EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/CHMP/486455/2016
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Ryzodeg

International non-proprietary name: insulin degludec / insulin aspart

Procedure No. EMEA/H/C/002499/II/0017

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

Note

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

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Table of contents

List of abbreviations

AE	adverse event
ANOVA	analysis of variance
BID	*bis in die* (twice daily)
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organisation
CTR	clinical trial report
CV%	coefficient of variation
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice
HbA1C	glycosylated haemoglobin
IAsp	insulin aspart
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDeg	insulin degludec
IDegAsp	insulin degludec/insulin aspart
IDet	insulin detemir (Levemir®)
ISPAD	International Society for Pediatric and Adolescent Diabetes
ITT	intent-to-treat
LOCF	last observation carried forward
MAA	marketing authorisation application
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
OAD	oral antidiabetic drug
OD	once daily
PDCO	Paediatric Committee, European Medicines Agency
PG	plasma glucose
PIP	paediatric investigation plan
PP	per protocol
PYE	patient-years of exposure
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SMPG	self-measured plasma glucose
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
US	United States

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 12 October 2015 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, II and IIIB

Extension of Indication to include paediatric population from 1 to 18 year of age for Ryzodeg; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 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 9.1.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0034/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0034/2015 was completed.

The PDCO issued an opinion on compliance for the PIP P/0034/2015.

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 were:

CHMP Rapporteur: Kristina Dunder CHMP Co-Rapporteur: N/A

PRAC Rapporteur: Qun-Ying Yue

Timetable	Actual dates
Submission date	12 October 2015
Start of procedure	31 October 2015
CHMP Rapporteur's preliminary assessment report circulated on	21 December 2015
PRAC Rapporteur's preliminary assessment report circulated on	21 December 2015
PRAC RMP advice and assessment overview adopted by PRAC on	14 January 2016
CHMP Rapporteur's updated assessment report circulated on	21 January 2016
Request for supplementary information and extension of timetable adopted by the CHMP on	28 January 2016
MAH's responses submitted to the CHMP on	26 February 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	29 March 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	29 March 2016
PRAC RMP advice and assessment overview adopted by PRAC on	14 April 2016
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	21 April 2016
Second request for supplementary information and extension of timetable adopted by the CHMP on	28 April 2016
MAH's responses submitted to the CHMP on	23 May 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	27 May 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	7 June 2016
PRAC RMP advice and assessment overview adopted by PRAC on	9 June 2016
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	16 June 2016
CHMP opinion	23 June 2016

2. Scientific discussion

2.1. Introduction

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

Insulin degludec/insulin aspart (IDegAsp) (Ryzodeg, EMEA/H/C/002499), is a soluble co-formulation of the long-acting insulin degludec (IDeg) and rapid-acting insulin aspart (IAsp). The IDegAsp co-formulation consists of 70% IDeg and 30% IAsp. IDegAsp is approved for use in adults in EU since 21 January 2013.

The current ISPAD (International Society for Paediatric and Adolescent Diabetes) guidelines for treatment of children and adolescents with T1DM state that premixed insulins (fixed ratio of basal and bolus insulins) are not recommended for paediatric use, since they remove the flexibility offered by separate adjustment of the two types. However, this guidance is predominantly based on evidence from studies in adolescents. Preadolescent children on premixed insulin, either alone or in combination with short- and intermediate-acting insulin, showed similar glycaemic control to those on a combination of short- and longer acting insulins. The ISPAD guidelines acknowledge that premixed insulins with rapid-acting analogues have recently become available and are used in some countries, particularly for prepubertal children on twice daily regimens. The guidelines also acknowledge that premixed insulins may be useful to reduce the number of injections when compliance (or adherence) to the regimen is a problem.

The paediatric clinical development programme for IDegAsp (EMEA-C-000479-PIP01-08-M03) was designed to build on the data already available for IDegAsp in adults and on the data for IDeg and IAsp administered as separate components in the paediatric population.

The bolus insulin component of IDegAsp, IAsp (marketed under the trade names NovoLog NovoRapid), is approved for the treatment of diabetes mellitus in adults, adolescents and children from the age of 2 years. The use of IAsp is well established globally in the paediatric population.

The basal insulin component of IDegAsp, IDeg (marketed under the trade name Tresiba), is approved for the treatment of diabetes mellitus in adults in EU since January 2013. The use of IDeg in adolescents and children from the age of 1 year was approved in the EU in January 2015. This approval was based on data from trial NN1250-3561 (referred to as Trial 3561) which was assessed in the paediatric variation application (EMEA/H/C/2498/11).

In this application, the MAH presents data from a 16-week trial NN5401-3816 (referred to as Trial 3816). Trial 3816 evaluated the efficacy and safety of IDegAsp with a main meal plus IAsp for the remaining meals vs. IDet plus meal-time IAsp in children and adolescents (aged 1 to less than 18 years) with T1DM to support the indication for IDegAsp in the paediatric and adolescent population. In addition to this, the applicant has resubmitted data from trial 3561 as a confirmatory therapeutic study in this application as well in the procedure EMEA/H/C/2498/11.

The data from trial 3816 study has been assessed in a recent study report for paediatric studies, P46 005, in June 2015, in accordance with article 46 of regulation (EC) No 1901/2006.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

Not applicable

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.

The clinical development programme for IDeg and IDegAsp in paediatric subjects consisted of the following components:

- Clinical pharmacology trial – Trial 1995 (Measure #2 of the IDeg paediatric investigational plan [PIP]):
  A randomised, single-centre, double-blind, two-period cross-over, single-dose trial investigating the pharmacokinetic properties of IDeg and IGlar in children (6-11 years),adolescents (12-17 years) and adults (18-65 years) with T1DM. This trial was submitted as part of the original Marketing authorisation application (MAA) for IDeg.
- Therapeutic confirmatory trial – Trial 3561(Measure #3 of the IDeg and IDegAsp PIP):
  A 26-week multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of IDeg and IDet in children and adolescents 1 to less than 18 years of age with T1DM on a basal-bolus regimen with insulin aspart (IAsp) as bolus insulin, followed by a 26-week extension investigating long-term safety.
- Pharmacokinetic/pharmacodynamic (PK/PD) modelling study (Measure #4 of the IDeg PIP and IdegAsp):
  A modelling study in children from 1 to less than 18 years of age, compared to adults, all with T1DM. The modelling study consisted of a population pharmacokinetic analysis based on data from Trials 1982, 1995 and 3561, and an exposure-response study, which was only based on data from Trial 3561. The objectives of the two analyses were to develop a population PK model for IDeg in children younger than 6 years and to conduct an exposure-response analysis focusing on this age group.
- Trial NN5401-1982 (Measure #6) of the IDegAsp PIP) (a single-dose trial in subjects with T1DM investigating the PK properties of insulin degludec/insulin aspart (IDegAsp) in children, adolescents and adults, aged from 6 to 65 years, were combined for the population PK analysis.
- Therapeutic confirmatory trial- Trial 3816 (Measure #7 of the IDegAsp PIP): Randomised, open-label, parallel-group, 16-week efficacy and safety non-inferiority study of insulin degludec / insulin aspart and insulin detemir with insulin aspart, in children and adolescents with type I diabetes mellitus, from 1 to less than 18 years of age.

- Tabular overview of clinical studies

Table 1 Overview of IDeg Asp and IDeg therapeutic confirmatory trials in paediatric subjects

Compound	Trial no.	Trial design	Treatment	Efficacy endpoints	No. subjects randomised/ exposed
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:* Change in HbA_{1c} *Secondary:* Change in FPG 8-point SMPG 4-point SMPG (16 weeks)	IDegAsp: 182/181 IDet: 180/179
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:* Change in HbA_{1c} *Secondary:* Change in FPG 8-point SMPG 4-point SMPG (after 26 weeks for main trial period and 52 weeks for extension period)	*Main trial period* IDeg: 174/174 IDet: 176/175 *Extension period* IDeg: --/152 IDet: --/128

BID: twice daily, IAsp: insulin aspart; FPG: fasting plasma glucose, HbA_{1c}: glycated haemoglobin, IDeg: insulin degludec, IDegAsp: insulin degludec/insulin aspart, IDet: insulin detemir; OD: once daily; SMPG: self-measured plasma glucose, T1DM: type 1 diabetes mellitus.

[a]According to IDet labelling.

