0-8 hours.

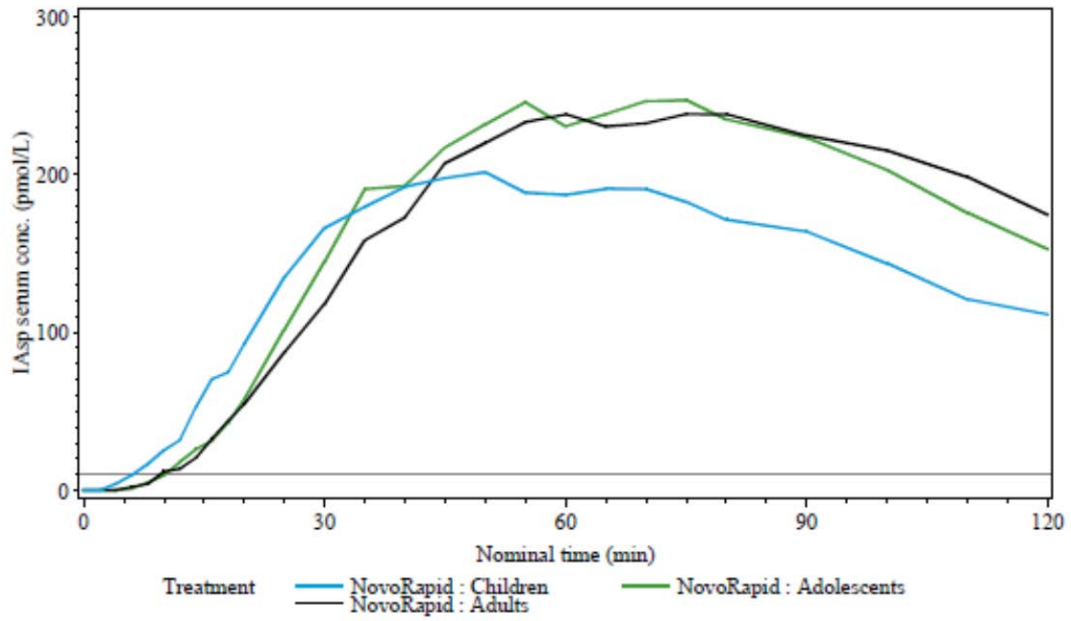

Figure 2 Mean serum insulin aspart profiles (NovoRapid) 0-2 hours.

Onset of appearance

The estimated onset of appearance of NovoRapid in children (9.83 minutes) and in adolescents (10.99 minutes) did not statistically significantly differ to that estimated for adults (12.28 minutes; Fieller age group ratio with children 0.80 [0.57;1.08]95% CI; Fieller age group ratio with adolescents 0.89 [0.72;1.12]95% CI). See Table 2.

The estimated time to 50% C_{max} following administration of NovoRapid in children (30.93 minutes) was not statistically significantly different to that estimated in adults (37.01 minutes; Fieller age group ratio 0.84 [0.64;1.06]95% CI), but was statistically significant for adolescents (31.27 minutes) compared to adults (Fieller age group ratio: 0.84 [0.72;1.00]95% CI). See Table 2.

Table 2 Statistical analysis of onset of appearance and time to 50% of C_{max}, NovoRapid.

	N	Estimate	95% CI
Onset of Appearance (min)			
LSMeans			
NovoRapid : Children	12	9.83	
NovoRapid : Adolescents	13	10.99	
NovoRapid : Adults	13	12.28	
Age group difference			
NovoRapid : Children - Adults		-2.45	[-5.63;0.73]
NovoRapid : Adolescents - Adults		-1.29	[-3.79;1.20]
Fieller age-group ratio			
NovoRapid : Children / Adults	12	0.80	[0.57;1.08]
NovoRapid : Adolescents / Adults	13	0.89	[0.72;1.12]
Time to 50% cmax (min)			
LSMeans			
NovoRapid : Children	12	30.93	
NovoRapid : Adolescents	13	31.27	
NovoRapid : Adults	13	37.01	
Age group difference			
NovoRapid : Children - Adults		-6.08	[-13.96;1.79]
NovoRapid : Adolescents - Adults		-5.74	[-11.42;-0.06]
Fieller Treatment Ratio			
NovoRapid : Children / Adults	12	0.84	[0.64;1.06]
NovoRapid : Adolescents / Adults	13	0.84	[0.72;1.00]

N: Number of subjects contributing to analysis, CI: Confidence interval
A linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method.

