15 September 2016
EMA/CHMP/605453/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NovoRapid

International non-proprietary name: insulin aspart

Procedure No. EMEA/H/C/000258/II/0112

Note

Variation 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

Table of contents

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANOVA	analysis of variance
BID	bis in die (twice daily)
CSII	continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
EDIC	Epidemiology of Diabetes Interventions and Complications
EU	European Union
FPG	fasting plasma glucose
HbA1c	glycosylated haemoglobin
IAsp	insulin aspart (NovoRapid)
IDeg	insulin degludec (Tresiba)
IDegAsp	insulin degludec/insulin aspart (Ryzodeg)
IDet insulin	detemir (Levemir)
ISPAD	International Society for Pediatric and Adolescent Diabetes
MMRM	mixed model for repeated measurements
OD	once daily
PYE	patient years of exposure
SAE	serious adverse event
SD	standard deviation
SMPG	self-measured plasma glucose
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
US	United states
vs	versus
PDCO	Paediatric Committee

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 30 May 2016 an application for a variation.

The following variation was requested:

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

Extension of Indication to include the use of NovoRapid in children from 1 to 2 years of age for the treatment of diabetes mellitus; as a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

Furthermore, the PI is brought in line with the latest QRD template version 10.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	30 May 2016
Start of procedure:	18 June 2016
CHMP Rapporteur Assessment Report	11 August 2016
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 September 2016
Opinion	15 September 2016

2. Scientific discussion

2.1. Introduction

T1DM is among the most common chronic diseases in children and adolescents, and accounts for between 70−90% of all diabetic cases in the paediatric population. T1DM is characterised by autoimmune destruction of the pancreatic beta-cells resulting in absolute insulin deficiency. Subjects with T1DM need complete exogenous insulin replacement to cover basal as well as meal-related (bolus) insulin requirements.

A recent publication in JAMA estimated the prevalence of T1DM in children aged 0 to ≤4 years, in the US in 2009, to be 0.29 cases per 1000 subjects (241 cases in 832.791 subjects). This shows that even if the prevalence of T1DM is low in the very young children compared to older age groups, the disease does exist in this age group, and there is a need for treatment in children down to 1 year.

A number of landmark studies have demonstrated the importance of maintaining tight glycaemic control to reduce the risk of long-term complications associated with diabetes. The DCCT study confirmed that intensified long-term glucose control reduces both the incidence and the progression of complications occurring in relation to T1DM in adults and adolescents ≥13 years of age.

NovoRapid is a rapid acting insulin analogue with a profile that resembles the physiological action profile of endogenous insulin. NovoRapid has been on the market worldwide for more than a decade for the treatment of diabetes mellitus, and has a well-established efficacy and safety profile based on extensive clinical experience and clinical trial data. It is approved for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

The efficacy and safety of NovoRapid in paediatric subjects have been further studied in two recently completed long-term therapeutic confirmatory trials (NN1250-3561 and NN5401-3816, referred to as trial **3561** and trial **3816**). Both trials were conducted in children and adolescents aged 1 to less than 18 years and provide information about the use of NovoRapid in this population including children down to 1 year of age.

The use of Tresiba and Levemir in children and adolescents from the age of 1 year was approved for treatment of diabetes mellitus in the EU in January 2015 (EMEA/H/C/2498/II/11) and July 2015 (EMEA/H/C/0528/II/70), respectively. These approvals were based on data from trial 3561.

The use of Ryzodeg in the treatment of diabetes mellitus in children and adolescents from the age of 2 year was approved in the EU in July 2016 (EMEA/H/C/2499/II/17) based on the results from trial **3816**.

In both trials, randomisation was stratified by age groups (1−5 years; 6−11 years and 12−17 years) according to European regulatory authority; the results for the age group 1−5 years are used to support the extension of use down to 1 year of age.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Overview of therapeutic confirmatory trials with IDeg+IAsp and IDet+IAsp (trial 3561) and IDegAsp+IAsp and IDet+IAsp (trial 3816) in paediatric subjects

Compound	Trial no.	Trial design	Treatment	Endpoints	No. subjects randomised/ exposed
IDeg	3561	• T1DM subjects • Age: 1– <18 years • 52 weeks (26 week main period + 26 week extension) • Parallel group • Open-label • Treat-to-target • Non-inferiority • Stratification by age (1–5, 6–11, 12–17 years)	IDeg OD or IDet OD/BID[a]. IAsp as meal-time insulin in both groups	*Primary efficacy:* • Change in HbA_{1c} *Secondary efficacy:* • Change in FPG • 8-point SMPG • 4-point SMPG • PK measurements *Safety:* • Adverse events • Hypoglycaemia • Hyperglycaemia • CGM in subset of subjects • Insulin antibodies • Clinical evaluation (physical examination and vital signs) • Laboratory assessments (haematology, biochemistry, lipids) • Insulin dose • Body weight and BMI	*Main trial period* IDeg: 174/174 IDet: 176/175 *Extension period* IDeg: --/152 IDet: --/128
IDegAsp	3816	• T1DM subjects • Age: 1– <18 years • 16 weeks • Parallel group • Open-label • Treat-to-target • Non-inferiority • Stratification by age (1–5, 6–11, 12–17 years)	IDegAsp OD or IDet OD/BID[a]. IAsp as meal-time insulin in both groups	*Primary efficacy:* • Change in HbA_{1c} *Secondary efficacy:* • Change in FPG • 8-point SMPG • 4-point SMPG *Safety:* • Adverse events • Hypoglycaemia • Hyperglycaemia • Clinical evaluation (physical examination and vital signs) • Laboratory assessments (haematology, biochemistry, lipids) • Insulin dose • Body weight and BMI	IDegAsp: 182/181 IDet: 180/179

2.3.2. Pharmacokinetics

No new pharmacokinetic data have been submitted in this application, which is considered acceptable.

2.3.3. Pharmacodynamics

No new pharmacodynamic data have been submitted in this application, which is considered acceptable.

2.4. Clinical efficacy

2.4.1. Main studies

Two long-term therapeutic confirmatory phase 3b trials (NN1250-3561 and NN5401-3816, referred to as trial 3561 and trial 3816) have been conducted which included paediatric subjects treated with NovoRapid. The primary objective of the two studies was to investigate the efficacy and safety of insulin degludec (IDeg) and insulin degludec/insulin aspart (IDeg/Asp), respectively. In both studies the comparator was insulin detemir (IDet).

Trial ID NN1250-3561: A trial investigating the efficacy and safety of insulin degludec (IDeg) plus meal time insulin aspart (IAsp) versus insulin detemir (IDet) once or twice daily plus meal time insulin aspart (IAsp) in children and adolescents with type 1 diabetes mellitus.

Trial ID NN5401-3816: A trial investigating the efficacy and safety of insulin degludec/insulin aspart (IDeg/Asp) once daily plus insulin aspart (IAsp)for the remaining meals versus insulin detemir (IDet) once or twice daily plus meal time insulin aspart (IAsp) in children and adolescents with type 1 diabetes mellitus.

Both trials were conducted in children and adolescents aged 1 to less than 18 years and provide information about the use of NovoRapid in this population including children down to 1 year of age. In both trials, randomisation was stratified by age groups (1−5 years; 6−11 years and 12−17 years); the results for the age group 1−5 years are used to support the extension of use down to 1 year of age.

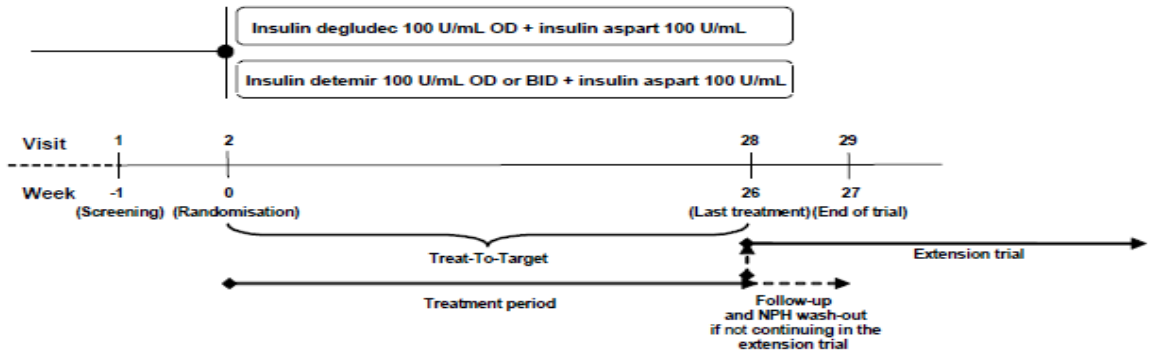
Methods

Trial 3561

This was a 26-week, open labelled, randomised (1:1), multinational, multi-centre, two arm parallel group, treat to target (TTT), safety and efficacy trial comparing insulin degludec with insulin detemir as basal insulin in combination with insulin aspart as bolus insulin in type 1 diabetes subjects between 1 and less than 18 years of age, followed by a 26-week extension investigating long term safety and immunogenicity.

The trial design was agreed in collaboration with PDCO as an integrated part of the PIP for IDeg and was further to provide some supporting efficacy and safety data for the age group 1-2 years, in accordance with the PIP for IDet.

Figure 1 Study design 3561



Following screening, eligible subjects were randomised in a 1:1 manner into one of the treatment groups. Randomisation was stratified according to age group (1 to less than 6 years, 6 to less than 12 years and 12 to less than 18 years of age). During the trial treatment period, all subjects were titrated according to the Insulin Titration Guideline. For subjects who only completed the main period (26 weeks of treatment) the duration was approximately 29 weeks. The trial included a screening visit (Visit 1), a randomisation visit (Visit 2), followed by 8 site visits (including one follow-up visit), and 18 phone contacts.

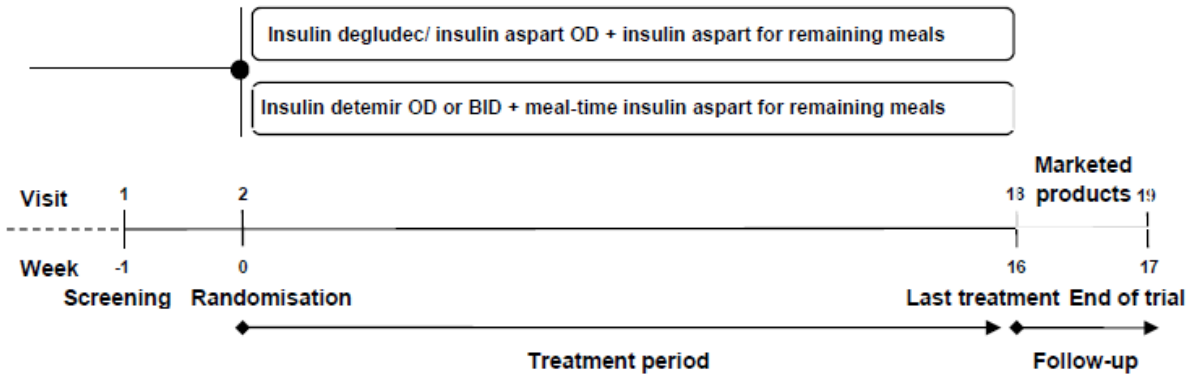
Trial 3816

This was a 16-week multi-national, multi-centre, open-label, two-arm, parallel group, randomised, treat-to-target (T-T-T), efficacy and safety trial comparing treatment with IDegAsp OD, with a main meal +

IAsp for the remaining meals vs. IDet + meal-time IAsp in children and adolescents with T1DM between 1 and less than 18 years of age.

The trial design was agreed upon with PDCO as a binding element of the PIP for IDegAsp.

Figure 2 Study design 3816



Following screening, the subjects were randomised 1:1 to the treatment groups and stratified by the age groups: 1 year to < 6 years; 6 years to <12 years; and 12 years <18 years. During the trial treatment period, all subjects were titrated according to the Insulin Titration Guideline Protocol. The total trial duration for the individual subjects was approximately 18 weeks. The trial included a screening visit (Visit 1) followed by a 16-week randomised treatment period and a follow-up visit (Visit 19) 7−12 days after the actual date of the last treatment visit (Visit 18).

Study participants

In both trials, eligible subjects were aged 1 to less than 18 years with T1DM, treated for at least 3 months on any insulin regimen (no oral antidiabetic drugs allowed), with a total daily insulin dose ≤2 units/kg and with an HbA1c value at screening ≤11%. Subjects with known hypoglycaemic unawareness or recurrent episodes of severe hypoglycaemia, as well as subjects with more than 1 event of diabetic ketoacidosis requiring hospitalisation within the last 3 months prior to the screening visit, were excluded from participation in the trials.

Treatments

At randomisation, subjects were to switch to either IDeg or IDet (trial **3561**) or IDegAsp or IDet (trial **3816**) from their previous insulin treatment in accordance with the titration guideline included as part of the protocol for trial **3561** and trial **3816**.

In both trials, IAsp was administered as bolus insulin in both treatment groups.

A treat-to-target approach with weekly contacts (visits or phone contacts) was implemented in order to ensure optimal glycaemic control for each individual subject. The titration algorithms for basal and bolus insulin specified the plasma glucose target and the recommended insulin dose adjustments at different plasma glucose levels. All subjects were to be individually titrated on a continuous basis according to a pre-specified plasma glucose target range adopted from the ISPAD 2009 guidelines. The fasting, pre-meal and bedtime plasma glucose target was 5.0−8.0 mmol/L.

All adjustments of insulin doses were made at the discretion of the investigator.

Titration of insulin aspart

In both trial **3561** and trial **3816**, IAsp was titration either by use of a sliding scale (Table 2) or according to the principles of flexible dosing (carbohydrate counting).

Table 2 Adjustment of IAsp doses – trial 3561 and trial 3816

Current bolus dose		≤5 Unit	>5 Unit
Lowest pre-meal or bedtime plasma glucose		Adjustment (units)	
mmol/L	mg/dL		
<5.0	<90	-1	-2
5.0–8.0	90–145	0	0
8.1–10.0	146–180	+½	+1
10.1–15.0	181–270	+1	+2
>15.0	>270	+1½	+3

IAsp = insulin aspart.

Objectives

Trial 3516

The primary objective was to confirm the efficacy of insulin degludec administered once daily plus mealtime insulin aspart in controlling glycaemia with respect to change from baseline in HbA1c after 26 weeks of treatment by comparing the difference in change in HbA1c between insulin degludec + insulin aspart and insulin detemir + insulin aspart to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.

Secondary objectives were to compare the efficacy and safety between the two treatment arms in terms of parameters of glycaemic control and safety.

Trial 3816

The primary objective was to confirm the efficacy of IDegAsp administered once daily plus meal-time IAsp for the remaining meals in controlling glycaemia with respect to change from baseline in HbA1c after 16 weeks of treatment. This is done by comparing the difference in change from baseline in HbA1c between IDegAsp + meal-time IAsp for the remaining meals and IDet + meal-time IAsp to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.

The secondary objectives were to compare the efficacy and safety between the two treatment groups.

Outcomes/endpoints

Trial 3561

The primary endpoint was

- Change from baseline in HbA1c (%) after 26 weeks of treatment (analysed by central laboratory).