Table 2 Summary of paediatric clinical pharmacology development programme

Trial ID	Trial Design	Trial Objectives	Treatment
Clinical pharmacology trial of IDegAsp			
NN5401-1982	Open-label, single-dose	PK, PD and safety profile in children (6–11 years), adolescents (12–17 years) and adults (18–65 years) with T1DM	IDegAsp: single dose of 0.5 units/kg
Clinical pharmacology trial of IDeg			
NN1250-1995	Randomised, double-blind, two-period crossover, single-dose	PK and safety profile in children (6–11 years), adolescents (12–17 years) and adults (18–65 years) with T1DM	IDeg: single dose of 0.4 units/kg IGlar: single dose of 0.4 units/kg
Therapeutic confirmatory trial of IDeg with PK assessments			
NN1250-3561	Randomised, open-label, two-arm parallel group	Efficacy, safety and PK in children and adolescents with T1DM (1–17 years)	IDeg OD vs. IDet OD/BID as basal insulin; both with IAsp as bolus insulin; 26 weeks treatment

BID: twice daily, IAsp: insulin aspart, IDeg: insulin degludec, IDegAsp: insulin degludec/insulin aspart, IDet: insulin determir, IGlar: insulin glargine, OD: once daily, PD: pharmacodynamic(s), PK: pharmacokinetic(s), T1DM: type 1 diabetes mellitus

2.3.2. Pharmacokinetics

Trial 1982 and Trial 1995 were single dose trials conducted at a single centre in Germany. In Trial 1982, 12 children (6–11 years), 13 adolescents (12–17 years) and 13 adults (18–65 years) were exposed to IDegAsp. In Trial 1995, 13 children (6–11 years), 13 adolescents (12–17 years) and 12 adults (18–65 years) were exposed to IDeg.

Trial 3561 was a multinational trial, conducted across 12 countries and including subjects from Europe (52%), the US (29%), Japan (16%) and South Africa (3%). A total of 350 subjects were randomised to receive either IDeg or IDet in a 1:1 ratio (174 received IDeg and 176 received IDet).

Approximately 98% of the subjects receiving IDeg completed the main 26-week treatment period. In the IDeg group, there were 43 children aged 1–5 years, 70 children aged 6–11 years and 61 adolescents aged 12–17 years. Blood samples were taken for evaluation of steady state PK at weeks 2, 12 and 26 (± 3 days).

IDeg has a long duration of action extending beyond the 24-hour dosing interval in a once-daily dosing regimen, and steady state is reached in 2–3 days. Therefore, the clinically relevant PK properties of IDeg at steady state were evaluated in a population PK analysis of data from the therapeutic confirmatory trial of IDeg in children and adolescents with T1DM (Trial 3561), together with single-dose data from the clinical pharmacology trials of IDegAsp (Trial 1982) and IDeg (Trial 1995). A total of 243 subjects were included in the population PK analysis.

The results were as follows:

Table 3Trial 1982, pair-wise comparison of pharmacokinetic endpoints for IAsp in IDegAsp after single-dose administration between children, adolescents and adults with T1DM

Comparison	$AUC_{IAsp,0-12,SD}$ (pmol·h/L) Mean ratio [95% CI]	$C_{max,IAsp,SD}$ (pmol/L) Mean ratio [95% CI]
Children (6–11 years) vs. adults	1.69 [1.02; 2.80]	1.66 [1.10; 2.51]
Adolescents (12–17 years) vs. adults	1.14 [0.76; 1.69]	1.16 [0.84; 1.61]

Trial 1982: IDegAsp 0.5 units/kg (0.35 units/kg IDeg; 0.15 units/kg of IAsp).
Statistical analyses were based on 12 children, 13 adolescents and 13 adults.
CI: confidence interval.

Table 4 Trial 1982, pair-wise comparison of pharmacokinetic endpoints for IDeg in IDegAsp after single-dose administration between children, adolescents and adults with T1DM

Comparison	$AUC_{IDeg,0-\infty,SD}$ (pmol·h/L) Mean ratio [95% CI]	$C_{max,IDeg,SD}$ (pmol/L) Mean ratio [95% CI]
Children (6–11 years) vs. adults	1.42 [0.94; 2.16]	1.38 [1.09; 1.76]
Adolescents (12–17 years) vs. adults	1.23 [0.96; 1.58]	1.16 [0.95; 1.42]

Trial 1982: IDegAsp 0.5 units/kg (0.35 units/kg IDeg; 0.15 units/kg of IAsp).
Statistical analyses were based on 11 children, 13 adolescents and 13 adults for $AUC_{IDeg,0-\infty,SD}$ and on 12 children, 13 adolescents and 13 adults for $C_{max,IDeg,SD}$.
CI: confidence interval.

Table 5 Trial 1995, Pharmacokinetic Primary Endpoint – Area under Curve, 0-inf for Insulin Degludec after Single Dose - Statistical Analysis

	FAS	N	Estimate	95% CI
AUC IDeg, 0-inf, SD (pmol*h/L)				
Least square means				
Children	12	12	145891	
Adolescents	13	13	130990	
Adults	12	12	98594	
Mean ratio				
Children/Adults			1.48	[0.98; 2.24]
Adolescents/Adults			1.33	[1.08; 1.64]
Cmax IDeg, SD (pmol/L)				
Least square means				
Children	12	12	3350	
Adolescents	13	13	3429	
Adults	12	12	2792	
Mean ratio				
Children/Adults			1.20	[0.90; 1.60]
Adolescents/Adults			1.23	[1.00; 1.51]

The endpoints are log-transformed and analysed using an ANOVA model with age group and period as fixed effects and with different error-terms for each age-group.

ANOVA: analysis of variance
CI: confidence interval
FAS: full analysis set
N: number of subjects contributing to the analysis

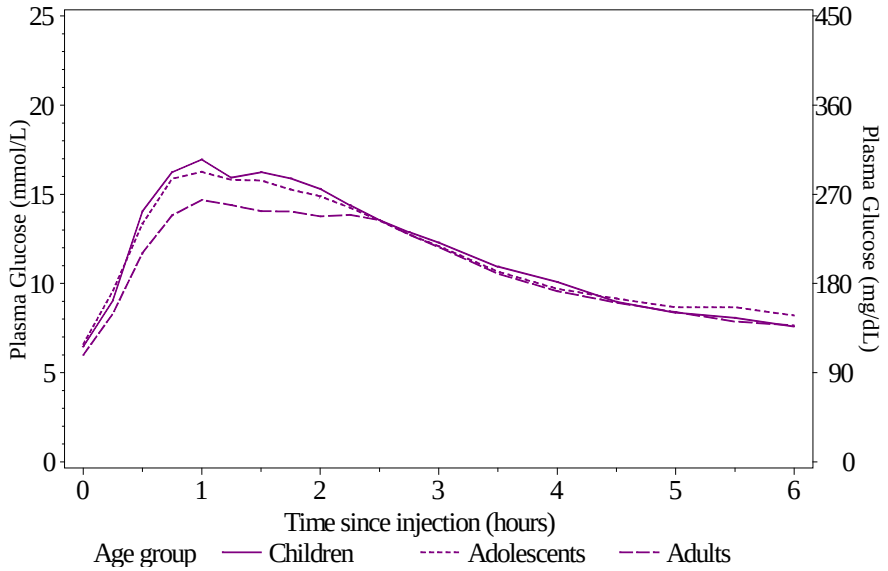
A population PK model for IDeg in children younger than 6 years was built. In addition to the single dose data from 36 subjects from Trial 1995, the population PK analysis also included steady-state data from 169 subjects from Trial 3561. The population PK analysis demonstrated that the steady-state IDeg exposure was independent of age and the estimated steady-state concentration-time profile for small children (1-5 years) was similar to that of children (6-11 years), adolescents (12-17 years) and adults (18-65 years).

2.3.3. Pharmacodynamics

The pharmacodynamic properties of IDegAsp in children and adolescents in comparison to adults were investigated in Trial 1982 by means of a meal test. Trial 1982 was a single-centre, open-label, parallel group trial with single-dose administration of 0.5 U/kg IDegAsp in children (6–11 years), adolescents (12–17 years) and adults (18–65 years) with T1DM.

The shape of the mean plasma glucose profiles obtained over a period of 6 hours following trial product administration and meal ingestion was similar in children, adolescents and adults.

Figure 1 6-Hour Mean Plasma Glucose Profiles after Single Dose IDegAsp in Children, Adolescents and Adults with T1DM



Trial 1982: 0.5 U/kg IDegAsp
A meal was served within two minutes after administration of IDegAsp.

The glucose-lowering effect of IDegAsp (as assessed from $AUC_{PG\ baseline,0\text{-}6h,std.meal,SD}$) was comparable for children, adolescents and adults although with a large between-subject variability. Maximum plasma glucose concentration after a standard meal ($PG_{max,meal,SD}$) and maximum plasma glucose excursion (Delta $PG_{max,meal,SD}$) were comparable for children, adolescents and adults based on descriptive statistics.