Early insulin exposure

None of the AUCs covering the first 2 hours of the meal test ($AUC_{IAsp\ 0\text{-}15min}$, $AUC_{IAsp,\ 0\text{-}30min}$, $AUC_{IAsp,\ 0\text{-}1h}$, $AUC_{IAsp,\ ,0\text{-}1½h}$ and $AUC_{IAsp,\ 0\text{-}2h}$) were statistically significantly different between children and adults, or between adolescents and adults.

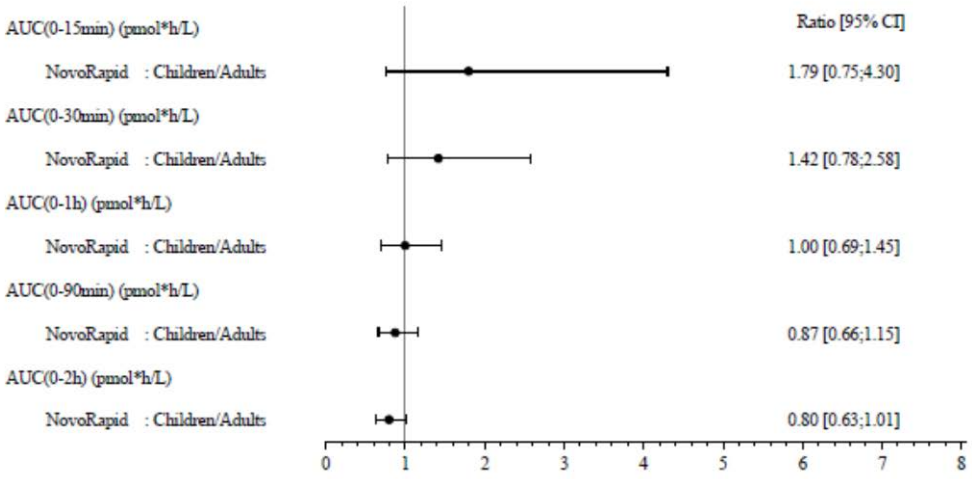

Figure 3 Plot of statistical analyses of insulin aspart early AUC endpoints, NovoRapid (children / adults).

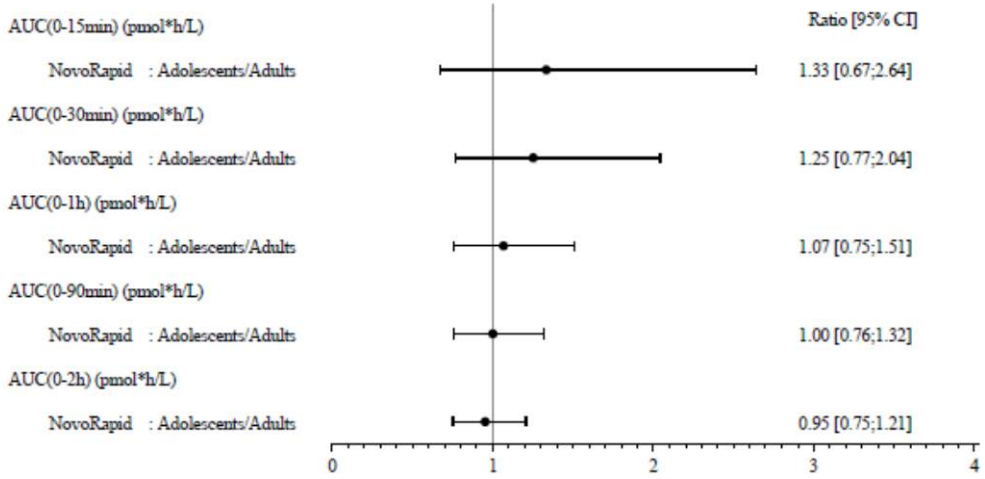

Figure 4 Plot of statistical analyses of insulin aspart early AUC enpoints, NovoRapid (adolescents / adults).