Supportive secondary efficacy endpoints:

- Change from baseline in FPG after 26 weeks of treatment (analysed by central laboratory)
- SMPG measurements (8-point profiles)
- 8-point profiles after 26 weeks and
- Mean of the 8-point profiles after 26 weeks

- Fluctuation in the 8-point profiles after 26 weeks
- Prandial PG increment from 8-point profiles after 26 weeks
- SMPG measurements (4-point profiles) obtained throughout the trial for dose adjustment
- Mean PG before breakfast after 26 weeks
- Within-subject variability as measured by CV% after 26 weeks

Trial 3816

The primary endpoint was:

- Change from baseline in HbA1c (%) after 16 weeks of treatment.

Secondary efficacy endpoints were:

- Change from baseline in FPG after 16 weeks of treatment
- SMPG measurements (4-point profiles) obtained throughout the trial for dose adjustments
  - o Mean PG before meals and before bedtime after 16 weeks of treatment
  - o Within subject variability as measured by the CV% after 16 weeks of treatment
- SMPG measurements (8-point profiles)
  - o 8-point profiles after 16 weeks of treatment
  - o Mean of the 8-point profiles after 16 weeks of treatment
  - o Fluctuation in the 8-point profiles after 16 weeks of treatment
  - o Prandial PG increment from 8-point profiles after 16 weeks of treatment

Sample size

In both studies the sample size was based on the primary endpoint using the similar assumptions; a one-sided significance level of 0.025, a mean treatment difference of 0 and a non-inferiority margin of 0.4% (in accordance with FDA guidance and for study **3816**, also in agreement with PDCO as an integrated part of the PIP for IDegAsp.). Based on experience from previous phase 3 trials in children and adolescents with T1DM treated with insulin a conservative estimate for the SD of 1.25% for HbA1c was used in the sample size calculation. The minimum sample size required to meet the primary objective with at least 80% power was 310 subjects.

Taking into account the estimated number of subjects excluded in the PP analysis set the total number of randomised subjects in each study was to be at least 346.

Randomisation

At the randomisation visit (Visit 2) eligible subjects (complying with all exclusion/inclusion criteria) were randomised 1:1using IV/WRS to either IDeg 100 U/mL or IDet 100 U/mL, both in combination with IAsp (trial **3561**) and to either IDegAsp or IDet, both in combination with meal-time IAsp (trial **3816**).

In both studies randomisation was stratified according to 3 age groups: 1 to less than 6 years; 6 to less than 12 years; 12 to less than 18 years of age.

For study **3561** to be in line with the approved PIP, the age-group distribution should be at least 80 children aged 1-5 years (both inclusive) and 250-260 children and adolescents aged 6-17 years (both inclusive). At least 30% and not more than 70% should be girls.

For study **3816** to be in accordance with the approved PIP, at least 60 randomised subjects had to be younger than 6 years at inclusion. Additionally at least 30% and not more than 70% were to be girls.

Blinding (masking)

The treatment in both studies was open-labelled due to the complexities involved with double blinded studies when using pen systems (**3561**) and since the treatment regimens required different number of daily injections (**3816**).

The internal Novo Nordisk safety committee and the external data monitoring committee (DMC) reviewed safety data on an ongoing basis. The internal safety committee was blinded and the DMC was unblinded. External classification of severe hypoglycaemia was performed blinded.

Statistical methods

The primary endpoint was the change from baseline in HbA1c (%) after 26 weeks of treatment (**3561**) or 16 weeks of treatment (**3816**), respectively. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.4%. Analyses of all endpoints were to be based on the Full Analysis Set (FAS) including all randomised subjects with the primary efficacy analysis to be repeated on the Per Protocol (PP) analysis set.

The PP analysis set in the two studies was similarly defined. In study **3561** the PP included subjects without any major protocol violations that may have affected the primary endpoint, subjects were to have been exposed for more than 12 weeks and to have a valid assessment necessary for deriving the primary endpoint. In study **3816**, the PP set consisted of all subjects in the FAS who complied with all exclusion/inclusion criteria, had a non-missing HbA1c at screening or randomisation, had at least one non-missing HbA1c after 12 weeks of exposure and had at least 12 weeks of exposure.

In study **3561** the primary analysis was performed using an analysis of variance (ANOVA) model with treatment, sex, region and age group as fixed factors and baseline HbA1c as covariate. Region was a factor with four levels (Europe (including Russia), United States (US), Japan and South Africa).

In study **3816** the primary analysis was initially to be based on an ANOVA but was changed to a MMRM model with Amendment no.1 (25 Feb 2014, upon request from FDA). All observed HbA1c measurements available post-randomisation at scheduled measurement times was analysed with a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. The model included treatment, sex, region, age-group and visit as factors and baseline HbA1c as covariate. Interactions between visit and all factors and covariates were also included in the model. Region was a factor with three levels (EU (including Russian Federation and Israel), North America and Other).

In study **3561** an analysis using MMRM and in study **3816** an analysis based on an ANOVA was performed as sensitivity analyses.

Statistical methods for the analyses of secondary endpoints were pre-defined and mainly in accordance with the primary analysis method used in the primary analysis in each of the study (ANOVA **3561**, MMRM **3816**).

For study **3561** it was stated that selected tables and figures were to be presented also by age group to get a description of key endpoints and parameters per age group.

In study **3816** it was stated that relevant endpoints (as a minimum demographics, Hba1c, FPG, SMPG, hypoglycaemia, hyperglycaemia and body weight) should also be presented descriptively by the 3 age groups.

In both studies, the Safety analysis set included all subjects receiving at least one dose of study medication. Safety data were mainly to be summarised descriptively. In both studies the number of treatment emergent hypoglycaemic episodes was to be analysed separately using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode is considered treatment emergent as offset. The model was to include treatment, sex, region and age group as fixed factors. In study **3816** it was further stated that the number of treatment emergent hyperglycaemic episodes and the number of treatment emergent hyperglycaemic episodes with ketosis were to be analysed separately using the same approach as above.

No interim analyses were performed during any of the studies.

A few (minor) changes were made in the SAP compared to the content in the study protocol for study 3561 and **3816** respectively. In study **3561** two additional/exploratory analyses were added post-hoc and in study **3816** one additional/exploratory analysis was added post-hoc.

Results

Participant flow

Study 3561

Table 3 Subject disposition – summary – trial 3561

	IDeg OD N (%)	IDet N (%)	Total N (%)
Screened			363
Screening Failures			13
Withdrawn before Randomisation			0
Randomised	174 (100.0)	176 (100.0)	350 (100.0)
Exposed	174 (100.0)	175 (99.4)	349 (99.7)
Withdrawn at/after Randomisation	4 (2.3)	11 (6.3)	15 (4.3)
Adverse Event	0 (0.0)	2 (1.1)	2 (0.6)
Withdrawal Criteria	4 (2.3)	7 (4.0)	11 (3.1)
Other	0 (0.0)	2 (1.1)	2 (0.6)
Completed	170 (97.7)	165 (93.8)	335 (95.7)
full analysis set	174 (100.0)	176 (100.0)	350 (100.0)
PP analysis set	171 (98.3)	167 (94.9)	338 (96.6)
safety analysis set	174 (100.0)	175 (99.4)	349 (99.7)

N: Number of subjects
%: Proportion of randomised subjects

A total of 363 subjects were screened and a total of 350 subjects were randomised to IDeg or IDet treatment. Of the subjects who were screening failures, 5 failed to meet inclusion criteria 6 (HbA1c ≤11%), 2 subjects failed inclusion criteria 7 (ability to perform 4 and 8 point profiles), 1 subject did not fulfil inclusion criteria 4 (minimum 3 months insulin use) and 5 subjects withdrew consent. Of the randomised subjects, 1 subject in IDet arm was withdrawn before being exposed to trial product, as the subject was newly diagnosed and therefore did not fulfil inclusion criteria 4.

A total of 335 (95.7%) subjects completed the trial. Of the 15 subjects who withdrew during the trial, 2

subjects (both IDet) withdrew due to adverse events. The most common reason for withdrawal (4 subjects in each arm) was fulfilment of withdrawal criteria 1 (subject withdrew consent).

For subject disposition for the age group 1-5 years old, see below under “Numbers analysed”.

Study 3816

Table 4 Subject disposition – summary – trial 3816

	IDegAsp OD N (%)	IDet N (%)	Total N (%)
Screened			387
Screening Failures			25
Withdrawn before Randomisation			0
Randomised	182 (100.0)	180 (100.0)	362 (100.0)
Exposed	181 (99.5)	179 (99.4)	360 (99.4)
Withdrawn at/after Randomisation	8 (4.4)	12 (6.7)	20 (5.5)
Adverse Event	1 (0.5)	0 (0.0)	1 (0.3)
Non-Compliance With Protocol	1 (0.5)	0 (0.0)	1 (0.3)
Withdrawal Criteria	6 (3.3)	10 (5.6)	16 (4.4)
Other	0 (0.0)	2 (1.1)	2 (0.6)
Completed	174 (95.6)	168 (93.3)	342 (94.5)
full analysis set	182 (100.0)	180 (100.0)	362 (100.0)
PP analysis set	174 (95.6)	171 (95.0)	345 (95.3)
safety analysis set	181 (99.5)	179 (99.4)	360 (99.4)

N: Number of subjects
%: Proportion of randomised subjects
PP: Per protocol

A total of 387 subjects were screened, of which 25 were screening failures and a total of 362 subjects were randomised to IDegAsp or IDet treatment. Of the subjects who were screening failures, 17 subjects did not meet inclusion criterion 6 (HbA1c ≤11%), 1 subject met exclusion criterion 2 (use of oral antidiabetic agents), 1 subject met exclusion criterion 9 (mental incapacity, unwillingness or language barriers, precluding adequate understanding or cooperation) and 6 subjects withdrew consent. Of the randomised subjects, 1 subject in the IDegAsp group was withdrawn before being exposed due to having withdrawn consent and 1 subject in the IDet group was withdrawn before being exposed due to having been randomised in error due to that the subject was randomised before receiving the results of Visit 1.

A total of 342 subjects (94.5%) completed the trial with a similar proportion of subjects completing

in both treatment groups. Of the 20 subjects who withdrew during the trial, 1 subject in the IDegAsp group withdrew due to an adverse event. The most common reason for withdrawal was fulfilment of withdrawal criterion 1 (withdrew consent). 1 subject in the IDegAsp treatment group withdrew due to non-compliance with the protocol and 2 subjects in the IDet treatment group withdrew due to other reasons.

For subject disposition for the age group 1-5 years old, see below under “Numbers analysed”.

Recruitment

Study **3561** was conducted at 72 sites in 12 countries as follows: Bulgaria 2 sites, Finland 5 sites, France 4 sites, Germany 3 sites, Italy 2 sites, Japan 15 sites, Netherlands 5 sites, Republic of Macedonia 2 sites, Russian Federation 6 sites, South Africa 2 sites, United Kingdom 4 sites, United States 22 sites.

Study **3816** was conducted at 63 sites in 14 countries as follows: Belgium: 3 sites; Brazil: 1 sites; Canada: 3 sites; Czech Republic 3 sites; Croatia: 2 sites; Israel: 6 sites; Macedonia: 2 sites; Poland: 3 sites; Russian Federation: 5 sites; Serbia: 4 sites; Slovenia: 1 sites; South Africa: 2 sites; Spain: 5 sites; and Unites States: 23 sites.

Conduct of the study

Study **3561** was initiated 16 January 2012 and was completed 08 February 2013. The data cut-off date was 13 March 2013. There were 6 substantial amendments to the protocol with amendments 1 and 2 implemented prior to trial initiation. Substantial amendment 3 (06 Mar 2012) was a global amendment to clarify the endpoints to be measured in the extension period. An additional secondary endpoint, measurement of insulin antibodies (IDeg specific, IDet specific, IAsp specific and antibodies cross-reacting to human insulin) after 26 weeks and 52 weeks of treatment was added. Amendment 4, 6 and 8 were non-global.

Study **3816** was initiated 17 October 2013 and was completed 07 November 2014. The data cut-off date (and database lock) was 26 November 2014. There were 2 global amendments to the protocol (both concerned changes within the Statistical Analysis Plan).

Baseline data

Study 3561

Demographic characteristics - all subjects

The trial population consisted of children and adolescents with T1DM aged between 1 to less than 18 years at randomisation. Males comprised 55.4% of the trial population. Approximately 29% of the subjects were from the US, 16% were from Japan and 52% were from Europe including the Russian Federation. The majority of subjects (75%) were 'White' and the second most common race was 'Asian non-Indian' (16%). Almost all subjects (97.1%) were 'not Hispanic or Latino'.

There were only minor differences between the treatment groups with regards to demographics and baseline characteristics.

Overall, the demographics and baseline characteristics were similar for the full analysis set and the extension trial set.

Age group demographics based on the extension trial set were similar to those based on the full analysis set.

Demographic characteristics - age groups

Overall, the baseline demographics for the three age groups in the IDeg+IAsp and IDet+IAsp treatment groups were in line with that of all subjects, except for the male/female ratio in children aged 1−5 years in the IDet+IAsp group, where more females than males were included.

Four (4) subjects aged 1 year were included; 2 to IDeg+IAsp (the youngest being 1.5 years) and 2 to IDet+IAsp (the youngest being 1.8 years).

Table 5 Descriptive statistics - age - children (1-5 years) - full analysis set

	IDeg OD	IDet	Total
Number of Subjects	43	42	85
Age (years)			
N	43	42	85
Mean (SD)	4.3 (1.1)	4.1 (1.1)	4.2 (1.1)
Median	4.7	4.0	4.3
Min ; Max	1.5 ; 5.7	1.8 ; 5.8	1.5 ; 5.8

Age group demographics based on the extension trial set were similar to those based on the full analysis set.

Diabetes characteristics - all subjects

At baseline, the mean baseline HbA1c was slightly higher in the IDeg+IAsp group (8.2%) as compared to the IDet+IAsp group (8.0%). The mean baseline FPG was higher in the IDeg+IAsp group (9.0 mmol/L [162.1 mg/dL]) than in the IDet+IAsp group (8.4 mmol/L [151.0 mg/dL]). Other baseline characteristics were similar in the two treatment groups. The baseline diabetes characteristics were similar based on the full analysis set and the extension trial set.

Diabetes characteristics - age groups

As would be expected, the mean baseline height, weight, BMI and duration of diabetes were lowest in children 1−5 years and highest in adolescents 12−17 years in both treatment groups. Only minor variations were observed in the diabetes characteristics across the age groups in the two treatment groups. In the IDeg+IAsp treatment group, the mean HbA1c was slightly higher in adolescents 12−17 years compared to the two younger age groups, whereas the mean FPG was lower. In the IDet+IAsp treatment group, the mean HbA1c was similar across the three age groups, while the mean FPG was lower in children aged 1−5 years than in the two other age groups. The diabetes characteristics based on the extension trial set were overall in line with those based on the full analysis set for both treatment groups, although mean HbA1c (7.8−8.2%) and FPG (7.7–9.6 mmol/L [137.9−172.4 mg/dL]) varied slightly more across the age groups.

Diabetes complications

A total of 4 subjects reported diabetes complications at screening (IDeg+IAsp: 1 subject with diabetic ketoacidosis; IDet+IAsp: 3 subjects with diabetic neuropathy).

Anti-diabetic regimen at screening

At screening, the vast majority of subjects (335; 95.7% of randomised subjects) were using basal/bolus therapy, of which 5 (1.4%) were using basal/bolus + premix. The remaining 15 (4.3%) were using “other” regimens (i.e., basal, bolus, premix alone or premix in combination with basal or bolus); “other” could also include a pump regimen.