Table 6 Plasma Glucose Endpoints after Single Dose IDegAsp in Children, Adolescents and Adults with T1DM

	N	$AUC_{PG\ baseline,0\text{-}6h,std.meal,SD}$		Delta $PG_{max,meal,SD}$		$PG_{max,meal,SD}$	
		Mean (SD)		Geom. mean (CV%)		Geom. mean (CV%)	
		mmol*min/L	mg/dL[a]	mmol/L	mg/dL[1]	mmol/L	mg/dL[1]
Children	12	1866 (1246)	33625 (22453)	12.3 (22)	221.6 (22)	18.9 (15)	340,6 (15)
Adolescents	13	1726 (851)	31102 (15335)	10.6 (25)	191.0 (25)	17.6 (16)	317.2 (16)
Adults	13	1615 (1223)	29102 (22038)	9.3 (35)	167.6 (35)	16.1 (20)	290.1 (20)

Trial 1982: 0.5 U/kg IDegAsp.
N: number of subjects contributing to the analysis; Geom. mean: geometric mean; SD: Standard deviation.
[a] Units in mg/dL has been calculated applying a conversion factor of 18.02 for the mean, geometric mean and SD values.

Table 7 Pair-wise Comparison of Plasma Glucose Endpoints after Single Dose IDegAsp between Children, Adolescents and Adults with T1DM

Age groups	$AUC_{PG\ baseline,0\text{-}6h,std.meal,SD}$ (mmol*min/L)
	Mean Difference [95% CI]
Children-Adults	257 [-778;1292]
Adolescents-Adults	137 [-765;1040]

Trial 1982: 0.5 U/kg IDegAsp.
CI: confidence interval.

In addition to the reporting by age group described in the objectives of Trial 1982, the pharmacodynamic properties of IDegAsp were also reported by pubertal status according to Tanner stage scoring. Based on the Tanner stage scores, 6 subjects were categorised as prepubertal, and 19 subjects were categorised as pubertal. In accordance with the pharmacodynamic response analysed by age group, there were no apparent differences between the pharmacodynamic response for the prepubertal, pubertal and adult groups.

2.3.4. Discussion on clinical pharmacology

Dedicated clinical pharmacology data for IDegAsp is available from the age of 6.

Following a single dose (studies 1982 and 1995), exposure and peak concentration of IAsp and IDeg were higher in children than in adolescents and adults.

The population PK analysis indicated that the steady-state IDeg exposure was independent of age and the estimated steady-state concentration-time profile for small children (1-5 years) was similar to that of children (6-11 years), adolescents (12-17 years) and adults (18-65 years).

The discrepancy between these pharmacokinetic analyses is deemed to not have any clinical implications considering that:

- IDegAsp is individually titrated
- Pharmacodynamic data from study 1982 indicate that the glucose lowering effect of the prandial component of IDegAsp is similar in children, adolescents and adults.
- Clinical efficacy and safety data in the population applied for has been obtained in study 3816.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology program is acceptable. The lower age limit for the indication is addressed in the clinical efficacy and clinical safety sections below.

2.4. Clinical efficacy

2.4.1. Main study- Trial 3816

The main study, trial 3816, investigated the efficacy and safety of insulin degludec/insulin aspart once daily plus insulin aspart for the remaining meals versus insulin detemir once or twice daily plus meal time insulin aspart in children and adolescents with type 1 diabetes mellitus (NN5401-3816)

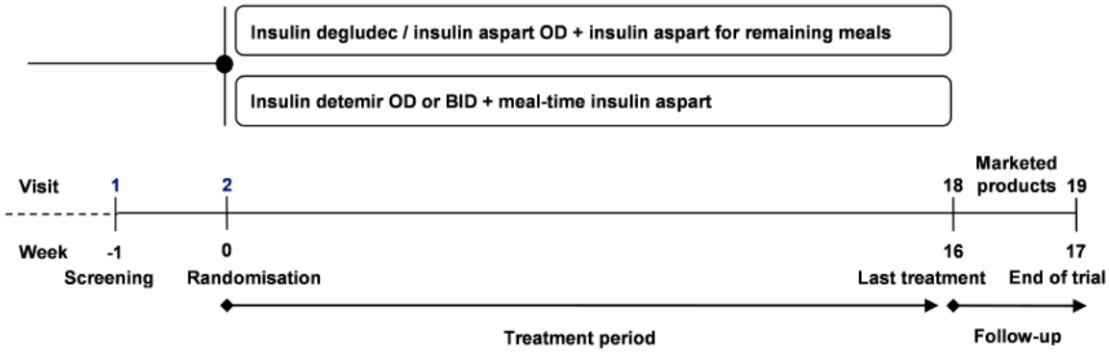
Methods

Trial 3816 was a 16-week multi-national, multi-centre, open-label, two-arm, parallel group, randomised 1:1), treat-to-target, efficacy and safety trial in children and adolescents with T1DM between 1 and 18 years of age. Subjects received one of the following treatment regimens:

- IDegAsp group: IDegAsp OD with a main meal + bolus IAsp for the remaining meals
- IDet group: IDet OD or twice daily (BID) + bolus IAsp at all meals.

Following screening, the subjects were randomised 1:1 to the treatment groups and stratified by age: children 1-5 years; children 6-11 years; and adolescents 12-17 years (**Figure 2**).

Figure 2 Trial 3816 study design



BID: twice daily, OD: once daily

Study participants-children and adolescents with T1DM aged 1 to less than 18 years of age. The trial included a total of 362 children and adolescents and was conducted at 63 sites in 14 countries. For key selection criteria see Table 8.

Table 8 Key selection criteria

Selection criteria[a]	Specifications
Inclusion criteria	
Subjects	Boys and girls diagnosed with T1DM
Age	Aged 1 to less than 18 years at randomisation
HbA_{1c}	≤11%
Current Therapy	• Ongoing daily treatment with insulin (any regimen) for at least 3 months prior to visit 1. No OADs are allowed • Total daily dose of insulin ≤ 2 units/kg
Exclusion criteria	• Known or suspected allergy to trial product(s) or related products • Significant concomitant disease, except for conditions associated with type 1 diabetes mellitus, which in the Investigator's opinion could interfere with the trial • Mental incapacity, unwillingness or language barriers, precluding adequate understanding or cooperation (child and parent should be evaluated as a unit) • The receipt of any investigational drug within 1 month prior to visit 1 • Known hypoglycaemic unawareness or recurrent severe hypoglycaemic events as judged by the Investigator • More than 1 diabetic ketoacidosis requiring hospitalisation within the last 3 months prior to visit 1 • Suffer from a life threatening disease (e.g., malignant cancer)

a) Complete list of inclusion and exclusion criteria is provided in Trial 3816 (M 5.3.5.1), seq. 0031

The open trial design is considered appropriate since the two treatment arms require different number of injections**.** The trial design was agreed upon with EMA (PDCO) as part of the paediatric investigation plan. The study duration is considered adequate since previous studies in adult T1DM patients comparing IDeg Asp with IDet have shown that HbA1c levels had stabilised after 12 to 16 weeks of treatment.

Treatments

Choice of comparator

IDet (as marketed under the trade name: Levemir®) was chosen as the comparator since it is a long-acting insulin analogue which is globally approved for the treatment of diabetes mellitus from the age of 2 years.

Choice of bolus/mealtime insulin

IAsp (as marketed under the trade name: NovoRapid® / NovoLog®) was chosen as mealtime insulin since it is a rapid-acting insulin analogue which is globally approved for the treatment of diabetes mellitus. It is indicated for use in children from the age of 2 years.

Dosing regimens and insulin dose

At randomisation, subjects were to switch to either IDegAsp or IDet from their previous insulin treatment. At randomisation the Investigator was to reduce the daily total insulin dose by 20 percent as per titration algorithm and aim to adjust the basal:bolus ratio to be between 50:50 and 30:70. IDegAsp was to be administered OD in connection with a main meal.

The titration algorithms for basal and bolus insulin specified the PG target and the recommended insulin dose adjustments at different PG levels. All subjects were to be individually titrated on a continuous basis according to a prespecified PG target range adopted from the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines (2009). The fasting, pre-meal and bedtime PG target was 5.0−8.0 mmol/L (90−145 mg/dL).

To optimise and maintain glycaemic control, the Investigators were in weekly contact with subjects, throughout the trial to discuss glycaemic control and hypoglycaemic episodes, and to assist the subjects in adjusting insulin doses. All insulin dose adjustments were made at the discretion of the Investigators.

Titration of insulin degludec/insulin aspart and insulin detemir

Basal insulin titration was done according to the lowest pre-breakfast SMPG value measured on the three days prior to the visit/phone contact for IDegAsp and IDet OD. For IDet BID the morning dose adjustment was to be based on the lowest pre-main evening meal SMPG value measured on the three days prior to the visit/phone contact and the evening dose was to be based on the respective pre-breakfast SMPG values.