Total insulin exposure

Estimated total exposure to NovoRapid was 411.88 pmol*h/L in children, 515.16 pmol*h/L in adolescents and 689.07 pmol*h/L in adults, meaning that total exposure was approximately 40% lower in children and 25% lower in adolescents compared to adults when dosed at 0.2 U/kg body weight, and these differences were significant. The mean absolute dose in the children group (8.3 U) was 47% lower than that in the adult group (15.6 U), and in the adolescent group (12.8 U) it was 18% lower than that in the adult group.

The maximum serum insulin aspart concentration for NovoRapid was similar between children and adults (age group ratio 0.91 [0.70;1.18]95% CI), and between adolescents and adult (age group ratio 0.91 [0.71;1.17]95% CI).

Table 3 Statistical analysis of total exposure and maximum concentration, NovoRapid.

		N	Estimate	95% CI
AUC(0-12h) (pmol*h/L)				
LSMeans				
NovoRapid	: Children	12	411.88	
NovoRapid	: Adolescents	13	515.16	
NovoRapid	: Adults	13	689.07	
Age group ratio				
NovoRapid	: Children/Adults		0.60	[0.51;0.70]
NovoRapid	: Adolescents/Adults		0.75	[0.65;0.87]
Cmax (pmol/L)				
LSMeans				
NovoRapid	: Children	12	254.41	
NovoRapid	: Adolescents	13	254.82	
NovoRapid	: Adults	13	280.01	
Age group ratio				
NovoRapid	: Children/Adults		0.91	[0.70;1.18]
NovoRapid	: Adolescents/Adults		0.91	[0.71;1.17]

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

Assessor's comment:

Insulin aspart was rapidly absorbed in all patient groups. Total exposure was 40% lower in children and 25% lower in adolescents compared to the adult group. C_{max} was 9% lower in both children and adolescents compared to adult patients. This is not completely consistent with the results from previously reported data which showed higher AUC and Cmax in children and adolescents than in adults. The paediatric studies are however relatively small which may explain the inter-study differences. The age of the patients included in the current study was also rather narrow (children 9-11 years, adolescents 13-17 years and adults 18-25 years) and not entirely representative of the full populations.

The Applicant concludes that in general, the pharmacokinetic responses were similar to adults, which is in agreement with previous observations. This is endorsed. The differences between children and adults have previously been considered not to be clinically relevant since insulin is individually titrated. This conclusion remains.

In summary: The pharmacokinetic conclusion remains the same.

Pharmacodynamic results

Mean baseline adjusted PG profiles for all age groups are shown for NovoRapid in Figure 5 and Figure 6.

A number of subjects received glucose interventions following administration of NovoRapid: 2 children, 1 adolescent and 5 adults. No interventions were made during the first 60 minutes, and the majority occurred between 120 minutes and 300 minutes following product administration. Because 38.5% of adults (5 subjects) received a glucose intervention, the assessment of mean change in PG concentration from 0-6 hours, of minimum PG levels, and the 0-6 hour PG profiles was affected, and it is most relevant to consider the pharmacodynamic endpoints covering the first 2 hours of the meal

test. In the children group, 2 subjects (16.7%) received an intervention, as did 1 (7.7%) adolescent subject.