In both treatment groups, IDet and IGlar were the most widely used basal insulin products at screening and IAsp was the most commonly used bolus insulin. IDet was used by 85 (48.8%) subjects randomised to IDeg+IAsp and 83 (47.2%) subjects randomised to IDet+IAsp. It was not recorded whether IDet was used OD or BID at trial entry. IGlar was used by 71 (40.8%) subjects in the IDeg+IAsp group and by 76 (43.2%) subjects in the IDet+IAsp group. IAsp was used by 115 (66.1%) subjects in the IDeg+IAsp group and by 123 (69.9%) subjects in the IDet+IAsp group. IDet and IGlar were also the most widely used basal insulin products at screening based on the extension trial set.

Demographic and baseline characteristics for subjects completing the main trial and not continuing in the extension trial period

Overall, the subjects (IDeg+IAsp: 18 [10.3%] subjects and IDet+IAsp: 37 [21.0%] subjects), who completed the main trial period without continuing in the extension trial period, were distributed evenly across the three age groups with both treatments (IDeg+IAsp: 9.8%−11.6%; IDet+IAsp: 19.7%−22.1%). The majority of subjects not continuing in the extension trial period came from the US, South Africa (these 12 subjects could not continue for administrative reasons, Japan, Finland and France. Compared to the subjects continuing in the extension period (mean age: 10.1 years, and mean duration of diabetes: 4.0−4.1 years), they were slightly younger (mean age: 9.0 and 9.5 years with IDeg+IAsp and IDet+IAsp, respectively) with a shorter duration of diabetes (mean duration: 3.3 and 3.9 years with IDeg+IAsp and IDet+IAsp, respectively).

The most commonly used basal insulin at screening in the subjects not continuing in the extension trial period was IDet, which was used by 8 (44.4%) subjects randomised to IDeg+IAsp and 21 (56.8%) subjects randomised to IDet+IAsp. The most commonly used bolus insulin was IAsp (used by 10 [55.6%] and 30 [81.1%] subjects randomised to IDeg+IAsp and IDet+IAsp, respectively).

Study 3816

Baseline and demographic characteristics - all subjects

The trial population consisted of children and adolescents with T1DM aged 1 to less than 18 years at randomisation. Females comprised 51.7% of the trial population. The trial was multinational with 60.2% of subjects from sites in Europe (including Israel and Russia), 34.5% from North America, 3.3% from South Africa and 1.9% from South America. The majority of subjects were 'White' (93.1%) and not Hispanic or Latino (92.3%). There were no major differences between the treatment groups with regards to demographics and baseline characteristics.

Baseline and demographic characteristics - age groups

Within each age group, the demographics and baseline characteristics were well matched between the treatment groups.

One (1) child included in the trial was 1 year old; this child was randomised to the IDet+IAsp group and was 1.9 years old. The youngest child in the IDegAsp+IAsp group was 2.2 years old.

Table 6 Descriptive statistics – age - children (1-5 years) - full analysis set

	IDegAsp OD	IDet	Total
Number of Subjects	41	41	82
Age (years)			
N	41	41	82
Mean (SD)	4.6 (1.1)	4.3 (1.1)	4.4 (1.1)
Median	4.6	4.3	4.3
Min ; Max	2.2 ; 6.0	1.9 ; 6.0	1.9 ; 6.0

Baseline diabetes characteristics – all subjects

The baseline diabetes characteristics were comparable between the treatment groups apart from slight differences in mean FPG and mean duration of diabetes. For the overall trial population, the mean FPG at baseline was slightly higher in the IDegAsp+IAsp group than in the IDet+IAsp group: 8.6 mmol/L (155.6 mg/dL) versus 8.1 mmol/L (146.5 mg/dL), respectively. The mean duration of diabetes was also slightly higher in the IDegAsp+IAsp group than in the IDet+IAsp group: 4.4 years versus 3.8 years, respectively.

Baseline diabetes characteristics – age groups

In children 1−5 years and 6−11 years, the baseline and diabetic characteristics were comparable in the treatment groups.

In adolescents 12−17 years, mean FPG was slightly higher in the IDegAsp+IAsp group: 9.0 mmol/L (162.4 mg/dL) compared to the IDet+IAsp group: 8.1 mmol/L (146.1 mg/dL). Otherwise the treatment groups were comparable.

Diabetic complications

Fewer diabetic complications were reported in the IDegAsp+IAsp group (reported by 5 subjects) than in the IDet+IAsp group (reported by 9 subjects).

Antidiabetic regimen at screening

Antidiabetic regimens at screening were overall similar in the treatment groups. At screening, the majority of subjects (333 subjects [92.0%]) were using basal-bolus insulin therapy, 5 (1.4%) were using basal-bolus + premix while 24 (6.6%) were using 'other' regimens (i.e., basal, bolus, premix alone or premix in combination with bolus); 'other' could also include an insulin pump regimen.

IDet was the most widely used basal insulin at screening followed by IGlar. IAsp was the most commonly used bolus insulin.

Approximately half the subjects had used IDet at screening/before randomisation: 75 (41.2%) in the IDegAsp+IAsp group and 95 (52.8%) in the IDet+IAsp group. IGlar was used by 77 (42.3%) and 70 (38.9%) of subjects, respectively. IAsp was used by 107 (58.7%) subjects in the IDegAsp+IAsp group and by 113 (62.8%) subjects in the IDet+IAsp group.

Numbers analysed

Study 3561

Table 7 Subject disposition - summary - children (1-5 years) – trial 3561

	IDeg OD N (%)	IDet N (%)	Total N (%)
Randomised	43 (100.0)	42 (100.0)	85 (100.0)
Exposed	43 (100.0)	41 (97.6)	84 (98.8)
Withdrawn at/after Randomisation	2 (4.7)	4 (9.5)	6 (7.1)
Adverse Event	0 (0.0)	1 (2.4)	1 (1.2)
Withdrawal Criteria	2 (4.7)	2 (4.8)	4 (4.7)
Other	0 (0.0)	1 (2.4)	1 (1.2)
Completed	41 (95.3)	38 (90.5)	79 (92.9)
full analysis set	43 (100.0)	42 (100.0)	85 (100.0)
PP analysis set	41 (95.3)	38 (90.5)	79 (92.9)
safety analysis set	43 (100.0)	41 (97.6)	84 (98.8)

N: Number of subjects
%: Proportion of randomised subjects
This table is based on randomized subjects

Study 3816

The subject disposition was well matched in the treatment groups for each of the 3 age groups as expected due to the stratification.

Table 8 Subject disposition - summary - children (1-5 years) – trial 3816

	IDegAsp OD N (%)	IDet N (%)	Total N (%)
Randomised	41 (100.0)	41 (100.0)	82 (100.0)
Exposed	40 (97.6)	41 (100.0)	81 (98.8)
Withdrawn at/after Randomisation	3 (7.3)	5 (12.2)	8 (9.8)
Withdrawal Criteria	3 (7.3)	5 (12.2)	8 (9.8)
Completed	38 (92.7)	36 (87.8)	74 (90.2)
full analysis set	41 (100.0)	41 (100.0)	82 (100.0)
PP analysis set	38 (92.7)	39 (95.1)	77 (93.9)
safety analysis set	40 (97.6)	41 (100.0)	81 (98.8)

N: Number of subjects
%: Proportion of randomised subjects
PP: Per protocol
This table is based on randomised subjects

Outcomes and estimation

Results are presented for all subjects first, in line with the objectives of the trials, followed by results for the age groups. Comparisons between treatment groups as well as comparisons between the age groups 1−5 years, 6−11 years and 12−17 years are described where the focus is on the age group 1−5 years. Notice that none of the trials were powered to compare endpoints between treatments within the three age groups. Therefore, no statistical analyses were performed between age groups and any trend within a given age group should be interpreted with caution considering the limited number of subjects within each age group.

- ***Primary endpoint***

Study 3561

Overall, IDeg effectively improved glycaemic control as measured by change in HbA1c and non-inferiority to IDet in terms of lowering HbA1c was confirmed, as the upper limit of the 95% CI for the estimated mean treatment difference was ≤ 0.4 %.

Table 9 HbA1c (%) after 26 weeks of treatment - primary statistical analysis – FAS – trial 3561

	FAS	N	Estimate	SE	95% CI
HbA1c (%)					
LSMeans					
IDeg OD	174	174	7.95	0.09	
IDet	176	176	7.80	0.08	
Change from Baseline					
LSMeans					
IDeg OD	174	174	-0.15	0.09	
IDet	176	176	-0.30	0.08	
Treatment Contrast					
IDeg OD - IDet			0.15		[-0.03 ; 0.32]

N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error of the mean
The response and change from baseline in the response after 26 weeks of treatment is analysed using an ANOVA method with treatment, sex, region and age group as fixed effects and baseline response as a covariate.
Missing data is imputed using last observation carried forward.

The PP analysis showed an estimated treatment difference in line with the main analysis, treatment difference IDeg OD- IDet 0.19 [95% CI; 0.01; 0.37]. The conclusion of the PP analysis is that it supports the primary analysis (non-inferiority) since the upper limit of the CI is below 0.4%.

HbA1c after 52 weeks - all subjects

After 52 weeks of treatment, the observed reduction in HbA1c was maintained in both treatment groups. The change from baseline in HbA1c after 52 weeks of treatment was similar with IDeg+IAsp and IDet+IAsp with an estimated treatment difference (IDeg+IAsp – IDet+IAsp) of -0.01%-points [-0.20; 0.19]95%CI). This result was supported by the sensitivity analyses.

The observed mean HbA1c was 7.9% and 7.8% after 52 weeks of treatment with IDeg+IAsp and IDet+IAsp, respectively (Table 10). The observed mean change from baseline was -0.27%-points with IDeg+IAsp and -0.22%-points with IDet+IAsp.

The change over time in HbA1c during the trial was similar with both treatments.

HbA1c after 52 weeks - age groups

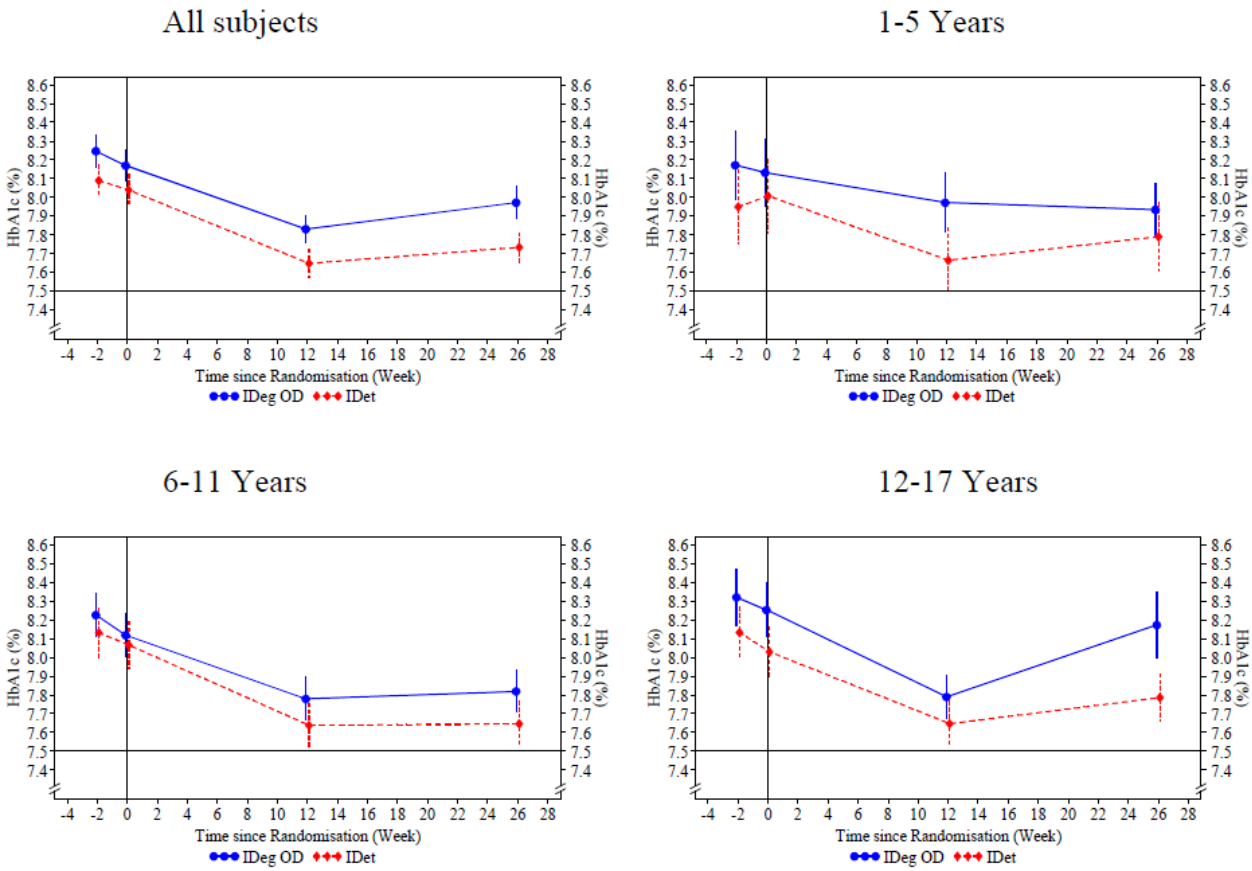
For children 1-5 years treated with IDeg a gradual decline in HbA1c over time was observed and with IDet mean HbA1c declined from baseline to week 12.

Table 10 HbA1c – at baseline, 26 weeks and 52 weeks – full analysis set – trial 3561

	IDeg OD + IAsp				IDet + IAsp			
	All subjects (N=174)	**1–5 years (N=43)**	**6–11 years (N=70)**	**12–17 years (N=61)**	**All subjects (N=176)**	**1–5 years (N=42)**	**6–11 years (N=68)**	**12–17 years (N=66)**
HbA_{1c} (%), mean (SD)								
Week 0	**8.2 (1.1)**	8.1 (1.2)	8.1 (1.0)	8.3 (1.1)	**8.0 (1.1)**	8.0 (1.3)	8.1 (1.0)	8.0 (1.1)
Week 26[a]	**8.0 (1.1)**	7.9 (0.9)	7.8 (0.9)	8.2 (1.4)	**7.7 (1.0)**	7.8 (1.2)	7.6 (1.0)	7.8 (1.0)
Week 52[a,b]	**7.9 (1.1)**	7.8 (0.9)	7.8 (1.1)	8.2 (1.3)	**7.8 (1.1)**	7.8 (1.1)	7.7 (1.1)	7.9 (1.1)

[a]Data based on last observation carried forward.
[b]HbA_{1c} at week 52 was a supportive secondary endpoint.
IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; N = number of subjects; OD = once daily; SD = standard deviation.

Figure 3 HbA1c (%) by treatment week – mean plot – trial 3561



FAS; LOCF imputed data. Error bars + - standard error (mean)

Study 3816

The primary objective of this trial was to confirm the efficacy of IDegAsp administered OD + meal-time IAsp for the remaining meals in controlling glycaemia with respect to change from baseline in HbA1c after 16 weeks of treatment. IDegAsp OD + IAsp maintained glycaemic control as measured by change in HbA1c and non-inferiority to IDet + IAsp in terms of changing HbA1c was confirmed, as the upper limit of the 95% CI for the mean treatment difference was ≤ 0.4%.