Table 9 Adjustment of IDegAsp and IDet doses

Current dose		**<5U**	**5−15U**	**> 15U**
Pre-breakfast or pre-main evening meal plasma glucose		Adjustment (units)		
mmol/L	mg/dL			
<5.0	<90	-½	-1	-2
5.0−8.0	90−145	0	0	0
8.1−10.0	146−180	+½	+1	+2
10.1−15.0	181−270	+1	+2	+4
>15.0	>270	+1½	+3	+6

Titration of insulin aspart

Titration of IAsp was done either by using sliding scale (see Table 1–5) or doing carbohydrate counting. IAsp titration was done once weekly based on the lowest of three SMPG values measured prior to the next meal and bedtime on the three days prior to the visit/phone contact:

- Pre-breakfast IAsp was to be adjusted according to the lowest SMPG measured pre-lunch
- Pre-lunch IAsp was to be adjusted according to the lowest SMPG measured before main evening meal
- Pre-main evening meal IAsp was to be adjusted according to the lowest SMPG measured at bedtime

Table 10 Adjustment of IAsp doses

Current bolus dose		**≤ 5U**	**> 5U**
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

Instead of the above titration guidance, IAsp could be titrated in accordance with principles of flexible dosing whereby the meal carbohydrate content and preprandial plasma glucose value were used to determine the bolus insulin dose. When using this method, bolus insulin dose adjustment was conducted multiple times daily in accordance with the insulin:carbohydrate ratio and the plasma glucose correction factor.

Insulin devices

All insulin devices used in the trial had the capacity to deliver insulin in increments of 0.5 units.

The choice of initial dose, comparator and bolus insulin is acceptable. However, nor IDet or IAsp are approved below the age of 2 years. A waiver for small children below the age of one with T1DM is included in the PIP for IDet. The inclusion of children > 1 years of age is in line with the PIP for IDegAsp.

Objectives

The primary objective of Trial 3816 was to compare the efficacy of IDegAsp administered OD plus meal-time IAsp for the remaining meals in controlling glycaemia with respect to change from baseline in HbA1c after 16 weeks of treatment.

Primary endpoint

The primary endpoint was change from baseline in HbA1c (%) after 16 weeks of treatment.

Secondary endpoints

- Change from baseline in FPG after 16 weeks of treatment
- SMPG measurements (8-point profiles)
  - 8-point profiles after 16 weeks of treatment
  - Mean of the 8-point profiles after 16 weeks of treatment
  - Fluctuation in the 8-point profiles after 16 weeks of treatment

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

Body Weight

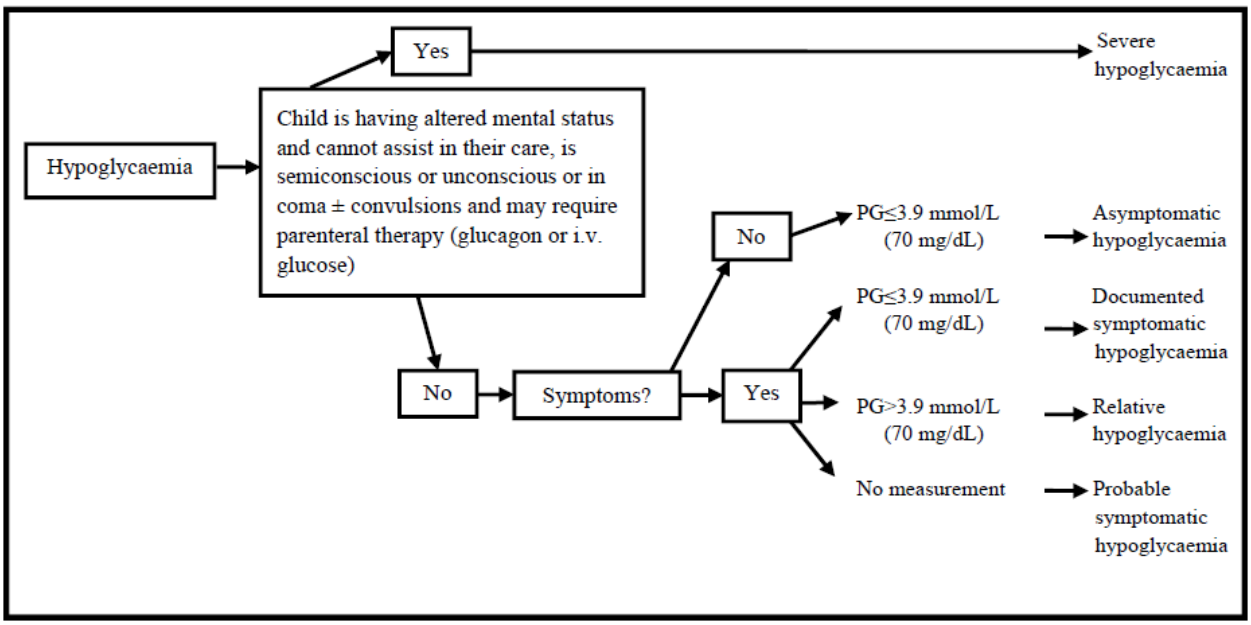
Body weight change from baseline was summarised descriptively.

Safety endpoints

The key safety parameters were insulin dose, AEs, incidence of hypoglycaemia, incidence of hyperglycaemia, vital signs, safety laboratory parameters and body weight/BMI.

The definitions of hypoglycaemic episodes from the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association (ADA) guidelines were used. (Figure 2)

Figure 3 Classification of hypoglycaemia according to ADA / ISPAD



The endpoints chosen is considered adequate and clinically relevant

Sample size

A total of 346 subjects were planned to be included in this trial, with a minimum of 300 expected to complete the trial. As specified in the PIP for IDegAsp,3 at least 344 paediatric patients had to be randomised (1:1 ratio) of which at least 60 had to be younger than 6 years of age at inclusion and at least 30% and not more than 70% had to be girls. Furthermore, based on feedback from FDA, 20−25% of those enrolled had to be enrolled from US sites.

Randomisation

Subjects randomised into the IDet treatment group were allowed to switch from OD to BID dosing. Randomisation was stratified by age groups (1 to less than 6 years; 6 to less than 12 years and 12 to less than 18 years) to ensure approximately equal distribution of subjects between the treatments within each age group

Blinding (masking)

N/A

Statistical methods

Sample size was determined based on the non-inferiority evaluation. The non-inferiority margin of 0.4% (absolute) was chosen in accordance with the FDA guidance and was an integral part of the PIP for IDegAsp. Sample size was determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D=0%). 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. With these assumptions, the minimum sample size required to meet the primary objective with at least 80% power was 310 subjects.

As this was a non-inferiority trial, sample size was determined such that the anticipated power was at least 80% in the evaluation of the per protocol (PP) analysis set. Assuming that 10% were to be excluded from the PP analysis set, the total number of randomised subjects was to be at least 346 subjects in order to have at least 80% power in the evaluation of the PP analysis set.

The following analysis sets were defined in the protocol and/or statistical analysis plan, prior to unblinding/release of the treatment randomisation, and in accordance with ICH E9.44

- Full analysis set (FAS) – included all randomised subjects. In exceptional cases subjects from the FAS could be eliminated. In such cases the elimination was to be justified and documented. The statistical evaluation of the FAS followed the intent-to-treat (ITT) principle and subjects contributed to the evaluation “as randomised”.
- Per protocol (PP) analysis set – consisted of all subjects in the FAS who fulfilled the following criteria:
    - Have not violated any inclusion criteria.
    - Have not fulfilled any exclusion criteria.
    - Have a non-missing HbA1c at screening or randomisation.
    - Have at least one non-missing HbA1c after 12 weeks of exposure. o Have at least 12 weeks of exposure.
- Safety analysis set (SAS) – included all subjects receiving at least one dose of the trial product or its comparator. Subjects in the safety set contributed to the evaluation “as treated”.

The statistical methods were acceptable.

Results

Recruitment / Numbers analysed

A total of 362 children and adolescents were randomised, of whom 360 received at least one dose of trial product and 342 completed the trial. Of those randomised, 82 were aged 1-5 years, 122 were aged 6-11 years and 158 were aged 12-17 years (**Table 11**, **Table 12**).