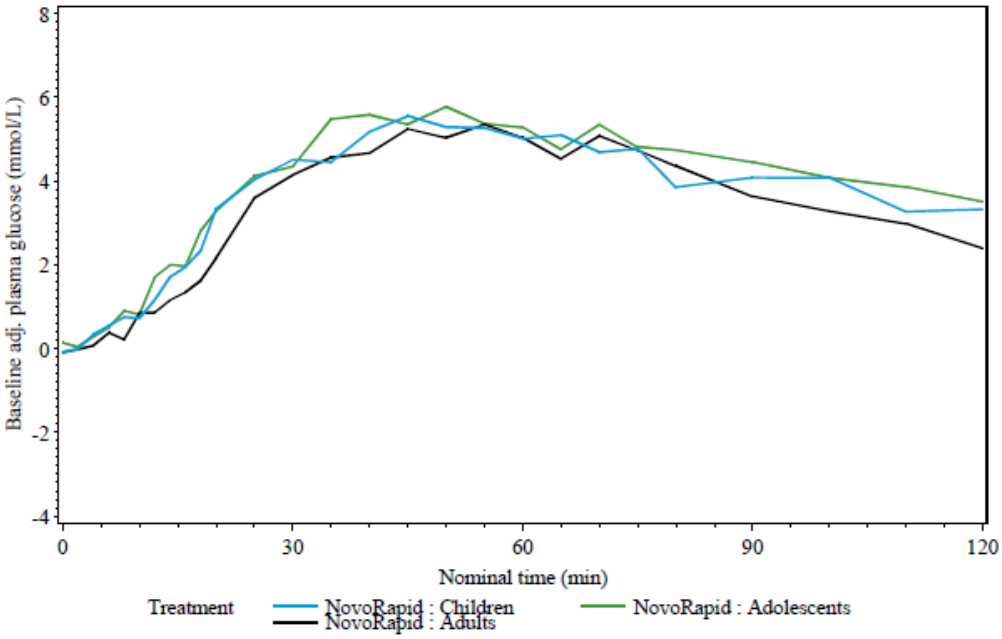

Figure 5 Mean baseline adjusted plasma glucose profiles, NovoRapid (0−2 hours)

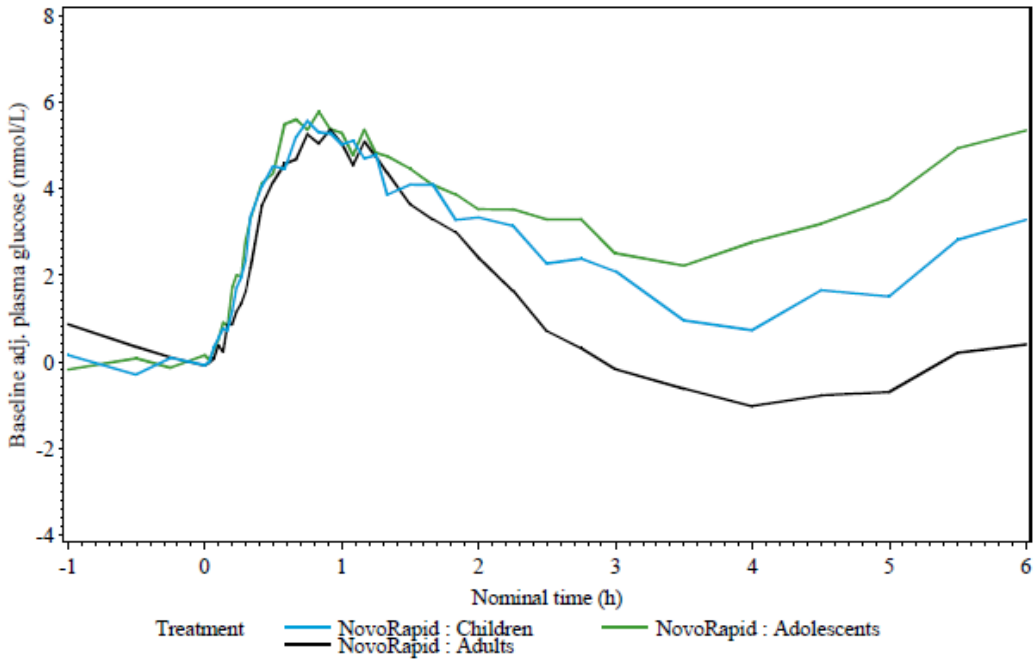

Figure 6 Mean baseline adjusted plasma glucose profiles, NovoRapid (0−6 hours)

Glucose-lowering effect by age group

Analyses of the pharmacodynamic endpoints showed no statistically significant difference in the glucose-lowering effect of NovoRapid between children and adults or between adolescents and adults. The estimated mean changes in PG during the first and second hours ($\Delta PG_{av,0\text{-}1h}$ and $\Delta PG_{av,0\text{-}2h}$) of the meal test tended to be larger in children and adolescents than in adults, although these differences

were not statistically significant (Table 4). These patterns were further supported by the estimated mean PG level at 1 hour and at 2 hours.