Table 11 Table HbA1c after 16 weeks of treatment - primary statistical analysis – FAS - trial 3816

	FAS	N	Estimate	SE	95% CI
HbA1c (%)					
LSMeans					
IDegAsp OD	182	177	7.79	0.07	
IDet	180	173	7.83	0.07	
Change from baseline					
LSMeans					
IDegAsp OD	182	177	-0.27	0.07	
IDet	180	173	-0.23	0.07	
Treatment Contrast					
IDegAsp OD - IDet			-0.04		[-0.23; 0.15]

FAS: Full analysis set, N: Number of subjects contributing to analysis, CI: Confidence interval,
SE: Standard error of the mean
All observed HbA1c measurements available post-randomisation at scheduled measurement times is analysed with a MMRM with an unstructured covariance matrix. The model includes treatment, sex, region, age-group and visit as factors and baseline HbA1c as covariate.
Interactions between visit and all factors and covariates are also included in the model.

All sensitivity analysis showed an estimated mean treatment difference in line with the main analysis and supported the conclusion of non-inferiority, as the upper limit of the 95% CI ≤ 0.4% and the estimated mean treatment differences were close to that for the primary analysis (–0.04%-points).

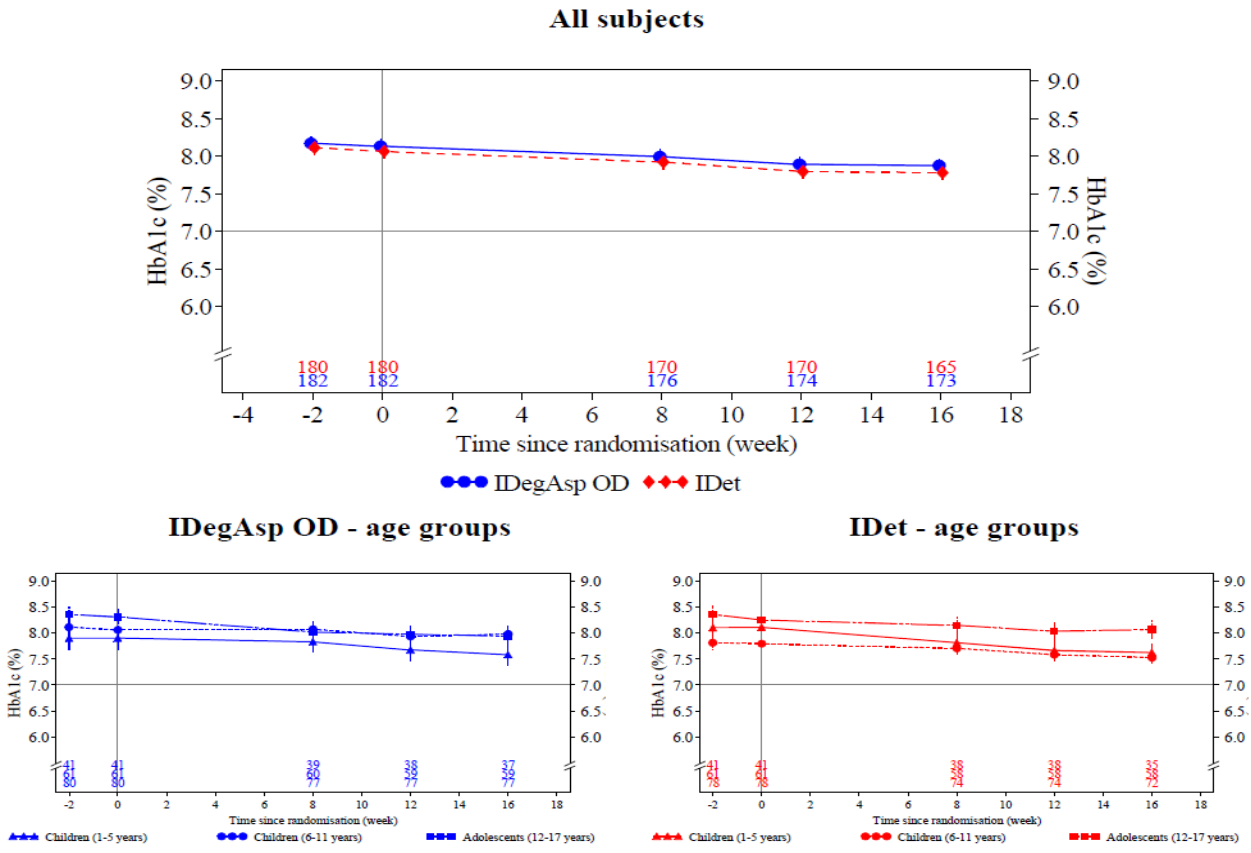
HbA1c - age groups

Table 12 HbA1c – at baseline and 16 weeks – full analysis set – trial 3816

	IDegAsp OD + IAsp				IDet + IAsp			
	All subjects (N=182)	1–5 years (N=41)	6–11 years (N=61)	12–17 years (N=80)	All subjects (N=180)	1–5 years (N=41)	6–11 years (N=61)	12–17 years (N=78)
HbA_{1c} (%), mean (SD)								
Week 0	**8.1 (1.2)**	7.9 (1.4)	8.1 (1.1)	8.3 (1.3)	**8.1 (1.2)**	8.1 (1.1)	7.8 (1.1)	8.2 (1.4)
Week 16	**7.9 (1.2)**	7.6 (1.2)	8.0 (1.2)	7.9 (1.2)	**7.8 (1.3)**	7.6 (1.0)	7.5 (0.9)	8.1 (1.6)

IAsp = insulin aspart; IDegAsp = insulin degludec/insulin aspart; IDet = insulin detemir; N = number of subjects; OD = once daily; SD = standard deviation.

Figure 4 HbA1c (%) by treatment week - mean plots (upper panel: all subjects; lower panel: age groups) – trial 3816



FAS; Observed data; Error bars + - standard error (mean). Numbers of subjects contributing to the data points are provided in the bottom section of each plot. In the lower panel, the age groups are presented from top to bottom: children 1-5 years, children 6-11 years, adolescents 12-17 years.

- ***Secondary endpoints***

Fasting plasma glucose

In trial **3561**, there was an overall observed reduction in mean FPG in the IDeg+IAsp treatment group, and an overall observed increase in the IDet+IAsp treatment group during the trial. Due to the sustained reduction in FPG in the IDeg+IAsp treatment group, the difference between the two treatments was more pronounced, and statistically significant at 52 weeks of treatment.

With IDeg+IAsp, a reduction in mean FPG was observed from baseline to 52 weeks in all three age groups; the reduction was most pronounced in children aged 1−5 years and 6−11 years. With IDet+IAsp, the mean FPG increased from baseline to 52 weeks in all three age groups where the increase was most pronounced in children aged 1−5 years.

In trial **3816**, the overall observed changes in mean FPG were minor in both treatment groups; a small reduction was seen in IDegAsp+IAsp treatment group and a minor increase was seen in the IDet+IAsp treatment group during the trial. No statistically significant difference was seen between the two groups.

No pattern in changes in mean FPG was observed from baseline to 16 weeks in the age groups. In the IDegAsp+IAsp treatment group, a reduction was observed in the age groups 1−5 years and 12−17 years whereas in the IDet+IAsp treatment group, a reduction was observed in the age group 6−11 years. An increase in FPG was observed for the other age groups.

Self-measured plasma glucose profile

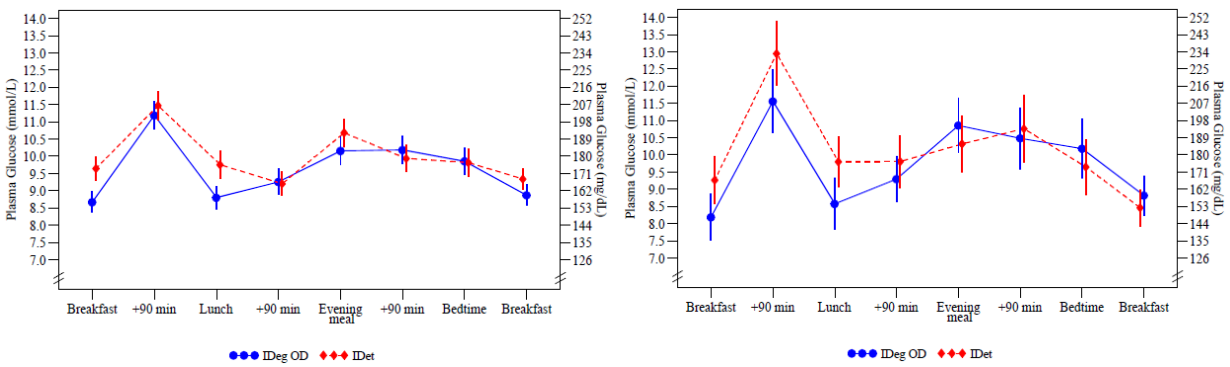
Trial 3561

8-point SMPG profiles

Throughout the trial in both treatment arms the 8 point SMPG profiles did not show the typical peak and trough profiles seen in adults with T1DM. In the IDeg arm there was a reduction in mean SMPG for the post-meal time points from baseline to 12 and 26 weeks.

In some cases there were differences in the shape of the 8 point SMPG profiles across age groups and treatment arms, but no firm conclusions could be drawn based on age group due to variability of the data and low sample size. Profiles of 8 point SMPG for the all subjects and children (1-5 years) at 26 are presented by treatment in Figure 5.

Figure 5 8-point self measured plasma glucose profile at 26 Weeks - mean plot – all subjects (left) and children 1-5 years (right) - full analysis set – trial 3561



After 52 weeks of treatment, SMPG values were statistically significantly lower with IDeg+IAsp than with IDet+IAsp at post-breakfast, post-dinner and pre-breakfast on the second day. The mean of the 8-point profile was also statistically significantly lower after 52 weeks of treatment with IDeg+IAsp than with

IDet+IAsp. There were no statistically significant treatment differences in prandial plasma glucose increments or in the fluctuation in SMPG at week 52.

Within the age groups, the observed results based on the 8-point SMPG profiles after 52 weeks of treatment were generally in line with those observed for all subjects. No obvious differences between age groups were observed for 8-point SMPG profiles, mean of the 8-point profiles, prandial increments or fluctuation with either treatment.

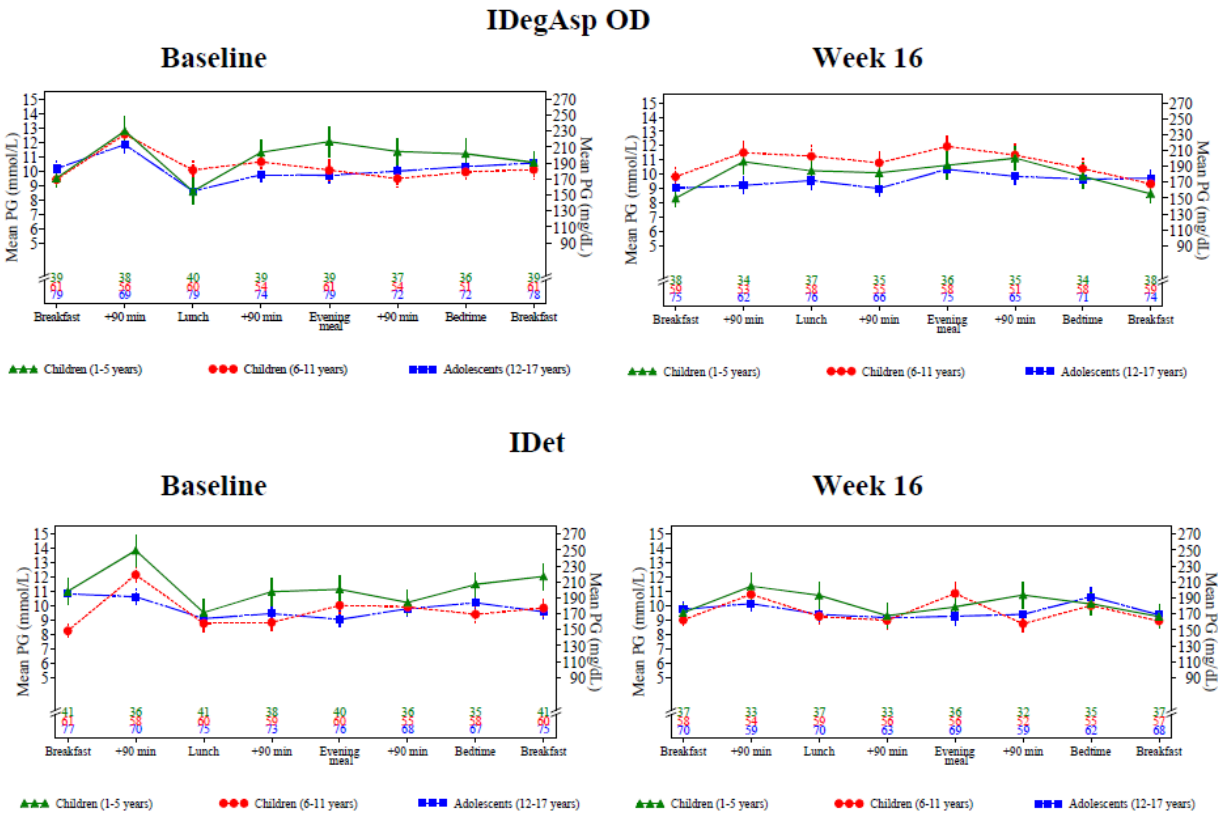
Trial 3816

8-point SMPG profiles

There were no statistically significant treatment differences in the mean of the 8-point profile, in prandial plasma glucose increments (mean of all meals, breakfast, lunch and main evening meal) or in the SMPG fluctuation at week 16.

Within the age groups, the shape of the 8-point SMPG profiles (Figure 5), fluctuation in plasma glucose and prandial increments followed the overall trend as seen for all subjects from baseline to week 16.

Figure 6 8-point self-measured plasma glucose profile at baseline (left) and week 16 (right) - mean plot – by age group - full analysis set – trial 3816



Treatment groups: IDegAsp = insulin degludec/insulin aspart + insulin aspart; IDet = insulin detemir + insulin aspart. OD = once daily.

Full analysis set; Observed data. Error bars +/- standard error (mean). Numbers of subjects contributing to the data points are provided in the bottom section of each plot.

PG = plasma glucose

Insulin dose over time

In both treatment groups in both trials, the mean total daily insulin dose increased gradually during the trial. At end of trial, the basal insulin requirement was higher in the IDet+IAsp treatment groups compared to the

IDeg+IAsp and IDegAsp+IAsp treatment groups. In trial **3561**, 64.0% of subjects were using IDet BID and in trial **3816**, 54.2% of subjects were using IDet BID at the end of the trial.

The difference between the treatment groups (IDeg+IAsp vs. IDet+IAsp and IDegAsp+IAsp vs. IDet+IAsp) was mainly due to the basal component, since bolus insulin doses were comparable for the treatment groups throughout the trials; the mean daily bolus insulin dose at end of trial was 0.55 and 0.58 units/kg for IDeg+IAsp and IDet+IAsp (trial **3561**) and 0.52 units/kg for both IDegAsp+IAsp and IDet+IAsp (trial **3816**).

In both treatment groups in both trials, the mean daily dose of both basal and bolus insulin was lowest in children aged 1−5 years and highest in adolescents aged 12−17 years. Also, the basal:bolus split indicated that children aged 1−5 years used less basal and more bolus insulin compared to older children and adolescents as exemplified by the data from trial **3561** (Table 13).