Table 11 Subject disposition – summary

	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

Table 12 Subject disposition – Trial 3816

		IDegAsp, N (%)	IDet, N (%)	Total, N (%)
All subjects	Screened			387
	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)
	Completed	174 (95.6)	168 (93.3)	342 (94.5)
1−5 years	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)
	Completed	38 (92.7)	36 (87.8)	74 (90.2)
6−11 years	Randomised	61 (100.0)	61 (100.0)	122 (100.0)
	Exposed	61 (100.0)	61 (100.0)	122 (100.0)
	Withdrawn at/after randomisation	1 (1.6)	2 (3.3)	3 (2.5)
	Completed	60 (98.4)	59 (96.7)	119 (97.5)
12−17 years	Randomised	80 (100.0)	78 (100.0)	158 (100.0)
	Exposed	80 (100.0)	77 (98.7)	157 (99.4)
	Withdrawn at/after randomisation	4 (5.0)	5 (6.4)	9 (5.7)
	Completed	76 (95.0)	73 (93.6)	149 (94.3)

The vast majority of subjects 94.5% completed the study. The withdrawals were relatively balanced between treatment groups and between age groups.

Conduct of the study

A treat-to-target approach with weekly contacts (visits or phone contacts) was implemented in order to ensure optimal glycaemic control for all subjects. The titration algorithms for basal and bolus insulin, which were provided in the protocol, specified the plasma glucose (PG) target and the recommended insulin dose adjustments at different PG levels. All subjects were to be individually titrated on a continuous basis according to a pre-specified PG target range adopted from the ISPAD 2009 guidelines. The fasting, pre-meal and bedtime PG target was 5.0−8.0 mmol/L (90−145 mg/dL). The insulin titration guideline provided guidance on adjustments of basal and bolus insulin. All adjustments of insulin doses were made at the discretion of the investigator.

Baseline data

Demographics and baseline characteristics

The trial population consisted of children and adolescents with T1DM aged from 1 to less than 18 years. Females comprised 51.7% of the trial population. Approximately 32% of the subjects were from the U.S, 13% were from the Russian Federation and 9% were from Israel. The majority of subjects (93.1%) were 'White'. The majority of subjects (92.3%) were not Hispanic or Latino.

The demographics and baseline diabetes characteristics at week 0 were comparable between the treatment groups apart from slight differences in mean FPG and mean duration of diabetes (Table 13).

For the overall study population, the mean (standard deviation [SD]) FPG at baseline was slightly higher in the IDegAsp group than in the IDet group: 8.6 (4.4) mmol/L versus 8.1 (4.2) mmol/L, respectively. The mean (SD) duration of diabetes was slightly higher in the IDegAsp group than in the IDet group: 4.4 (3.7) years versus 3.8 (3.2) years, respectively.

Table 13 Baseline and diabetes characteristics - descriptive statistics - full analysis set

	IDegAsp OD	IDet	Total
Number of Subjects	182	180	362
Age (years)			
N	182	180	362
Mean (SD)	10.5 (4.3)	10.8 (4.6)	10.6 (4.5)
Median	11.0	11.4	11.2
Min ; Max	2.2 ; 17.8	1.9 ; 17.9	1.9 ; 17.9
Height (m)			
N	180	179	359
Mean (SD)	1.41 (0.24)	1.42 (0.27)	1.42 (0.25)
Median	1.44	1.48	1.46
Min ; Max	0.90 ; 1.87	0.83 ; 1.91	0.83 ; 1.91
Body Weight (kg)			
N	182	180	362
Mean (SD)	41.1 (20.7)	42.9 (21.2)	42.0 (20.9)
Median	39.4	39.9	39.7
Min ; Max	12.1 ; 117.1	9.4 ; 104.4	9.4 ; 117.1
BMI (kg/m^2)			
N	180	179	359
Mean (SD)	19.2 (4.2)	19.6 (4.0)	19.4 (4.1)
Median	18.4	18.6	18.5
Min ; Max	11.0 ; 35.1	12.8 ; 31.9	11.0 ; 35.1
Duration of Diabetes (years)			
N	182	180	362
Mean (SD)	4.4 (3.7)	3.8 (3.2)	4.1 (3.5)
Median	3.1	2.8	3.0
Min ; Max	0.3 ; 14.6	0.3 ; 13.9	0.3 ; 14.6
HbA1c (%)			
N	182	180	362
Mean (SD)	8.1 (1.2)	8.1 (1.2)	8.1 (1.2)
Median	8.0	8.0	8.0
Min ; Max	5.1 ; 11.1	5.4 ; 10.9	5.1 ; 11.1
FPG (mmol/L)			
N	172	166	338
Mean (SD)	8.6 (4.4)	8.1 (4.2)	8.4 (4.3)
Median	7.7	7.2	7.4
Min ; Max	0.5 ; 20.7	1.9 ; 25.1	0.5 ; 25.1

BMI: Body mass index, FPG: Fasting plasma glucose, N: Number of subjects, OD; once daily; SD: Standard deviation

Diabetic complications were overall similar in the treatment groups. In total, 14 (3.9%) subjects had diabetic complications at screening: 9 (2.5%) subjects had diabetic neuropathy, 4 (1.1%) subjects had microalbuminuria and 1 (0.3%) subject was diagnosed with cataract diabetic. There were 5 events of diabetic complications in 5 subjects within the IDegAsp group and 9 events of diabetic complications in 9 subjects within the IDet group.

At the time of inclusion in the trial, 92.0% of subjects were using basal + bolus therapy. The most commonly used basal insulins were IDet (45.3%) and insulin glargine (40.6%). The most commonly used bolus insulin was IAsp (58.6%).

Baseline characteristics were generally well balanced between treatment groups. Only one child under the age of 2 years was included (IDet) and the youngest child included in the IDegAsp was aged 2.2 years. Duration of diabetes was slightly longer in the IDegAsp treated group, however, numerically more diabetes complications were reported in the IDet treated group.

Outcomes and estimation

Efficacy results

Primary endpoint

IDegAsp OD + IAsp effectively maintained glycaemic control and was non-inferior to IDet + IAsp in terms of change from baseline in HbA1c, with an estimated mean treatment difference (IDegAsp OD – IDet) of −0.04%-points [−0.23; 0.15]95% CI (Table 8). Superiority was not confirmed.

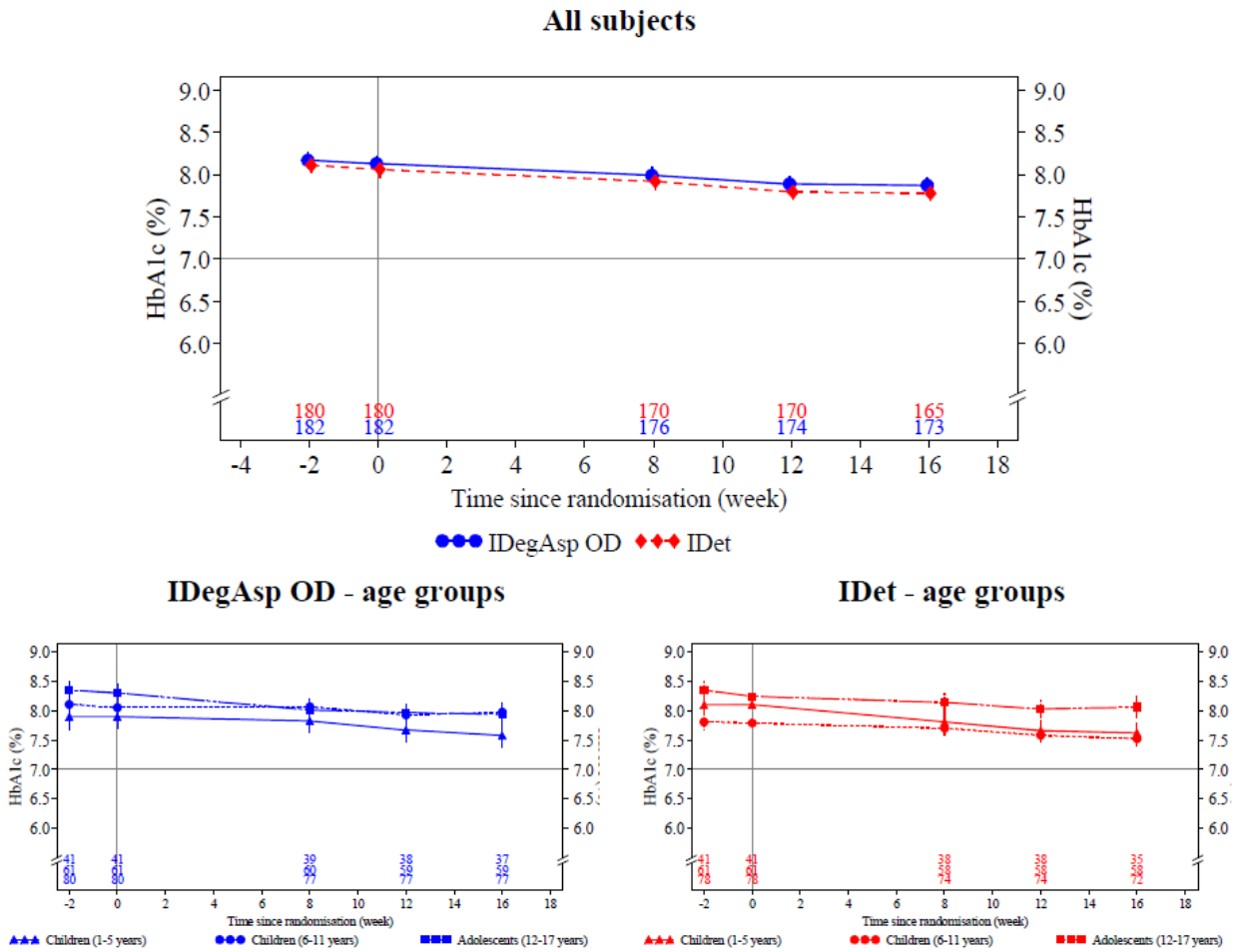
Table 14 Trial 3816 HbA1c after 16 weeks of treatment - primary statistical analysis – full analysis set

	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.