Table 4 Statistical analysis of plasma glucose lowering endpoints (1 and 2 hours), NovoRapid

	N	Estimate	95% CI
PG mean change 1h (mmol/L)			
LSMeans			
NovoRapid : Children	12	3.72	
NovoRapid : Adolescents	13	3.79	
NovoRapid : Adults	13	2.99	
Age group difference			
NovoRapid : Children - Adults		0.73	[-0.58;2.04]
NovoRapid : Adolescents - Adults		0.79	[-0.38;1.97]
PG mean change 2h (mmol/L)			
LSMeans			
NovoRapid : Children	12	4.02	
NovoRapid : Adolescents	13	4.10	
NovoRapid : Adults	13	2.93	
Age group difference			
NovoRapid : Children - Adults		1.09	[-0.99;3.17]
NovoRapid : Adolescents - Adults		1.17	[-0.59;2.93]
PG1h (mmol/L)			
LSMeans			
NovoRapid : Children	12	12.63	
NovoRapid : Adolescents	13	12.82	
NovoRapid : Adults	13	11.79	
Age group difference			
NovoRapid : Children - Adults		0.84	[-1.62;3.30]
NovoRapid : Adolescents - Adults		1.03	[-1.03;3.09]
PG2h (mmol/L)			
LSMeans			
NovoRapid : Children	12	10.86	
NovoRapid : Adolescents	13	10.91	
NovoRapid : Adults	13	9.02	
Age group difference			
NovoRapid : Children - Adults		1.84	[-1.45;5.13]
NovoRapid : Adolescents - Adults		1.89	[-0.98;4.76]

N: Number of subjects contributing to analysis, CI: Confidence interval
A linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects, subject as a random effect and PG predose as a covariate was used in the analysis. Ratios and the corresponding CIs were estimated using Fieller's method.

As shown in Table 5, ΔPG_{max} in children following treatment with NovoRapid was not statistically significantly different to that in adults (Fieller age group ratio 1.24 [0.90;1.71]95% CI), but was statistically significantly greater in adolescents compared to adults (Fieller age group ratio 1.32 [1.01;1.78]95% CI).

The observed mean time to reach maximum PG concentration (t_{PGmax}) with NovoRapid was highly variable for children (78.75 minutes; SD 91.38 minutes) and adolescents (173.88 minutes; SD 145.42 minutes), but there was less variability in the adult group (58.62 minutes; SD 17.83 minutes).

The high proportion of adults receiving glucose interventions confounds meaningful interpretation of the endpoints $\Delta PG_{av,0\text{-}6h}$ and PG_{min}.

Table 5 Statistical analysis of mean maximum plasma glucose excursion, NovoRapid

	N	Estimate	95% CI
PGmax excursion (mmol/L)			
LSMeans			
NovoRapid : Children	12	7.33	
NovoRapid : Adolescents	13	7.82	
NovoRapid : Adults	13	5.91	
NovoRapid : Children - Adults		1.42	[-0.58;3.42]
NovoRapid : Adolescents - Adults		1.91	[0.16;3.67]
Fieller age-group ratio			
NovoRapid : Children / Adults	12	1.24	[0.90;1.71]
NovoRapid : Adolescents / Adults	13	1.32	[1.01;1.78]

N: Number of subjects contributing to analysis, CI: Confidence interval
A linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects, subject as a random effect and PG predose as a covariate was used in the analysis. Ratios and the corresponding CIs were estimated using Fieller's method.

Assessor's comment:

The MAH concludes that the analyses of the pharmacodynamic endpoints showed no statistically significant difference in the glucose-lowering effect of NovoRapid between children and adults or between adolescents and adults over the first 2 hours of the meal test. This conclusion is endorsed. Due to the need for interventions in the adult group, no firm conclusions can be drawn on the PD data beyond 2 hours after dosing.

The mean maximum plasma glucose excursion was similar in children and adults but was 32% greater in adolescents compared to adults (Fieller age group ratio: 1.32 [1.01;1.78]95% CI).