Table 13 Basal-bolus split of total daily insulin dose (units/kg) - summary – children (1−5 years), children (6−11 years) and adolescents (12−17 years) – safety analysis set – trial 3561

	IDeg OD + IAsp Basal / Bolus	IDet +IAsp Basal / Bolus
Children 1-5 Years		
Visit 3 (Week 1)	36 / 64	38 / 62
Visit 56 (Week 52)	36 / 64	42 / 58
Children 6-11 Years		
Visit 3 (Week 1)	43 / 57	45 / 55
Visit 56 (Week 52)	41 / 59	48 / 52
Adolescents 12-17 Years		
Visit 3 (Week 1)	44 / 56	45 / 55
Visit 56 (Week 52)	43 / 57	51 / 49

Basal: Percentage basal insulin, Bolus: Percentage bolus insulin
Basal:bolus split is derived from mean doses computed from last observation carried forward imputed data.

Analysis performed across trials (pooled analyses and meta-analysis)

Insulin aspart was administered as bolus insulin in both treatment groups in both trials but different basal insulin products were administered in **trial 3561** (IDeg and IDet) and in **trial 3816** (IDegAsp and IDet); the data for these two trials have therefore not been pooled.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The data provided to support NovoRapid for use in paediatric patients down to 1 year of age comes from two 3b studies; study **3561** with the extension study **3561 Ext** and study **3816**. Both studies were multi-national, multi-centre, open-label, two-arm, parallel group, randomised, treat-to-target, efficacy and safety studies. Both studies were conducted in children and adolescents aged 1 to less than 18 years. At the time-point for initiation of Study **3816**, Study **3561** had been completed. None of the studies (**3561**,

3816), were explicitly designed to assess the treatment efficacy of insulin aspart/NovoRapid in terms of HbA1c reduction among younger children.

Study **3561** comprised a 26-week treatment period followed by a 26-week extension investigating long term safety (**3561 Ext**) and compared IDeg (test drug; marketed under the trade name Tresiba) with IDet (active comparator; marketed under the trade name Levemir). Study **3816** comprised a 16-week treatment period and compared IDegAsp (test drug; marketed under the trade name Ryzodeg) with IDet (active comparator). In both trials, Insulin Aspart was given as bolus insulin in combination with IDeg, IDegAsp and IDet as basal insulin.

The primary endpoint was change from baseline in HbA1c (%) at week 26, study **3561** and week 16, study **3816**, respectively. The primary objective was to show non-inferiority using a non-inferiority margin of 0.4%. The same assumptions were used in both studies for the calculation of the sample size. In both studies randomisation was 1:1 stratified by age groups (1−5 years; 6−11 years and 12−17 years). The statistical analysis approach was similar in the two studies although differed with regard to the primary analysis method. Overall, the analysis approach in each of the study is acceptable.

Both studies were seemingly adequately designed and conducted according to their primary and secondary objectives, respectively.

In each of the study, insulin aspart was given as bolus insulin in combination with different basal insulins in all treatment groups, hence, no assessments are available where the efficacy of insulin aspart has been compared to alternative bolus insulin keeping the basal insulin unchanged. Further, while it is an advantage that both studies were stratified by age none of the studies were powered to allow for statistical comparisons between the age groups. Therefore no statistical analyses were performed between age groups. Separate results for the age groups have however been presented to facilitate descriptive comparisons between treatment groups as well as between the age groups 1−5 years, 6−11 years and 12−17 years within treatment group. To support the proposed extension of indication focus has been on the subgroup of subjects 1-5 years of age. Although the target number of subjects (to comply with approved PIPs) in this subgroup in each of the study was reached; at least 80 subjects in study **3561** and at least 60 subjects in study **3816** respectively, they comprise however the smallest subgroups and hence provides only limited data.

In study **3561** a total of 350 children/adolescents were randomised, all but one in the IDet treatment group received study treatment. Of the randomised subjects, 24.3% (85/350) was in the age group 1-5 years, 39.4% (138/350) in the age group 6-11 years and 36.3% (127/350) in the age group 12-17 years. Overall, a high proportion of the subjects completed the 26-week treatment period (95.7%) with, however, the lowest proportion among the youngest children; 92.9% (79/85) in the age group 1-5 years, 98.6% (136/138) in the age group 6-11 and 94.5% (120/127) in the age group 12-17. Across subgroups, there was slightly more completers in the IDeg OD than in the IDet treatment arm.

In study **3816** a total of 362 children/adolescents were randomised, all but one in each treatment arm received study treatment. In study **3816** the age distribution was similar as seen in study **3561** with 22.7% (82/362), 33.7% (122/362) and 43.6% (158/362) in the age group 1-5 years, 6-11 years and 12-17 years of age respectively. Also in this study, a high proportion of the subjects completed the 16-week treatment period (94.5%) with most non-completers in the age group 1-5 years 90.2% (74/82) to be compared with 97.5% (119/122) in the age group 6-11 and 94.3% (149/158) in the age group 12-17. Across subgroups, there was slightly more completers in the IDegAsp OD than in the IDet treatment arm.

In total five (5) subjects aged 1-2 years were included. Four (4) subjects aged 1 year were included in trial **3561**; 2 to IDeg+IAsp (minimum age 1.5 years) and 2 to IDet+IAsp (minimum age 1.8 years). One (1) child included in trial **3816** was 1 year old; this child was randomised to the IDet+IAsp group and was 1.9 years

old. The youngest child in the IDegAsp+IAsp group was 2.2 years old. Thus the number of patients in the age group 1-2 years is very limited.

Assessment of paediatric data on clinical efficacy

Based on the primary and secondary objectives in each of the study focus was on the analyses of the primary and secondary endpoints based on all subjects.

In study **3561** IDeg improved glycaemic control as measured by change in HbA1c and non-inferiority to IDet in terms of lowering HbA1c was confirmed, as the upper limit of the 95% CI for the estimated mean treatment difference was ≤ 0.4 %.

In study **3816**, IDegAsp OD + IAsp maintained glycaemic control as measured by change in HbA1c and non-inferiority to IDet + IAsp in terms of changing HbA1c was confirmed, as the upper limit of the 95% CI for the mean treatment difference was ≤ 0.4%.

With regards to secondary endpoints, FPG decreased in the groups treated with IDeg (trial **3561**) or IDegAsp (trial **3816**) whereas FPG increased slightly with IDet in both trials. No relevant differences were observed between age groups. Thus the differences observed were most probably related to the basal insulin.

There were no differences in the 8-point SMPG profiles, mean of the 8-point profiles, prandial increments or fluctuation between age groups in either of the trials. As these measures provide some information on the action of the bolus insulin, i.e. on the control of post-prandial glucose increments, the data provide some reassurance that the effect of insulin aspart is not different in the age group 1-5 years compared to older children/adolescents.

The bolus insulin dose did not change much in any of the groups in either of the trials; instead the increase in total insulin dose was mainly due to an increase in basal insulin dose. It is noted that in the youngest age group, a somewhat higher proportion of the total insulin dose is given as bolus insulin compared to the older age groups. This may reflect a greater need to make dose adjustments due to changes in activity and food intake in this group.

2.4.3. Conclusions on the clinical efficacy

Since none of the studies (**3561, 3816**) were designed to evaluate treatment with insulin aspart with regards to the effect on HbA1c, no assessments of the efficacy of insulin aspart per se can be made. Outcomes per age groups are presented descriptively, the number of subjects within age groups however being limited with the lowest number of children in the age group 1-5 years of age. Hence, no firm conclusions on the efficacy of insulin aspart per se or in the subgroup of small children (less than 2 years, in total 5 children) can be drawn. The data, however, does not indicate any differences in post-prandial glucose control either between treatment groups or between age groups. Furthermore, the efficacy with regards to HbA1c did not differ between age groups.

2.5. Clinical safety

Introduction

NovoRapid has been on the market worldwide for more than a decade for the treatment of diabetes mellitus and is approved for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. The safety profile is well known, with the major safety issue being hypoglycaemia.

Patient exposure

In trial **3561**, the total exposure was 161.5 years in the IDeg+IAsp treatment group and 147.4 years in the IDet+IAsp treatment group. The mean exposure was comparable between the two treatment groups during the main part of the trial (first 26 weeks), but higher in the IDeg+IAsp treatment group than in the IDet+IAsp treatment group during the last 26 weeks, reflecting the higher proportion of subjects continuing on IDeg+IAsp compared to IDet+IAsp in the extension period of the trial. Approximately 87% of subjects in the IDeg+IAsp treatment group and 70% of subjects in the IDet+IAsp treatment group were exposed to the trial products for at least 49 weeks. Overall, the exposure between treatment groups was similar across all three age groups as expected due to the stratification. In total, 23.6%, 40.4% and 36.0% of children aged 1–5 years, 6–11 years and 12–17 years were exposed. Four (4) subjects aged 1 year were exposed; 2 to IDeg+IAsp (both exposed for 1 year) and 2 to IDet+IAsp (1 exposed for 26 weeks and 1 for 1 year).

Table 14 Exposure – descriptive statistics – safety analysis set – trial 3561

	IDeg OD + IAsp	IDet + IAsp	Total
Number of Subjects	174	175	349
Total Exposure, yrs	161.5	147.4	308.9
Children (1-5 yrs)	38.9 (24.1)	34.1 (23.1)	73.0 (23.6)
Children (6-11 yrs)	66.3 (41.0)	58.5 (39.7)	124.7 (40.4)
Adolescents (12-17 yrs)	56.3 (34.9)	54.8 (37.2)	111.1 (36.0)
Exposure (yrs)			
N	174	175	349
Mean (SD)	0.93 (0.19)	0.84 (0.26)	0.88 (0.23)
Median	1.00	1.00	1.00
Min ; Max	0.07 ; 1.08	0.02 ; 1.03	0.02 ; 1.08

N: Number of subjects, SD: Standard deviation

In trial **3816**, the total exposure was 54.8 years in the IDegAsp+IAsp treatment group and 53.9 years in the IDet+IAsp treatment group. Approximately 96% of subjects were exposed for ≥16 weeks of treatment. The exposure between treatment groups was similar across all three age groups as expected due to the stratification. In total, 22.3%, 40.4% and 43.6% of children aged 1–5 years, 6–11 years and 12–17 years were exposed. One (1) subject aged 1 year was exposed; the subject was treated with IDet+IAsp and exposed for 0.3 years.

Table 15 Exposure – descriptive statistics – safety analysis set – trial 3816

	IDegAsp OD + IAsp	IDet + IAsp	Total
Number of Subjects	181	179	360
Total Exposure, yrs	54.77	53.92	108.7
Children (1-5 yrs)	12.0 (21.9)	12.2 (22.7)	24.2 (22.3)
Children (6-11 yrs)	18.7 (34.1)	18.3 (34.0)	37.0 (40.4)
Adolescents (12-17 yrs)	24.1 (44.0)	23.3 (43.3)	47.4 (43.6)
Exposure (yrs)			
N	181	179	360
Mean (SD)	0.30 (0.03)	0.30 (0.04)	0.30 (0.04)
Median	0.31	0.31	0.31
Min ; Max	0.06 ; 0.35	0.02 ; 0.34	0.02 ; 0.35

N: Number of subjects, SD: Standard deviation, yrs: Years

Adverse events

Common adverse events

Trial 3561

The proportion of subjects reporting AEs and the rate of AEs were similar in the IDeg+IAsp and the IDet+IAsp treatment groups (92.5% vs. 89.7% and 906 vs. 859 events per 100 PYE, respectively) (Table 16). The majority of AEs in both treatment groups were non-serious, mild or moderate in severity and considered unlikely related to basal insulin and bolus insulin. Approximately 97% of all AEs in either treatment group had an outcome of recovered or recovering at end of trial.

Table 16 Adverse events –safety analysis set – trial 3561

IDeg OD + IAsp						IDet + IAsp					
	N (SAS)	n	(%)	E	R		N (SAS)	n	(%)	E	R
All subjects,	N=174	161	(92.5)	1462	906	All subjects,	N=175	157	(89.7)	1266	859
1-5 yrs,	N=43	39	(90.7)	510	1310	1-5 yrs,	N=41	35	(85.4)	296	868
6-11 yrs,	N=70	64	(91.4)	532	803	6-11 yrs,	N=68	60	(88.2)	562	961
12-17 yrs,	N=61	58	(95.1)	420	746	12-17 yrs,	N=66	62	(93.9)	408	744

% = percentage of subjects; E= number of events; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; n = number of subjects with adverse events; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.

The most frequently reported AEs across treatments were 'nasopharyngitis', 'headache', 'blood ketone body increased', 'upper respiratory tract infections', 'pyrexia', 'hypoglycaemia', 'oropharyngeal pain' and 'cough'.

The percentage of subjects reporting AEs was similar across treatment groups in all three age groups. The rate of AEs was also similar across treatment groups and age groups, except for a higher rate of AEs reported for children aged 1−5 years in the IDeg+IAsp treatment group compared to the IDet+IAsp treatment group (1310 vs. 868 events per 100 PYE) (Table 16). The higher rates of AEs in the IDeg+IAsp 1−5 year age group were scattered across several SOCs, with the highest rates observed in relation to 'infections and infestations', 'respiratory disorders' and 'gastrointestinal disorders'. Further, higher rates of 'blood ketone increased' were reported in the 1−5 year age group compared to the other age groups.

Table 17 Frequent adverse events (≥10%), children 1-5 years - trial 3561 main-ext

	IDeg OD + IAsp				IDet + IAsp				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	43				41				84			
Events	35	(81.4)	282	725	32	(78.0)	192	563	67	(79.8)	474	649
Infections and infestations												
Nasopharyngitis	20	(46.5)	55	141	14	(34.1)	32	94	34	(40.5)	87	119
Upper respiratory tract infection	10	(23.3)	15	39	7	(17.1)	19	56	17	(20.2)	34	47
Rhinitis	5	(11.6)	10	26	7	(17.1)	13	38	12	(14.3)	23	31
Gastrointestinal disorders												
Vomiting	11	(25.6)	16	41	6	(14.6)	10	29	17	(20.2)	26	36
Diarrhoea	7	(16.3)	8	21	7	(17.1)	10	29	14	(16.7)	18	25
Abdominal pain upper	6	(14.0)	9	23	2	(4.9)	5	15	8	(9.5)	14	19
Abdominal discomfort	5	(11.6)	9	23	2	(4.9)	3	9	7	(8.3)	12	16
Abdominal pain	5	(11.6)	5	13					5	(6.0)	5	7
Respiratory, thoracic and mediastinal disorders												
Cough	14	(32.6)	31	80	7	(17.1)	13	38	21	(25.0)	44	60
Oropharyngeal pain	8	(18.6)	9	23	5	(12.2)	5	15	13	(15.5)	14	19
Investigations												
Blood ketone body increased	15	(34.9)	42	108	17	(41.5)	41	120	32	(38.1)	83	114
General disorders and administration site conditions												
Pyrexia	15	(34.9)	36	93	12	(29.3)	23	67	27	(32.1)	59	81
Nervous system disorders												
Headache	9	(20.9)	20	51	8	(19.5)	13	38	17	(20.2)	33	45
Metabolism and nutrition disorders												
Hypoglycaemia	8	(18.6)	17	44	3	(7.3)	5	15	11	(13.1)	22	30

N: Number of subjects, %: Percentage of subjects, E: Number of events,
R: Event rate per 100 exposure years.

Trial 3816

The proportion of subjects reporting AEs and the rate of AEs were similar in the IDegAsp+IAsp and IDet+IAsp treatment groups (77.9% vs. 74.9% and 915 vs. 853 events per 100 PYE) (Table 18). The majority of the AEs in both treatment groups were non-serious, mild in severity and considered unlikely related to basal insulin and bolus insulin. Approximately 75% of all subjects in both treatment groups had an outcome of recovered at end of trial.