The trend for the development of HbA1c over time was similar in the IDegAsp and IDet group, with a minor reduction from baseline to week 16. HbA1c at baseline (week 0) was similar in the IDegAsp and IDet group with an observed mean (SD) of 8.1% in the IDegAsp group and 8.1% in the IDet group. At week 16 the observed mean (SD) HbA1c was 7.9% in the IDegAsp group and 7.8% in the IDet group. The observed change from baseline to week 16 was −0.3%-point in both the IDegAsp and IDet group, calculated based on subjects with available HbA1c measurements at both baseline and week 16. Within both the IDegAsp and the IDet treatment group, the trend for HbA1c was similar in all age groups, with a minor reduction from baseline to week 16.

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



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.

Sensitivity analyses were performed and all sensitivity analysis showed an estimated mean treatment difference in line with the main analysis and supported the conclusion of non-inferiority.

Both treatments showed a lowering trend for HbA1c. The primary endpoint was reached showing that IDegAsp was non-inferior to IDet+Asp. There was no statistically significant difference between the two treatment arms. The upper limit of the CI was 0.15% which is well within both the pre-defined non-inferiority margin of 0.4 % and the currently recommended non-inferiority margin of 0.3 %.

A similar trend for HbA1c reduction was observed in all age groups irrespective of treatment.

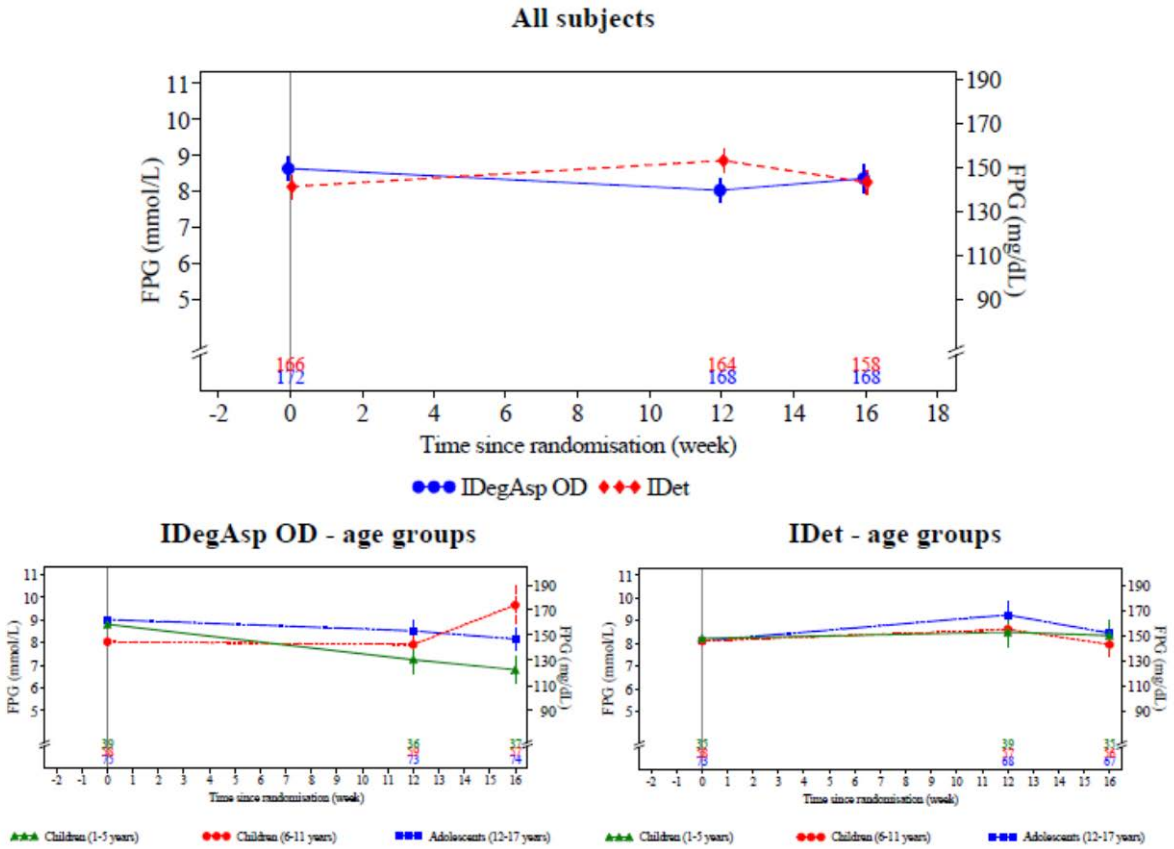
Sensitivity analyses were all in line with the primary analysis, thus the outcome appears robust.

Secondary endpoints

Fasting plasma glucose

After 16 weeks of treatment, FPG was 8.4 mmol/L with IDegAsp OD + IAsp and 8.3 mmol/L with IDet + IAsp. The observed mean change from baseline at week 16 was −0.3 mmol/L with IDegAsp OD + IAsp and −0.1 mmol/L with IDet + IAsp. The estimated mean treatment difference (IDegAsp OD – IDet) was not statistically significant, 0.31 mmol/L [−0.70; 1.33]95%CI mmol/L.

Figure 5 Trial 3816 Fasting plasma glucose by treatment week – mean plots



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.

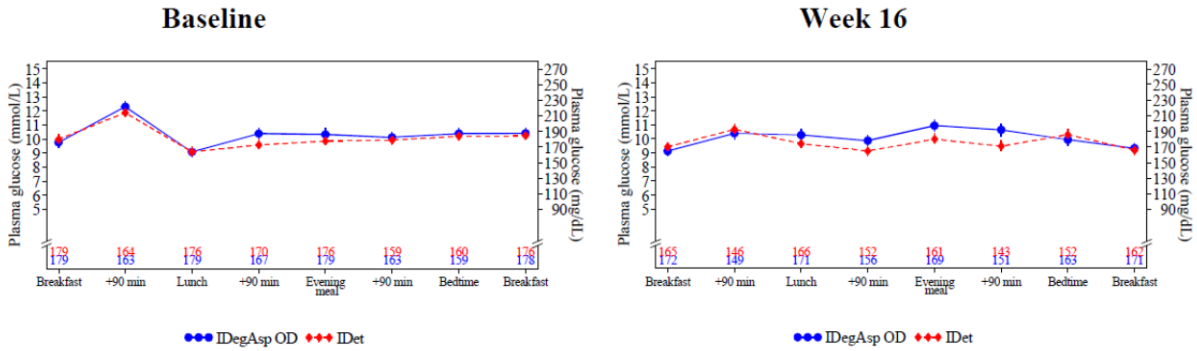
Within the IDegAsp treatment group mean FPG followed the overall trend (as seen for all subjects) from baseline to week 16 in children 1-5 years and adolescents 12-17 years, and tended to increase in children 6-11 years, which was caused by a few outliers with elevated FPG levels at week 16.

Within the IDet treatment group mean FPG followed the overall trend (as seen for all subjects) from baseline to week 16 in all age groups.

8-point self-measured plasma glucose profiles

There were no statistically significant treatment differences in the mean of the 8 point profile, in prandial PG increments (mean of all meals, breakfast, lunch and main evening meal) or in the SMPG fluctuation at 16 weeks. Trends were similar for the shape of the 8-point SMPG profiles across age groups at week 16 for both treatment groups.

Figure 6 Trial 3816 8-point self-measured plasma glucose profiles



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.

4-point SMPG for dose adjustment

There were no statistically significant treatment differences in pre-breakfast, pre-lunch, pre-main evening meal or pre-bedtime SMPG at 16 weeks.