The findings are in line with previously presented data, also reflected in the SmPC of NovoRapid.

Safety results

Extent of exposure

The dose level for both dosing visits was 0.2 U/kg body weight, and the actual dose (U) was calculated using body weight measured prior to the first dose administration (visit 2). The relative dose was calculated based on the actual body weight at the dosing visit. For each subject, the actual dose remained the same at both dosing visits. No subject experienced a body weight change in excess of 5% between dosing visits. On average, children received 8.3 U, adolescents 12.8 U, and adults 15.6 U.

Adverse events

A treatment emergent adverse event (TEAE) was defined, for each treatment period, as an AE with onset in the 7 day period following first trial product administration. AEs were allocated to the trial product last received before onset of the AE.

There were 11 AEs reported by 9 subjects outside of the treatment period. The majority of these AEs (6 events in 6 subjects) occurred before any product had been administered. The remaining 5 events (3 subjects) were considered unlikely related to trial drug and were not considered TEAEs as they occurred outside of the 7-day period following trial product administration.

TEAEs were reported evenly across the age groups; in total, 7 TEAEs were reported in 5 subjects. Of these, 1 event was of moderate severity; the remainder were mild in severity. The SOC under which the greatest number of TEAEs was reported was gastrointestinal disorders (2 TEAEs). All TEAEs were single occurrences with no obvious pattern. All TEAEs were resolved by the end of the trial.

There were no treatment emergent SAEs (including deaths) or medical events of special interest (MESIs).

In total, 3 TEAEs (2 subjects) were considered by the investigator to be possibly related to a trial product, both in adolescents: single events of vomiting, nausea and pyrexia. All subjects recovered from the TEAEs reported in the trial. No subject withdrew from the trial due to an AE.

No adverse events related to abnormal vital signs or other safety assessment evaluations were reported during this trial.

Assessor's comment:

The number of AEs was low and relatively evenly distributed between age groups. No new safety concerns arise from the reported data.

Hypoglycaemia

In total, 11 treatment emergent hypoglycaemic episodes were reported by 9 subjects during the trial (Table 8). There were 7 documented symptomatic episodes and 4 asymptomatic episodes. Two episodes were confirmed hypoglycaemia according to the Novo Nordisk definition, and occurred in adults. Most hypoglycaemic episodes (8) were experienced by adults, possibly reflecting the lower relative amount of standardised meal administered compared to that administered to children and adolescents. Most episodes (90%) were reported after 2 hours following administration.

Sixteen subjects received glucose interventions due to low PG levels: 3 children, 1 adolescent and 12 adults. The majority of the interventions occurred after 120 minutes post-treatment. Interventions were made for both treatment groups, and any apparent imbalance between treatments in an age group is considered to be due to the low number of subjects and episodes.

There were no severe treatment emergent hypoglycaemic episodes.

Table 6 Treatment emergent hypoglycaemic episodes, NovoRapid

	NovoRapid								
	Children			Adolescents			Adults		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of subjects	12			13			13		
All events	2	(16.7)	2	1	(7.7)	1	6	(46.2)	8
Documented symptomatic	2	(16.7)	2	1	(7.7)	1	3	(23.1)	4
Asymptomatic	0			0			4	(30.8)	4
Additional class.									
Confirmed	0			0			2	(15.4)	2
Diurnal	2	(16.7)	2	1	(7.7)	1	6	(46.2)	8
Documented symptomatic	2	(16.7)	2	1	(7.7)	1	3	(23.1)	4
Asymptomatic	0			0			4	(30.8)	4

Assessor's comment:

Most of the hypoglycaemias observed occurred in adults. The MAH proposes that this reflects the lower relative amount of standardised meal administered compared to that administered to children and adolescents, which appears adequate. The majority of events (10/11) were observed between 2 and 5 hours after dosing. No severe treatment emerging hypoglycaemic events were reported.

2.3.3. Discussion on clinical aspects

Data from trial NN1218-3888 has been submitted in accordance with Article 46 of Regulation (EC) No1901/2006. The study was conducted as part of the currently ongoing development programme for a new faster-acting insulin aspart formulation and NovoRapid was selected as comparator.