Table 18 Adverse events – safety analysis set – trial 3816

	IDegAsp OD + IAsp					IDet + IAsp				
N (SAS)		n	(%)	E	R	N (SAS)		n	(%)	E	R
All subjects,	N=181	141	(77.9)	501	915	All subjects,	N=179	134	(74.9)	460	853
1–5 yrs,	N=40	35	(87.5)	143	1192	1–5 yrs,	N=41	26	(63.4)	86	702
6–11 yrs,	N=61	44	(72.1)	148	792	6–11 yrs,	N=61	48	(78.7)	166	905
12–17 yrs,	N=80	62	(77.5)	210	872	12–17 yrs,	N=77	60	(77.9)	208	891

% = percentage of subjects; E= number of events; IAsp = insulin aspart; IDegAsp = insulin degludec/insulin aspart; IDet = insulin detemir; n = number of subjects with adverse events; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.

The most frequently reported AEs in both treatment groups were “headache”, “nasopharyngitis”, “abdominal pain upper”, “pyrexia” and “vomiting”.

No unexpected differences among the three age groups were observed with respect to type of AEs. In the IDegAsp+IAsp treatment group, a higher rate of AEs was observed for children 1–5 years compared to the other age groups whereas a lower rate of AEs for children 1–5 years compared to the other age groups was observed in the IDet+IAsp treatment group (Table 18). The higher rate of AEs in the 1–5 year age group in the IDegAsp+IAsp treatment group were scattered across several SOCs, with the highest rates observed in relation to “infections and infestations”, “general disorders and administration site condition (pyrexia)” and “gastrointestinal disorders”.

Table 19 Frequent adverse events (≥10%), children 1-5 years - trial 3816

	IDegAsp OD + IAsp				IDet + IAsp				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	40				41				81			
Events	35	(87.5)	143	1192	26	(63.4)	86	702	61	(75.3)	229	945
Infections and infestations												
Nasopharyngitis	9	(22.5)	12	100	8	(19.5)	12	98	17	(21.0)	24	99
Influenza	3	(7.5)	4	33	5	(12.2)	7	57	8	(9.9)	11	45
Upper respiratory tract infection	4	(10.0)	5	42	4	(9.8)	4	33	8	(9.9)	9	37
Rhinitis	4	(10.0)	5	42	2	(4.9)	2	16	6	(7.4)	7	29
Gastrointestinal disorders												
Vomiting	10	(25.0)	12	100	5	(12.2)	6	49	15	(18.5)	18	74
Respiratory, thoracic and mediastinal disorders												
Cough	5	(12.5)	5	42					5	(6.2)	5	21
General disorders and administration site conditions												
Pyrexia	11	(27.5)	15	125	3	(7.3)	5	41	14	(17.3)	20	82
Metabolism and nutrition disorders												
Hypoglycaemia	5	(12.5)	6	50	2	(4.9)	2	16	7	(8.6)	8	33

N= Number of subjects in the safety analysis set
n= number of subjects with adverse events
%= Percentage of subjects
E= Number of events
R= Event rate per 100 patient years of exposure

Adverse events by relation to trial products

Please note that an AE assessed as possibly or probably related to basal insulin (IDeg, IDegAsp or IDet) may also have been assessed as related to bolus insulin (IAsp). Further, an AE may also have been assessed as related to basal insulin only or to bolus insulin only. The number of AEs assessed as related to basal insulin and bolus insulin can therefore not be added to give the total number of AEs assessed as related to treatment.

Trial 3561

The vast majority of AEs were considered unlikely related to basal and bolus insulin as judged by the investigator.

The rate of AEs considered as having a probable relation to basal insulin was comparable between treatments; 20 vs. 19 events per 100 PYE with IDeg+IAsp and IDet+IAsp, respectively. The rate of AEs considered to have a possible relation to basal insulin was 50 vs. 39 events per 100 PYE.

The rate of AEs considered as having a probable relation to bolus insulin was comparable between treatments with IDeg+IAsp and IDet+IAsp; 26 vs. 19 events per 100 PYE, respectively. The rate of AEs considered to have a possible relation to bolus insulin was 53 vs. 45 events per 100 PYE.

The most notable differences in AEs judged related to IDeg and/or IAsp and IDet and/or IAsp were related to ‘hypoglycaemia’, ‘blood ketone body increased’, and ‘administration site conditions’.

Trial 3816

The vast majority of AEs were considered unlikely related to IDegAsp, IDet and IAsp.

The overall rates of AEs considered possibly or probably related to IDegAsp vs. IDet were 47 vs. 37 per 100 PYE (26 vs. 20 events, respectively) and the overall rates of AEs considered possibly or probably related to IAsp, were 37 vs. 32 per 100 PYE (20 vs. 17 events, respectively). The most notable differences between the IDegAsp+IAsp and IDet+IAsp groups were hypoglycaemia-related AEs considered possibly or probably related to treatment, followed by events related to gastrointestinal disorders.

Within the SOC 'gastrointestinal disorders', more events were reported as related to IDet compared to IDegAsp (5 vs. 0 events, respectively). All events were single occurrences under different preferred terms except for 2 events of 'vomiting'. Further, more events were reported as related to IAsp in the IDet+IAsp group compared to the IDegAsp+IAsp group (5 vs. 1 events, respectively). All events were single occurrences under different preferred terms.

Serious adverse event / deaths / other significant events

Trial 3561

No deaths were reported.

The rates of SAEs were generally low and similar for IDeg+IAsp and IDet+IAsp, both overall, across severity and causality categories, and with respect to recovery. The majority of SAEs were considered unlikely related to IDeg, IDet and IAsp and with an outcome of 'recovered' at end of trial. The low number of subjects with SAEs as well as the low number of SAEs should be taken into consideration when evaluating rates between treatment groups as these comparisons are based on a low number of subjects with few events (Table 20).

Table 20 Serious adverse events – safety analysis set – trial 3561

	IDeg OD + IAsp					Det + IAsp				
N (SAS)	n	(%)	E	R	N (SAS)	n	(%)	E	R
All subjects, N=174	18	(10.3)	25	15	All subjects, N=175	16	(9.1)	24	16
1-5 yrs, N=43	6	(14.0)	9	23	1-5 yrs, N=41	7	(17.1)	13	38
6-11 yrs, N=70	5	(7.1)	8	12	6-11 yrs, N=68	6	(8.8)	8	14
12-17 yrs, N=61	7	(11.5)	8	14	12-17 yrs, N=66	3	(4.5)	3	5

% = percentage of subjects; E= number of events; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; n = number of subjects with adverse events; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.

The most frequently reported SAEs in both treatment groups were related to infections, hypoglycaemia and hyperglycaemia ("ketosis", "diabetic ketoacidosis" and "blood ketone body increased"); however, no SAEs were reported by ≥5% of subjects.

Five (5) hypoglycaemia-related SAEs in each treatment group were considered possibly or probably related to basal insulin. In each treatment group, 4 of the 5 hypoglycaemia-related SAEs considered related to IDeg and IDet were also considered related to IAsp and 1 event in each treatment group was considered related to IDeg or IDet only. No hypoglycaemia-related SAEs were related to IAsp only.

Within each of the age groups, the number of subjects reporting SAEs was low (Table 20) and hence a comparison of SAEs across treatment groups within age groups is not considered to be clinically meaningful. In both treatment groups, most of the events were single episodes in a single subject. Hypoglycaemia related SAEs were seen in all age groups whereas hyperglycaemia ("ketosis", "diabetic ketoacidosis" and "blood ketone body increased") was only reported in the youngest age group.

Trial 3816

No deaths were reported.

The rates of SAEs were generally low, however, higher with IDegAsp+IAsp than with IDet+IAsp (Table 21). No differences were seen between treatment groups with respect to severity and causality categories, and with respect to recovery. The low number of SAEs should be taken into consideration when evaluating rates between treatment groups as these comparisons are based on a low number of subjects with few events.

Table 21 Serious adverse events – safety analysis set – trial 3816

	IDegAsp OD + IAsp						IDet + IAsp				
N (SAS)		n	(%)	E	R	N (SAS)		n	(%)	E	R
All subjects,	N=181	11	(6.1)	14	26	All subjects,	N=179	7	(3.9)	7	13
1-5 yrs,	N=40	3	(7.5)	4	33	1-5 yrs,	N=41	3	(7.3)	3	24
6-11 yrs,	N=61	4	(6.6)	4	21	6-11 yrs,	N=61	1	(1.6)	1	5
12-17 yrs,	N=80	4	(5.0)	6	25	12-17 yrs,	N=77	3	(3.9)	3	13

% = percentage of subjects; E= number of events; IAsp = insulin aspart; IDegAsp = insulin degludec/insulin aspart; IDet = insulin detemir; n = number of subjects with adverse events; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.

For IDegAsp+IAsp, the most frequently reported SAEs were hypoglycaemia-related AEs (6 events compared to 1 event in the IDet+IAsp treatment group). All other SAEs were single occurrences in both treatment groups and no SAEs were reported by ≥5% of subjects.

All but 1 of the hypoglycaemia related SAEs events in the IDegAsp+IAsp treatment group were considered possibly or probably related to IDegAsp and 4 of these events were also considered related to IAsp. The event in the IDet+IAsp treatment group was considered unlikely related to IDet but possibly related to IAsp.

Within each of the age groups, the number of subjects reporting SAEs was low and hence no clinically meaningful conclusions can be drawn for SAE trends at age group level (Table 21). The majority of the SAEs were single events. Hypoglycaemia related SAEs were seen in all age groups and hyperglycaemia related SAEs were seen in the age groups 1−5 years ('hyperglycaemia') and 12−17 years ('diabetic ketoacidosis').

Laboratory findings

Hypoglycaemia

Definitions of hypoglycaemia

In both trials, classification of hypoglycaemia was performed in accordance with the ISPAD 2009 classification18, which are in line with the principles underlying the ADA classification. Furthermore, hypoglycaemia was classified according to a Novo Nordisk definition of 'confirmed hypoglycaemia'. In normal physiology, hypoglycaemia symptoms occur at a plasma glucose level of approximately <3.1 mmol/L. Therefore, Novo Nordisk used this cut-off value to define 'confirmed hypoglycaemia'.

In addition, classification of ISPAD defined severe hypoglycaemia was performed by an independent, external paediatric endocrinologist in both trials. Assessing whether a hypoglycaemic episode fulfils this broad definition of severe hypoglycaemia is challenging, particularly when considering the more subjective criteria of 'altered mental status and cannot assist in his own care' for episodes involving young children. Due to this challenge, an independent, external paediatric endocrinologist conducted a blinded pre-specified classification of all reported episodes of severe hypoglycaemia to ensure a centralised expert assessment of severe hypoglycaemia. The assessment was based on case narratives and laboratory values. The statistical comparison of rates of severe hypoglycaemia was based on the investigator's classification.

Confirmed hypoglycaemia

Trial 3561

The rate of confirmed hypoglycaemia was similar for the IDeg+IAsp and IDet+IAsp treatment groups (5771 vs. 5405 episodes per 100 PYE; Table 22) and no statistically significant difference was seen. The majority of the confirmed hypoglycaemic episodes occurred during daytime (diurnal) in both treatment groups.

In both treatment groups, the rate of confirmed hypoglycaemia was either lower or similar for children aged 1–5 years compared to the overall rate (Table 22). The majority of the confirmed hypoglycaemic episodes occurred during the daytime (diurnal) across all age groups.

Table 22 Confirmed hypoglycaemic episodes – safety analysis set – trial 3561

IDeg OD + IAsp					IDet + IAsp				
N (SAS)	**n**	**(%)**	**E**	**R**	**N (SAS)**	**n**	**(%)**	**E**	**R**
All subjects, N=174	171	(98.3)	9317	5771	All subjects, N=175	168	(96.0)	7967	5405
1-5 yrs, N=43	42	(97.7)	2248	5776	1-5 yrs, N=41	40	(97.6)	1221	3579
6-11 yrs, N=70	69	(98.6)	4304	6495	6-11 yrs, N=68	65	(95.6)	3999	6840
12-17 yrs, N=61	60	(98.4)	2765	4913	12-17 yrs, N=66	63	(95.5)	2747	5011

% = percentage of subjects with the event; E= number of events; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; n = number of subjects with confirmed hypoglycaemia; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.
Confirmed hypoglycaemia was defined as hypoglycaemic episodes confirmed by plasma glucose <3.1 mmol/L or severe (according to ISPAD 2009 classification).

Trial 3816

Similar rates of confirmed hypoglycaemia were observed in the IDegAsp+IAsp and IDet+IAsp treatment groups (4623 vs. 4955 episodes per 100 PYE; Table 23) with no statistically significant difference between the groups. The majority of the confirmed hypoglycaemic episodes occurred during daytime (diurnal) in both treatment groups.

In both treatment groups, the rate of confirmed hypoglycaemia was lower for children aged 1–5 years compared to the overall rate (Table 23). As seen in trial **3561**, a higher rate of confirmed hypoglycaemia was seen in children aged 6–11 years. The majority of the confirmed hypoglycaemic episodes occurred during the daytime (diurnal) across all age groups.

Table 23 Confirmed hypoglycaemic episodes – safety analysis set – trial 3816

IDegAsp OD + IAsp					IDet + IAsp				
N (SAS)	**n**	**(%)**	**E**	**R**	**N (SAS)**	**n**	**(%)**	**E**	**R**
All subjects, N=181	168	(92.8)	2532	4623	All subjects, N=179	164	(91.6)	2672	4955
1–5 yrs, N=40	39	(97.5)	520	4335	1–5 yrs, N=41	37	(90.2)	559	4564
6–11 yrs, N=61	56	(91.8)	960	5140	6–11 yrs, N=61	58	(95.1)	1065	5809
12–17 yrs, N=80	73	(91.3)	1052	4366	12–17 yrs, N=77	69	(89.6)	1048	4490

% = percentage of subjects with the event; E= number of events; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; n = number of subjects with confirmed hypoglycaemia; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.
Confirmed hypoglycaemia was defined as hypoglycaemic episodes confirmed by plasma glucose <3.1 mmol/L or severe (according to ISPAD 2009 classification).

Severe hypoglycaemia

Trial 3561

The majority of subjects in both treatment groups had no episodes of ISPAD defined severe hypoglycaemia (82% and 86% of subjects with IDeg+IAsp and IDet+IAsp, respectively) and the percentage of days without ISPAD defined severe hypoglycaemia was similar (99.9%) for the two treatment groups. The overall number and rate of ISPAD defined severe episodes of hypoglycaemia were higher in the IDeg+IAsp treatment group than the IDet+IAsp treatment group (Table 24), but no statistically significant difference between treatment groups was seen.

When evaluating severe hypoglycaemia it is important to note that these were distributed unevenly between subjects. In all, 11 subjects (3.2%) reported 4 or more episodes of ISPAD defined severe hypoglycaemia: 8 subjects in the IDeg+IAsp treatment group (3 in the age group 1−5 years, 4 in the age group 6−11 years and 1 in the age group 12−17 years) and 3 subjects in the IDet+IAsp treatment group (2 in the age group 6−11 years and 1 in the age group 12−17 years. In the IDeg+IAsp treatment group, these 8 subjects (4.6%) accounted for more than half of all reported episodes of severe hypoglycaemia (42 events). In the IDet+IAsp treatment group, these 3 subjects (1.7%) accounted for 17 events (35%).

The majority of the ISPAD defined severe hypoglycaemic episodes (close to 80%) occurred during daytime (diurnal) in both treatment groups. In the majority of cases, bolus insulin was the last insulin administered prior to the event.

Table 24 Severe hypoglycaemic episodes – safety analysis set – trial 3561

IDeg OD + IAsp					IDet + IAsp				
N (SAS)	**n**	**(%)**	**E**	**R**	**N (SAS)**	**n**	**(%)**	**E**	**R**
All subjects, N=174	31	(17.8)	82	51	All subjects, N=175	24	(13.7)	48	33
1-5 yrs, N=43	8	(18.6)	19	49	1-5 yrs, N=41	6	(14.6)	11	32
6-11 yrs, N=70	14	(20.0)	47	71	6-11 yrs, N=68	11	(16.2)	20	34
12-17 yrs, N=61	9	(14.8)	16	28	12-17 yrs, N=66	7	(10.6)	17	31

% = percentage of subjects with the event; E= number of events; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; n = number of subjects with severe hypoglycaemia; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.

Severe hypoglycaemia: subject has altered mental status and cannot assist in his care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or i.v. glucose).

The evaluation of ISPAD defined severe hypoglycaemia was based on few subjects in each age group (6 to 14 subjects across age groups) with relatively few episodes and the data should be interpreted with caution. In both treatment groups, the rate of ISPAD defined severe hypoglycaemia was similar for children aged 1−5 years compared to the overall rate (Table 24). The higher rate in the 6−11 year age group in the IDeg+IAsp treatment group was driven by 5 subjects reporting 22 of the 28 episodes reported during the extension period.

An independent, external paediatric endocrinologist conducted a blinded pre-specified classification ('altered mental status and cannot assist in his care', 'semiconscious or unconscious' and 'coma ± convulsion') of all reported episodes of ISPAD defined severe hypoglycaemia to ensure a centralised expert assessment of severe hypoglycaemia. In the age groups 1−5 years, 6−11 years and 12−17 years, 'altered mental status and cannot assist in his care' was seen in 9 subjects (14 episodes), 15 subjects (35 episodes) and 8 subjects (15 episodes), respectively. 'Semiconscious or unconscious' was seen in 1 subject (1 episode), 8 subjects (8 episodes) and 4 subjects (8 episodes) in the age groups 1−5 years, 6−11 years and 12−17 years, respectively. 'Coma ± convulsion' was seen in 6 subjects (10 episodes), 4 subjects (5 episodes) and 3 subjects (3 episodes) in the age groups 1−5 years, 6−11 years and 12−17 years, respectively.

The rate of severe hypoglycaemic episodes assessed by the independent, external paediatric endocrinologist was lower in both treatment groups and for all age groups compared to the rate of severe ISPAD defined hypoglycaemic episodes.

Trial 3816

The majority of subjects in both treatment groups had no severe hypoglycaemic episodes (93.9% and 98.3% in the IDegAsp+IAsp and IDet+IAsp treatment groups, respectively). The majority of the severe hypoglycaemic episodes occurred during daytime (diurnal) in both treatment groups. The overall number and rate of ISPAD defined severe episodes of hypoglycaemia were higher in the IDegAsp+IAsp treatment group than the IDet+IAsp treatment group (Table 25), but no statistically significant difference between treatment groups was seen.

Table 25 Severe hypoglycaemic episodes – safety analysis set – trial 3816

	IDegAsp OD + IAsp					IDet + IAsp			
N (SAS)	**n**	**(%)**	**E**	**R**	**N (SAS)**	**n**	**(%)**	**E**	**R**
All subjects, N=181	11	(6.1)	14	26	All subjects, N=179	3	(1.7)	4	7
1–5 yrs, N=40	4	(10.0)	5	42	1–5 yrs, N=41	2	(4.9)	2	16
6–11 yrs, N=61	3	(4.9)	4	21	6–11 yrs, N=61	0	(0)	0	0
12–17 yrs, N=80	4	(5.0)	5	21	12–17 yrs, N=77	1	(1.3)	2	9

% = percentage of subjects with the event; E= number of events; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; n = number of subjects with confirmed hypoglycaemia; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.

Confirmed hypoglycaemia was defined as hypoglycaemic episodes confirmed by plasma glucose <3.1 mmol/L or severe (according to ISPAD 2009 classification).

The evaluation of ISPAD defined severe hypoglycaemia was based on few subjects in each age group (0 to 4 subjects across age groups) with few episodes. Consequently, comparisons within age groups should be interpreted with caution. In both treatment groups, the rate of ISPAD defined severe hypoglycaemia was higher for children aged 1–5 years compared to the overall rate (Table 25).

As in trial **3561**, a blinded pre-specified classification of all reported episodes of ISPAD defined severe hypoglycaemia was conducted by an independent, external paediatric endocrinologist. "Altered mental status and cannot assist in his care" was seen in 2 subjects in each age group (with 3, 2 and 2 episodes in the age groups 1–5 years, 6–11 years and 12–17 years, respectively). "Semiconscious or unconscious" was seen in 3 subjects (3 episodes) and 2 subjects (3 episodes) in the age groups 1–5 years and 12–17 years, respectively. "Coma ± convulsion" was seen in 1 subject in each age group (with 1, 2 and 1 episodes in the age groups 1–5 years, 6–11 years and 12–17 years, respectively).

Except for 1 event in the IDegAsp+IAsp treatment group, all the ISPAD defined severe hypoglycaemic episodes was also assessed as severe by the external paediatric endocrinologist.

Nocturnal hypoglycaemia

Trial 3561

Nocturnal confirmed hypoglycaemic episodes

The proportions of subjects with nocturnal confirmed hypoglycaemia were similar for the two treatment groups, while the observed rate of nocturnal confirmed episodes was lower with IDeg+IAsp compared to IDet+IAsp, (603 and 760 episodes per 100 PYE, respectively) (Table 26), but no statistically significant difference between treatment groups was seen.

The rate of nocturnal confirmed hypoglycaemic episodes increased with increasing age in both treatment groups (Table 26). The higher rate in adolescents compared to the younger age groups may be attributed to

adolescent lifestyle as they are expected to be more active during the period defined as “nocturnal” in this trial.

Table 26 Nocturnal confirmed hypoglycaemic episodes – safety analysis set – trial 3561

IDeg OD + IAsp					IDet + IAsp				
N (SAS)	n	(%)	E	R	N (SAS)	n	(%)	E	R
All subjects, N=174	133	(76.4)	973	603	All subjects, N=175	125	(71.4)	1120	760
1-5 yrs, N=43	27	(62.8)	169	434	1-5 yrs, N=41	24	(58.5)	85	249
6-11 yrs, N=70	52	(74.3)	382	577	6-11 yrs, N=68	52	(76.5)	423	724
12-17 yrs, N=61	54	(88.5)	422	750	12-17 yrs, N=66	49	(74.2)	612	1116

% = percentage of subjects with the event; E= number of events; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; n = number of subjects with event; N = number of subjects in the safety analysis set; OD = once daily; R = event rate per 100 patient years of exposure; SAS = safety analysis set; yrs = years.

Confirmed hypoglycaemia: subject has altered mental status and cannot assist in his care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or i.v. glucose) and/or have a recorded plasma glucose <3.1 mmol/L. Nocturnal period: The period between 23:00 and 07:00 (both included).

Nocturnal severe hypoglycaemic episodes

The number of nocturnal severe hypoglycaemic episodes was low in both treatment groups; 18 episodes in 10 subjects in the IDeg+IAsp treatment group and 10 episodes in 9 subjects in the IDet+IAsp treatment group corresponding to a rate of 11 and 7 episodes per 100 PYE, respectively, which precluded meaningful statistical comparison between treatments.

In children aged 1−5 years and adolescents aged 12−17 years, 3 nocturnal severe hypoglycaemic episodes were reported in each treatment group. In the age group 6−11 years, 12 episodes in 7 subjects were reported in the IDeg+IAsp treatment group and 4 episodes in 4 subjects in the IDet+IAsp treatment group.

Trial 3816

Nocturnal confirmed hypoglycaemic episodes

The observed rates of nocturnal confirmed hypoglycaemic episodes were similar with IDegAsp+IAsp and IDet+IAsp (577 and 540 episodes per 100 PYE) and there was no statistically significant difference between treatment groups.

As seen in trial **3561**, the rate of nocturnal confirmed hypoglycaemic episodes increased with increasing age in both treatment groups (Table 27).

Table 27 Nocturnal confirmed hypoglycaemic episodes – safety analysis set – trial 3816

IDegAsp OD + IAsp					IDet + IAsp				
N (SAS)	n	(%)	E	R	N (SAS)	n	(%)	E	R
All subjects, N=181	101	(55.8)	316	577	All subjects, N=179	106	(59.2)	291	540
1–5 yrs, N=40	18	(45.0)	55	459	1–5 yrs, N=41	21	(51.2)	52	425
6–11 yrs, N=61	38	(62.3)	108	578	6–11 yrs, N=61	34	(55.7)	85	464
12–17 yrs, N=80	45	(56.3)	153	635	12–17 yrs, N=77	51	(66.2)	154	660

N: number of subjects in the safety analysis set, n: number of subjects with confirmed hypoglycaemia. SAS: safety analysis set, %: Percentage of subjects with the event, E: Number of events, R: Event rate per 100 patient year(s) of exposure.

Nocturnal confirmed hypoglycaemia: subject has altered mental status and cannot assist in his care,is semiconscious or unconscious,or in coma ± convulsions and may require parenteral therapy (glucagon or i.v. glucose) and/or have a recorded plasma glucose <3.1 mmol/L.

Nocturnal period: the period between 23:00 and 07:00 (both included).

Nocturnal severe hypoglycaemic episodes

The number of nocturnal severe hypoglycaemic episodes was low in both treatment groups (2 episodes in each group), which precluded meaningful statistical comparison between treatments. In the IDegAsp+IAsp treatment group, both nocturnal severe hypoglycaemic episodes were reported in 1 subject (age group 6–11 years) and the episodes in the IDet+IAsp treatment group were reported by 1 subject in the age group 1–5 years and 1 subject in the age group 12–17 years.

Hyperglycaemia

Trial 3561

In trial **3561**, the threshold for defining hyperglycaemia was 11.1 mmol/L, which is considered relatively low especially for a paediatric T1DM population. Thus, the high number of hyperglycaemic episodes is not surprising. In both treatment groups, all subjects experienced hyperglycaemic episodes and with similar observed rates (Table 28); no statistically significant difference between treatment groups was seen.

A statistically significantly lower rate of hyperglycaemic episodes with ketosis (blood ketones >1.5 mmol/L) was observed with IDeg+IAsp compared to IDet+IAsp. The lower rate of ketosis with IDeg+IAsp was observed across all age groups (Table 28) which is consistent with the lower rate of "blood ketone bodies increased" reported as AEs with IDeg+IAsp compared to IDet+IAsp.

In both treatment groups, children aged 1–5 years had a higher rate of hyperglycaemic episodes with ketosis compared to the two older age groups, albeit these differences were based on a relatively low number of subjects with ketosis (Table 28).

Table 28 Hyperglycaemic episodes and episodes of ketosis – safety analysis set – trial 3561

	IDeg OD + IAsp				IDet + IAsp			
	N	(%)	E	R	N	(%)	E	R
All subjects	174				175			
Hyperglycaemic episodes	174	(100.0)	58679	36344	175	(100.0)	52831	35840
Episodes of ketosis	29	(16.7)	109	68	45	(25.7)	161	109
Children (1-5 years)	43				41			
Hyperglycaemic episodes	43	(100.0)	15272	39241	41	(100.0)	10452	30634
Episodes of ketosis	14	(32.6)	52	134	17	(41.5)	55	161
Children (6-11 years)	70				68			
Hyperglycaemic episodes	70	(100.0)	25766	38885	68	(100.0)	25226	43148
Episodes of ketosis	9	(12.9)	33	50	17	(25.0)	54	92
Adolescents (12-17 years)	61				66			
Hyperglycaemic episodes	61	(100.0)	17641	31349	66	(100.0)	17153	31288
Episodes of ketosis	6	(9.8)	24	43	11	(16.7)	52	95

N: Number of subjects, %: Percentage of subjects with the event, E: Number of events,
R: Event rate per 100 patient year(s) of exposure
Hyperglycaemic episodes: all episodes registered in hyperglycaemic episode form
Episodes of ketosis: self-monitored blood ketones >1.5 mmol/L

Trial 3816

In trial **3816**, the threshold for defining hyperglycaemia was higher than the threshold in trial **3561** (14.0 mmol/L compared to 11.1 mmol/L). A similar proportion of subjects experienced hyperglycaemic episodes; 39.8% with IDegAsp+IAsp and 40.8% with IDet+IAsp (Table 29) and no statistically significant difference between treatment groups was seen in rates of hyperglycaemic episodes.

Further, no statistically significant differences between treatment groups in the rates of hyperglycaemic episodes with ketosis were seen (blood ketones >1.5 mmol/L). In the IDegAsp+IAsp treatment group 6

events were reported for 4 subjects compared to 12 events reported for 8 subjects in the IDet+IAsp treatment group (Table 29).

Across the three age groups, children aged 6–11 years in the IDegAsp+IAsp treatment group had a higher rate of hyperglycaemic episodes compared to the other age groups in both treatment groups. Within each of the age groups, the number of subjects reporting hyperglycaemic episodes with ketosis was low (Table 29).

Table 29 Hyperglycaemic episodes and episodes of ketosis – safety analysis set – trial 3816

	IDegAsp OD + IAsp				IDet + IAsp			
	N	(%)	E	R	N	(%)	E	R
All subjects	181				179			
Hyperglycaemic episodes	72	(39.8)	599	1094	73	(40.8)	449	833
Episodes of ketosis	4	(2.2)	6	11	8	(4.5)	12	22
Children 1-5 years	40				41			
Hyperglycaemic episodes	19	(47.5)	98	817	14	(34.1)	117	955
Episodes of ketosis	2	(5.0)	3	25	2	(4.9)	4	33
Children 6-11 years	61				61			
Hyperglycaemic episodes	25	(41.0)	327	1751	25	(41.0)	139	758
Episodes of ketosis	1	(1.6)	1	5	3	(4.9)	3	16
Adolescents 12-17 years	80				77			
Hyperglycaemic episodes	28	(35.0)	174	722	34	(44.2)	193	827
Episodes of ketosis	1	(1.3)	2	8	3	(3.9)	5	21

N: Number of subjects, %: Percentage of subjects with the event, E: Number of events, R: Event rate per 100 patient year(s) of exposure
Hyperglycaemic episodes: All episodes registered in hyperglycaemic episode form with plasma glucose >14.0 mmol/L where subject looks/feels ill
Ketosis: Blood ketones >1.5 mmol/L

Antibodies

Antibodies to trial products were only measured in trial **3561**.

There was no indication of a differential development of tolerance to insulin with IDeg and IDet, nor was there any indication of antibody development against IAsp. The observed mean levels of insulin antibodies cross-reacting to human insulin decreased slightly with IDeg and increased slightly with IDet. The same patterns were observed for the three age groups, though the mean levels at baseline varied slightly with age being highest in children aged 1–5 years in both treatment groups.

The levels of IDeg-, IDet- and IAsp-specific antibodies remained low throughout the treatment period and the same pattern was observed for the three age groups. No apparent correlation between antibodies and HbA1c or between antibodies and total daily insulin dose was seen.