In this report, only data relevant for the assessment of efficacy and safety of NovoRapid in the paediatric population is discussed. Evaluation of the full clinical trial report will be conducted at submission of the marketing authorisation application for faster-acting insulin aspart.

Insulin aspart was rapidly absorbed in all patient groups. Total exposure was 40% lower in children and 25% lower in adolescents compared to the adult group. Cmax was 9% lower in both children and adolescents compared to adult patients. This is not completely consistent with the results from previously reported data which showed higher AUC and Cmax in children and adolescents than in adults. The paediatric studies are however relatively small which may explain the inter-study differences. The age of the patients included in the current study was also rather narrow (children 9-11 years, adolescents 13-17 years and adults 18-25 years) and not entirely representative of the full populations.

The Applicant concludes that in general, the pharmacokinetic responses were similar to adults, which is in agreement with previous observations. This is endorsed. The differences between children and adults have previously been considered not to be clinically relevant since insulin is individually titrated. This conclusion remains.

The analyses of the pharmacodynamic endpoints showed no statistically significant difference in the glucose-lowering effect of NovoRapid between children and adults or between adolescents and adults over the first 2 hours of the meal test. Due to the need for interventions in the adult group, no firm conclusions can be drawn on the PD data beyond 2 hours after dosing. The mean maximum plasma glucose excursion was similar in children and adults but was 32% greater in adolescents compared to adults (Fieller age group ratio: 1.32 [1.01;1.78]95% CI).

The PD findings presented with this submission are in line with previously presented data, also reflected in the SmPC of NovoRapid.

No new safety concerns arise from the reported data. Most of the hypoglycaemias observed occurred in adults, probably due to the lower relative amount of standardised meal administered compared to that administered to children and adolescents. No severe treatment emerging hypoglycaemic events were reported.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The data presented is in line with previously presented PK/PD data for NovoRapid in children and adolescents. No new safety concerns arise from the reported data. No updates to the PI are needed.

The benefit risk balance for NovoRapid remains positive.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.

Annex. Line listing of all completed studies included in the development program

Clinical studies

Overview of completed paediatric clinical trials with NovoRapid.

Trial Phase	Trial name	Population	Number of subjects	Key dates
ANA-1415 Phase 4	Meal-related insulin aspart therapy versus meal related human insulin therapy in children 2-6 years of age with T1DM, a multi-centre randomised, open-labelled, crossover, safety and efficacy trial	Children aged 2−6 years T1DM	26	FPFV: 19 Jun 2002 LPLV: 15 Oct 2003
ANA/DCD/043/DK Phase 1	A single centre, randomised double-blind cross-over study on the pharmacokinetics of insulin aspart and soluble human insulin in paediatric diabetic subjects	Children aged 6−17 years T1DM	18	FPFV: 27 Aug 1998 LPLV: 01 Dec 1998
NN304-1813 Phase 4	Detemir® and NovoRapid® in children with T1DM. A randomised, multicentric, open labelled, parallel group trial with insulin aspart and insulin detemir, investigating the glycaemic effect and profile in children with T1DM, of two separate Levemir® + NovoRapid® injections and extemporaneous mixing. The paediatric MIXING trial	Children aged 6−18 years T1DM	25	FPFV: 18 Sep 2007 LPVL: 13 Mar 2009
ANA/DCD060 Phase 3	Insulin aspart (insulin analogue X14) versus Novolin R, in combination therapy with Novolin NPH in the treatment of paediatric patients with IDDM: an open-labeled, randomized, parallel group, multi-centre study	Children aged 6−17 years T1DM	123	FPFV: 18 Dec 1997 LPLV: 08 Jul 1999
ANA-1200 Phase 3	A multi-centre, randomised, open-labelled, cross-over, efficacy and safety comparison of postprandial and preprandial administration of Insulin aspart in children and adolescents with T1DM	Children aged 6−17 years T1DM	76	FPFV: 10 Feb 2000 LPLV: 31 Jul 2000

Abbreviations: FPFV = first patient first visit; LPLV = last patient last visit; T1DM = Type 1 diabetes mellitus