Clinical laboratory evaluations

Mean biochemistry, haematology and lipid laboratory values remained stable during trials **3561** and **3816**, and there were no apparent differences between the two treatment groups in the mean level of the specific laboratory parameters assessed. The majority of subjects' values remained within the reference ranges at baseline and at the end of trial. Few clinically relevant changes from baseline in individual laboratory parameters were reported as AEs. None of the AEs were severe or serious and none were considered as having a possible or probable relation to IDeg, IDegAsp, IDet or IAsp.

Other safety assessments

No clinically relevant differences from baseline to end of treatment were observed for vital signs and physical examination between IDeg+IAsp and IDet+IAsp (trial **3561**) or between IDegAsp+IAsp and IDet+IAsp (trial **3816**).

An increase in weight SD score was seen in the IDeg+IAsp and IDegAsp+IAsp treatment groups and a decrease was seen in both IDet+IAsp treatment groups during the treatment periods (52 weeks for trial **3561** and 16 weeks for trial **3816**). The changes from baseline were statistically significantly different between treatment groups indicating less weight gain with IDet+IAsp compared with IDeg+IAsp and IDegAsp+IAsp. This is in accordance with the results from previous studies showing that adult and paediatric subjects with T1DM and adults with T2DM typically gain less weight with IDet than with other basal insulin products.

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

In trial **3561**, 3 subjects (1 from each age group, all in the IDet+IAsp treatment group) withdrew from the trial due to an AEs: 1 due to "wrong dose administered" (non-serious), 1 due to "anxiety disorder"(serious) and 1 due to "hypoglycaemia seizure" (serious). The anxiety disorder was considered unlikely related to IDet and IAsp while the two other events were considered probably or possibly related to IDet and IAsp.

In trial **3816**, 1 subject (age group 6−11 years, IDegAsp+IAsp treatment group) was withdrawn from the trial due to a non-serious AE of "hypoglycaemic seizure". The event was considered probably related to IDegAsp and unlikely related to IAsp. Additionally, 1 subject (age group 12−17 years, IDet+IAsp treatment group) withdrew due to "intermittent but recurrent hypoglycaemia attributed to trial product" reported under "other" reasons for withdrawal.

Post marketing experience

Review of the cumulative post-marketing safety data received for children aged above 1 year and below 2 years in the period from 1 January 2002 to 27 February 2016 has not identified any safety concerns in connection with the use of NovoRapid in this age group. The evaluation is based on more than 45 case reports. Further, no unexpected or medically significant patterns have been observed in the cumulative post-marketing experience of NovoRapid in type, distribution or seriousness of post-marketing adverse drug reactions reported for children aged 1 year, as compared to children aged 2 to 18 years.

2.5.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

The focus of this safety discussion will be on the data generated in the age group 1-5 years. In total the two trials have generated 97 years of exposure in this age group. Five children aged 1-2 years were included in the two trials. From the exposure data it may be concluded that all these children completed the main studies and three out of four children included in trial **3561** also completed the extension phase of the study. Thus, albeit limited, these data indicate that the treatment with insulin aspart in children aged 1-2 years old is tolerated.

Although the percentage of patients reporting AEs was lowest in the youngest age group in trial **3561**, the reporting rate per 100 exposure years was highest in this group. The most common events were related to infections and GI disorders as may be expected in this age group. "Blood ketone body increased" was reported at a higher rate in the youngest age group compared to the safety analysis set (114 events per 100 PYE vs 70 events per 100 PYE). In trial **3816**, a comparable pattern was observed. The highest rates were observed for infections and GI disorders, again which are common SOCs for AEs for this paediatric age group.

In both trials, only a small proportion of events were considered probably or possibly related to insulin treatment (in the range of 10%, many events assessed related to both basal and bolus insulin). The rate of events considered related was numerically similar for basal and bolus insulin.

In both trials, the number of SAEs were few and in most cases not considered related to treatment. Ten hypoglycaemia events were recorded in trial **3561**, none of which was considered related to IAsp only. Hyperglycaemia and hyperglycaemia related events were only reported in the youngest age group. In trial **3816**, seven hypoglycaemia events were recorded, one of which was considered related to IAsp only. Hyperglycaemia and hyperglycaemia related events were reported in the youngest and oldest age groups.

Hypoglycaemia, being the major safety issue with insulin treatment, was analysed in detail. Acceptable definitions of hypoglycaemia were applied and severe hypoglycaemia events were also assessed by an independent external paediatric endocrinologist.

In trial **3561**, compared to the overall rate of confirmed hypoglycaemias, the event rates were similar or lower in the age group 1-5 years. In trial **3816**, the event rates were lower in the age group 1-5 years in both treatment arms. The highest rate was observed in children aged 6–11 years in both trials, which may be due to challenges in controlling glycaemia during school hours. Most hypoglycaemias occurred during daytime, thus may be potentially be attributable to bolus insulin.

The majority of patients never experienced any severe hypoglycaemia (82-86% in trial **3561** and 94-98% in trial **3816**). The rate of severe hypoglycaemias did not differ in the youngest age group compared to the overall population in trial **3561** but was higher in the youngest age group compared to the overall population in trial **3816**. This is possibly related to the basal insulin therapy as mixed insulin (IDegAsp) offers less flexibility in dosing. It is noted that bolus insulin was often the latest insulin dose given before the event at least in trial **3561**.

The rate of nocturnal hypoglycaemias was lower in the youngest age group compared to the overall population in both trials. Very few severe nocturnal events were recorded (28 events, trial **3561**; 4 events, trial **3816**). In the youngest age group, in total 6 episodes occurred in in trial **3561** and 1 in trial **3816**.

Hyperglycaemia, being a marker for inadequate insulin dosing, was also analysed in more detail. In trial **3561** a low cut-off for hyperglycaemia was applied which in part explains the high rates observed in this trial. No relevant differences between age groups were observed. Events of ketosis were more frequent in the youngest age group. This may possibly be related to the higher rates of “infections and infestations” observed in the youngest age group, but also that fluctuations in blood glucose levels are usual. It may also be that insulin is sometimes given at too low doses in this age group due to fear of hypoglycaemia which may be more difficult to diagnose and handle in young children. In trial **3816**, a higher cut-off was applied which is reflected in lower rates of hyperglycaemia in this trial. Apart from a higher reporting in children 6-11 years treated with IDegAsp, the rates were comparable across age groups. Again the rate of ketosis was somewhat higher in the age group 1-5 years.

There was no difference in the levels of IDeg-, IDet- and IAsp-specific antibodies across age groups and the levels remained low.

As expected, clinical laboratory evaluations did not show any relevant changes.

Some differences in weight were observed between treatment groups, with less weight gain in the IDet treated groups. This is in line with previous data for IDet.

No subjects in the age group 1-5 years of age withdrew due to AEs.

During the period from 1 January 2002 to 27 February 2016 for which NovoRapid has been on the market, the MAH claims that no safety concerns have arisen for the age group 1-2 years. This is based on 45 case reports.

2.5.2. Conclusions on clinical safety

With trials **3561** and **3816**, additional safety data on insulin aspart has been provided for children and adolescents. In particular, data in 165 younger children 1-5 years of age is available, including five children 1-2 years of age. The data give no indication of a different safety profile in younger children compared to older children and no new safety concerns arise. Notably, the rate of hypoglycaemias was numerically lower in the youngest age group compared to the older age groups. A higher occurrence of hyperglycaemia related events in the youngest age group possibly reflects the difficulties in calculating the optimal dose in these children while avoiding hypoglycaemia.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

No RMP was submitted with this variation, and this was accepted. The information in the RMP can be aligned at the occasion of the next RMP update.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The following changes to the SmPC were accepted in the context of this variation.

4.1 Therapeutic indications

NovoRapid is indicated for treatment of diabetes mellitus in adults, adolescents and children aged 1 ~~2~~ year~~s~~ and above.

4.2 Posology and method of administration

Paediatric population

NovoRapid can be used in children and adolescents ~~and children~~ aged 1 ~~2~~ year~~s~~ and above in preference to soluble human insulin when a rapid onset of action might be beneficial ~~(see sections 5.1 and 5.2).~~, f~~F~~or example, in the timing of the injections in relation to meals (see sections 5.1 and 5.2).

The safety and efficacy of NovoRapid in children below 1 ~~2~~ year~~s~~ of age have not been established. No data are available.

4.4 Special warnings and precautions for use

Hypoglycaemia

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Especially in children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake, physical activities and current blood glucose level in order to minimise the risk of hypoglycaemia.

5.1 Pharmacodynamic properties

Paediatric population

The efficacy and safety of NovoRapid given as bolus insulin in combination with either insulin detemir or insulin degludec as basal insulin has been studied for up to 12 months, in two randomised controlled clinical

trials in adolescents and children aged 1 to less than 18 years (n=712). The trials included 167 children aged 1-5 years, 260 aged 6-11 and 285 aged 12-17. The observed improvements in HbA1c and the safety profiles were comparable between all age groups.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Both studies (**3561, 3816**) were designed to evaluate the efficacy in terms of glycaemic control, i.e. HbA1c, of the basal insulin regimens. Therefore no firm conclusions on the effect of insulin aspart on HbA1c per se or in the subgroup of small children (less than 2 years, in total 5 children) can be drawn. There is no indication of a difference in the effect on HbA1c across age groups. The 8-point SMPG profiles, which reflect the effect of the bolus insulin on postprandial glucose levels, were comparable between treatments and across age groups.

Uncertainty in the knowledge about the beneficial effects

No comparisons between insulin aspart and other bolus insulins have been provided.

Risks

Unfavourable effects

The safety data from trials **3561** and **3816** is based on a total of 709 children and adolescent out of which 165 patients were aged 1-5 years. In total the two trials have generated 97 years of exposure in the youngest age group. Five children aged 1-2 years were included in the two trials. From the exposure data it may be concluded that all these children completed the main studies and three out of four children included in trial **3561** also completed the extension phase of the study. Thus, albeit limited, these data indicate that the treatment with insulin aspart in children aged 1-2 years old is well tolerated.

The reporting rate of adverse events per 100 exposure years was highest in the age group 1-5 years in both trials. The most common events were related to infections and GI disorders as may be expected in this age group. “Blood ketone body increased” was reported at a higher rate in the youngest age group compared to the safety analysis set in trial **3561** (114 events per 100 PYE vs 70 events per 100 PYE). In both trials, only a small proportion of events were considered probably or possibly related to insulin treatment (in the range of 10%, many events assessed related to both basal and bolus insulin therefore no exact figure is given).

In both trials, SAEs were few and in most cases not considered related to treatment. Ten (10) hypoglycaemia events classified as SAEs were recorded in trial **3561**, none of which was considered related to IAsp only. Hyperglycaemia and hyperglycaemia related events, classified as SAEs, were only reported in the youngest age group. In trial **3816**, seven (7) hypoglycaemia events classified as SAEs were recorded, one (1) of which was considered related to IAsp only. Hyperglycaemia and hyperglycaemia related events were reported in the youngest and oldest age groups.

In trial **3561**, compared to the overall rate of confirmed hypoglycaemias, the event rates were similar or lower in the age group 1-5 years. In trial **3816**, the event rates were lower in the age group 1-5 years in both treatment arms. The highest rate was observed in children aged 6–11 years in both trials, which may be due

to challenges in controlling glycaemia during school hours. Most hypoglycaemias occurred during daytime, thus may be potentially be attributable to bolus insulin.

The majority of patients never experienced any severe hypoglycaemia (82-86% in trial **3561** and 94-98% in trial **3816**). The rate of severe hypoglycaemias did not differ in the youngest age group compared to the overall population in trial **3561** but was higher in the youngest age group compared to the overall population in trial **3816**. This is possibly related to the basal insulin therapy as mixed insulin (IDegAsp) offers less flexibility in dosing. It is noted that bolus insulin was often the latest insulin dose given before the event at least in trial **3561**. The rate of nocturnal hypoglycaemias was lower in the youngest age group compared to the overall population in both trials. Very few severe nocturnal events were recorded (28 events, trial **3561**; 4 events, trial **3816**). In the youngest age group, in total 6 episodes occurred in in trial **3561** and 1 in trial **3816**.

Hyperglycaemia, being a marker for inadequate insulin dosing, was also analysed in more detail. In trial **3561**, no relevant differences between age groups were observed. Events of ketosis were more frequent in the youngest age group. This may possibly be related to the higher rates of “infections and infestations” observed in the youngest age group, but also that fluctuations in blood glucose levels are usual. It may also be that insulin is sometimes given at too low doses in this age group due to fear of hypoglycaemia which may be more difficult to diagnose and handle in young children. In trial **3816**, apart from a higher reporting in children 6-11 years treated with IDegAsp, the rates were comparable across age groups. Again the rate of ketosis was somewhat higher in the age group 1-5 years.

There was no difference in the levels of IDeg-, IDet- and IAsp-specific antibodies across age groups and the levels remained low, and as expected, clinical laboratory evaluations did not show any relevant changes. Some differences in weight were observed between treatment groups, with less weight gain in the IDet treated groups. This is in line with previous data for IDet.

Notably, no subjects in the age group 1-5 years of age withdrew due to AEs.

No safety concerns have arisen for the age group 1-2 years from post-marketing experience.

Uncertainty in the knowledge about the unfavourable effects

No comparative data have been provided, however, the two trials submitted have provided an substantially expanded safety data base in the youngest age group, 1-5 years.

Importance of favourable and unfavourable effects

T1DM is rare in very young children but insulin treatment is mandatory to prevent death, irrespective of age. With the current submission, further data to support the use of NovoRapid in children aged 1-2 year has been provided. Although the studies were not designed to investigate the efficacy of the bolus treatment, but the basal insulin, the data is considered sufficient to support that NovoRapid is efficient also in the age group 1-2 years of age since no differences in efficacy was observed between age groups.

In this context it should be noted that the use of insulin aspart in children aged 2 years and older was approved in procedure EMEA/H/C/258/II/34 in March 2005, based on one open label, cross-over trial conducted in 26 children, aged 2-6 years, with type I diabetes in which 12 weeks treatment with IAsp and human insulin was compared. In this trial, six children were between 6-7 years old, while only four children were younger than four years. The CHMP considered, however, that on scientific grounds it would be possible to extrapolate experience from older children to provide sufficient reassurance regarding efficacy and safety within the claimed age range. With the data submitted with trials **3561** and **3816**, the clinical experience within the trial context is expanded with a relatively large number of subjects in the age 1-5 years (165 patients) without any indication of a different effect when compared to older children and

adolescents. Although the number of patients in the age group 1-2 years is low (5 subjects), there is no reason to believe that the effect is different in this age group compared to patients aged 2 years and above.

With trials **3561** and **3816**, additional safety data on insulin aspart has been provided for children and adolescents. In particular, data in younger children 1-5 years of age is available, including data in five children 1-2 years of age. The data give no indication of a different safety profile in younger children compared to older children and no new safety concerns arise. Hypoglycaemia occurred, with one exception (IDeg/Asp treated children), at similar or lower rates than in other age groups. A higher occurrence of hyperglycaemia related events in the youngest age group possibly reflects the difficulties in calculating the optimal dose in these children while avoiding hypoglycaemia. Taking into account that children aged 1-2 year possibly are under closer monitoring by their caregivers than older children, hypo- and hyperglycaemic events can be handled. Furthermore, all children in the age group 1-2 years completed the studies, indicating that the treatment was well tolerated.

Benefit-risk balance

The benefit-risk balance for NovoRapid in the treatment of diabetes mellitus in children aged 1-2 year of age is considered positive.

4. Recommendations

Outcome

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

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

Extension of Indication to include the use of NovoRapid in children from 1 to 2 years of age for the treatment of diabetes mellitus; as a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.