Within-subject variability as measured by coefficient of variation (%) after 16 weeks

Within-subject variability in pre-breakfast SMPG after 16 weeks was similar for the two treatment groups; estimated mean treatment ratio IDegAsp OD/IDet = 1.02 [0.91; 1.14]95%CI.

No statistically significant different was seen between the treatment arms in any of the secondary endpoints which supports that IDegAsp OD+IAsp for the remaining meals is non-inferior to IDet or BID+ mealtime IAsp.

Exploratory endpoints

Insulin doses over time – Trial 3816

In clinical practice, determination of insulin dose is based upon individual needs, considering the balance between glycaemic control and risk of hypoglycaemia.

Trial 3816 was conducted with a treat-to-target principle; the insulin dose was adjusted for each individual subject with the aim of achieving similar pre-breakfast SMPG targets for each treatment group, with acceptable risk of hypoglycaemia. There was an observed transient increase in pre-breakfast SMPG at the beginning of the trial, possibly related to the protocol-recommended 20% total insulin dose reduction at randomisation. This is not considered relevant for clinical practice, as dose adjustment at switching should take into consideration current glycaemic control and insulin regimen.

Overall, the mean total insulin dose increased slightly in both treatment groups from week 1 to week 16 (from 0.79 to 0.88 units/kg in the IDegAsp group and from 0.89 to 1.01 units/kg in the IDet group). At the end of the treatment period there was a 14% lower total daily insulin dose requirement in the IDegAsp group compared to the IDet group, primarily consisting of a 28% lower basal daily dose requirement.

The lower basal insulin requirement in the IDegAsp group vs. the IDet group may be related to the fact that 54.2% of subjects were using IDet BID at the end of the trial, as it is well-known that BID dosing generally leads to higher basal doses.The daily bolus insulin dose (total IAsp administered including the IAsp component of IDegAsp) was similar between the two treatments

Number of injections

In trial 3816 a similar level of glycaemic control was achieved with a lower total number of injections per day in the IDegAsp group compared to the IDet group (mean of 3.6 vs. 4.9 total injections per day, respectively, at week 16).The Applicant has provided these data in the RSI.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15 Summary of efficacy for NN5401-3816

Title: A trial investigating the efficacy and safety of insulin degludec/insulin aspart once daily plus insulin aspart for the remaining meals versus insulin detemir once or twice daily plus meal time insulin aspart in children and adolescents with type 1 diabetes mellitus.			
Study identifier	Trial ID: NN5401-3816; EudraCT number: 2012-003566-41; Study identifier: NCT01835431. See Trial 3816 (M 5.3.5.1), seq. 0031.		
Design	This was a 16-week, open labelled, randomised, multinational, multi-centre, two arm parallel group, treat-to-target, efficacy and safety trial comparing insulin degludec/insulin aspart (IDegAsp) once daily (OD) + IAsp with insulin detemir (IDet) as basal insulin in combination with insulin aspart (IAsp) as bolus insulin in paediatric subjects with type 1 diabetes between 1 and less than 18 years of age. Following screening, eligible subjects were randomised in a 1:1 manner to receive IDegAsp OD or IDet (OD or twice daily (BID) as required). To ensure equal distribution between the two treatments in each age group, randomisation was stratified as follows: children 1-5 years, children 6-11 years and adolescents 12-17 years. Randomised subjects were to attend 9 site visits (including one follow-up visit), and 10 phone contacts. Key visits were at weeks 0, 1, 2, 4, 8, 12 and 16 where assessments for primary and secondary endpoints were performed. A follow up visit was performed one week after the last trial treatment.		
	Duration of main period:		16 weeks of treatment + 1 week follow-up
Hypothesis	To confirm the efficacy of IDegAsp administered OD plus meal-time IAsp for the remaining meals in controlling glycaemia with respect to change from baseline in HbA_{1c} after 16 weeks of treatment. This was done by comparing the difference in change from baseline in HbA_{1c} 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 was confirmed, to a superiority limit of 0%. None of the secondary endpoints were analysed as confirmatory endpoints.		
Treatments groups	IDegAsp OD + IAsp for the remaining meals		A total of 182 subjects were randomised to IDegAsp dosed OD as basal insulin treatment + IAsp for the remaining meals. The total treatment duration was 16 weeks.
	IDet OD or BID + meal time IAsp		A total of 180 subjects were randomised to IDet dosed OD or BID according to approved labelling + IAsp as meal time insulin. The total treatment duration was 16 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 16 weeks of treatment	See Hypothesis.
	Supportive secondary endpoint	Change from baseline in fasting plasma glucose (FPG) after 16 weeks of treatment	Change from baseline in FPG after 16 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	8-point self-measured plasma glucose (SMPG) profiles: 8-point profiles after 16 weeks of treatment	8-point SMPG profiles after 16 weeks of treatment were compared between treatment groups and assessed by statistical analysis. This analysis was added post-hoc to be consistent with analysis of previous trials.
	Supportive secondary endpoint	8-point SMPG profiles: Mean of the 8-point profiles after 16 weeks of treatment	Mean of the 8-point SMPG profiles after 16 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.

	Supportive secondary endpoint	8-point SMPG profiles: Fluctuation in the 8-point profiles after 16 weeks of treatment	Fluctuation in the 8-point SMPG profiles after 16 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	8-point SMPG profiles: Prandial PG increment from 8-point profiles after 16 weeks of treatment	Meal increments in SMPG after 16 weeks of treatment were compared between treatments groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	4-point SMPG profiles: Mean SMPG before meals and before bedtime after 16 weeks of treatment	Mean pre-breakfast, pre-lunch, pre-main evening meal and pre-bedtime SMPG values after 16 weeks of treatment were compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	4-point SMPG profiles: Within-subject variability of pre-breakfast SMPG as measured by CV% after 16 weeks of treatment	Within-subject variability of pre-breakfast SMPG as measured by CV% after 16 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
Database lock	26-November-2014		

Results and Analysis	
Analysis description	**Primary analysis and key supportive secondary endpoints**
Analysis population and time point description	The FAS (n=362) included all randomised subjects. The PP analysis set (n = 345) consisted of all subjects in the FAS who fulfilled the following criteria: • Have not violated any inclusion criteria • Have not fulfilled any exclusion criteria • Have non-missing HbA_{1c} at screening or randomization • Have at least one non-missing HbA_{1c} after 12 weeks of exposure • Have at least 12 weeks of exposure. The SAS (n=360) included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of all endpoints were based on the FAS. Safety data were summarised using the SAS. Statistical analyses were conducted on the change from baseline to week 16. The population consisted of male and female paediatric subjects with type 1 diabetes mellitus with a mean (standard deviation; SD) age of 10.6 (4.5) years (range: 1.9 to 17.9 years) and mean (SD) BMI of 19.4 (4.1) kg/m^2 (range: 11.0 to 35.1 kg/m^2) at baseline. Mean (SD) duration of diabetes was 4.1 (3.5) years (range: 0.3 to 14.6 years) and mean (SD) HbA_{1c} was 8.1% (1.2%) (range: 5.1% to 11.1%) at baseline. At screening, 93.4% subjects were being treated with a basal-bolus insulin regimen (92.9% in the IDegAsp group and 93.9% in the IDet group); 45.3% were being treated with IDet (39.6% in the IDegAsp group and 51.1% in the IDeg group). A total of 95.6% of subjects in the IDegAsp group and 93.3% of subjects in the IDet group completed the trial.
Statistical methods	**Primary Endpoint Analysis** All observed HbA_{1c} and FPG measurements available post-randomisation at scheduled measurement times were analysed using 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 relevant baseline as covariate. Interactions between visit and all factors and covariates were also included in the model. **Sensitivity Analysis** The primary efficacy analysis was repeated on the PP analysis set and the set of completed subjects. The following sensitivity analyses were performed using the FAS only. Change from baseline in HbA_{1c} after 16 weeks of treatment was analysed using an analysis of variance (ANOVA) method with treatment, sex, region and age group as fixed factors and baseline HbA_{1c} as covariate and where the missing values were imputed using the Last Observation Carried Forward (LOCF) method. All observed HbA_{1c} measurements available post-randomisation at scheduled measurement times were also analysed with an MMRM with an unstructured covariance matrix where the only factors were treatment and visit and baseline HbA_{1c} was included as a covariate. The two interactions between visit and treatment and visit and baseline HbA_{1c} were included in the model. **Secondary Endpoints** All observed FPG values, mean and fluctuation in the 8-point SMPG profile, prandial PG increment and mean before meals and before bedtime in the 4-point SMPG profile after 16 weeks of treatment were analysed separately using an MMRM with an unstructured covariance matrix. In each case, the model included treatment, sex, region, age group and visit as factors and the relevant baseline value as covariate. Interactions between visit and all factors and covariates were included in the model. Fluctuation in the 8-point SMPG profile was logarithmically transformed before analysis. All observed 8-point profile (SMPG) measurements available post-randomisation at scheduled measurements times were analysed with an MMRM with an unstructured covariance matrix. The model included treatment, sex, region, age group, time-point within the 8-point profile and visit as

Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	-0.04
		95% CI	[-0.23; 0.15]
	Supportive secondary endpoint: Change from baseline in FPG (mmol/L) after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	0.31
		95% CI	[-0.70; 1.33]
	Supportive secondary endpoint: Mean of the 8-point SMPG profiles (mmol/L) after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	-0.06
		95% CI	[-0.62; 0.51]
	Supportive secondary endpoint: Fluctuation in the 8-point SMPG profiles (mmol/L) after 16 weeks of treatment	Comparison groups	IDegAsp OD/IDet
		Treatment contrast	1.09
		95% CI	[0.98; 1.22]
	Supportive secondary endpoint: Prandial PG increment at breakfast (mmol/L) from 8-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	-0.49
		95% CI	[-1.79; 0.82]
	Supportive secondary endpoint: Prandial PG increment at lunch (mmol/L) from 8-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	0.17
		95% CI	[-1.17; 1.51]
	Supportive secondary endpoint: Prandial PG increment at evening meal (mmol/L) from 8-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	0.19
		95% CI	[-1.27; 1.65]
	Supportive secondary endpoint: Prandial PG increment for all meals (mmol/L) from 8-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	0.15
		95% CI	[-0.65; 0.95]
	Supportive secondary endpoint: Mean PG before breakfast (mmol/L) from 4-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	-0.12
		95% CI	[-0.79; 0.56]
	Supportive secondary endpoint: Mean PG before lunch (mmol/L) from 4-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	0.54
		95% CI	[-0.22; 1.31]
	Supportive secondary endpoint: Mean PG before evening meal (mmol/L) from 4-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	0.45
		95% CI	[-0.29; 1.19]
	Supportive secondary endpoint: Mean PG before bedtime (mmol/L) from 4-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD – IDet
		Treatment contrast	0.28
		95% CI	[-0.54;1.11]
	Supportive secondary endpoint: Within-subject variability (CV%) in pre-breakfast SMPG from 4-point SMPG profiles after 16 weeks of treatment	Comparison groups	IDegAsp OD/IDet
		Treatment ratio	1.02
		95% CI	[0.91; 1.14]
Notes	ANOVA: analysis of variance; BID: twice daily; BMI: body mass index; CI: confidence interval; CV: coefficient of variance; FAS: full analysis set; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A1c; IAsp: insulin aspart; IDet: insulin detemir; IDegAsp: insulin degludec/insulin aspart; LOCF: last observation carried forward; MMRM: mixed model for repeated measurements; OD: once daily, PG: plasma glucose; PP: per protocol; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose.		

2.4.2. Supportive study- Trial 3561

Introduction

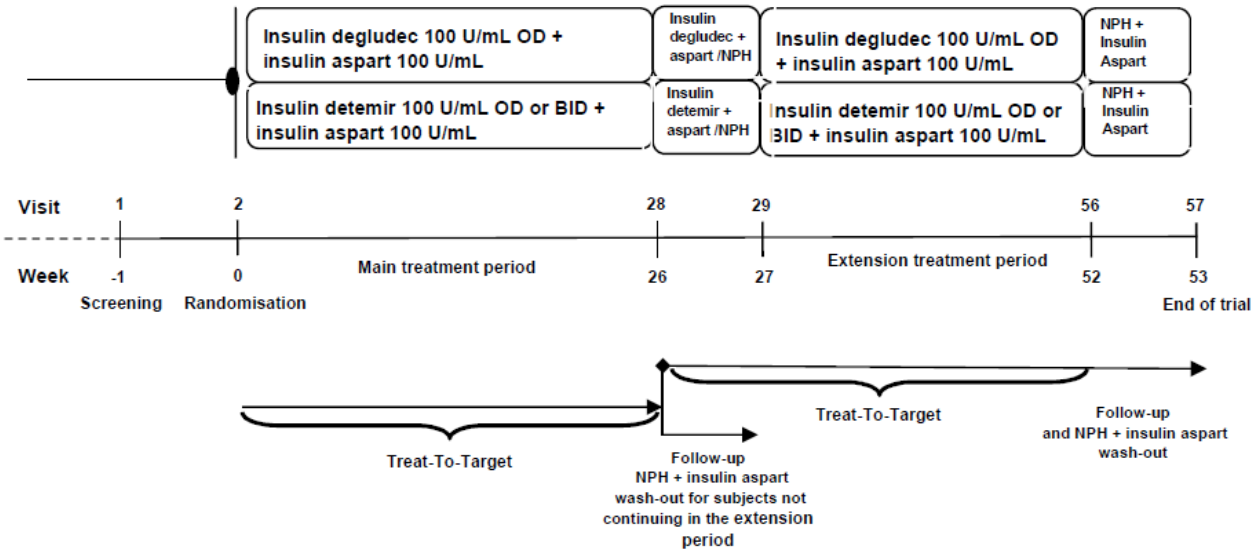
A trial investigating the efficacy and safety of insulin degludec in children and adolescents with type 1 diabetes mellitus (Trial 3561)

Trial 3561 was a 1:1 randomised safety and efficacy trial comparing IDeg and IDet as basal insulin in combination with insulin aspart (IAsp) as bolus insulin in children and adolescents aged 1 to less than 18 years with T1DM. Trial 3561 were divided into a 26-week main trial period followed by a 26-week extension period for those who consented to continue in the extension trial.

This study report was assessed in the procedure EMEA/H/C/II/11. The use of IDeg in adolescents and children from the age of 1 year was approved in the EU in January 2015.

A short description of this study with the main findings is given below.

Figure 7 Trial 3561 – trial design



A total of 346 subjects were planned to be included in this trial, with a minimum of 300 planned to complete the main part and a minimum of 200 planned to complete the extension. As specified in the PIPs for IDeg and IDet, at least 80 of the randomised subjects had to be children aged 1-5 years (both inclusive), and at least 30% and no more than 70% should be girls. Eligible subjects were 1 to less than 18 years of age, diagnosed with T1DM, treated for at least 3 months on any insulin regimen (no OADs were allowed), with a total daily insulin dose ≤ 2.00 units/kg and at screening HbA1c was to be ≤ 11%. Subjects with clinically significant concomitant diseases were not included in this trial. Subjects who met all of the inclusion criteria and none of the exclusion criteria were eligible to participate in the trial.

Primary Objective

The primary objective of Trial 3561 was to confirm the efficacy of IDeg administered once daily plus mealtime IAsp in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA1c) after 26 weeks of treatment. This was done by comparing the difference in change in HbA1c between IDeg + IAsp and IDet + IAsp to with a non-inferiority limit of 0.4%, and if non-inferiority was confirmed with a superiority limit of 0%.

Efficacy endpoints

The primary endpoint was change from baseline in HbA1c (%) after 26 weeks of treatment.

Secondary endpoints

Efficacy was addressed in terms of the following assessments from which endpoints were to be calculated, analysed and presented:

- Change from baseline in HbA1cafter 52 weeks of treatment (analysed by central laboratory)
- Change from baseline in fasting plasma glucose (FPG) after 26 and 52 weeks (analysed by central laboratory)
- SMPG measurements (8-point profiles)after 26 and 52 weeks
    - 8-point profiles
    - Mean of the 8-point profiles
    - Fluctuation in the 8-point profiles
    - Prandial PG increment from 8-point profiles
- SMPG measurements (4-point profiles) obtained throughout the trial for dose adjustment and analysed after 26 and 52 weeks
    - Mean PG before breakfast
    - Within-subject variability as measured by CV%
- Steady state IDeg and IDet plasma concentrations (during the first 26 weeks of treatment).

Continuous glucose measurements (CGM), hypoglycaemia and hyperglycaemia were regarded as safety parameters.

Table 16 Subject disposition for Trial 3561 main trial period and extension period

	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)
Completed main trial	170 (97.7)	165 (93.8)	335 (95.7)
Withdrawn at/after randomisation and before extension	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 main trial. Did not consent to participate in extension	18 (10.3)	37 (21.0)	55 (15.7)
Included in extension	152 (87.4)	128 (72.7)	280 (80.0)
Withdrawn during extension	1 (0.6)	6 (3.4)	7 (2.0)
Adverse event	0 (0.0)	1 (0.6)	1 (0.3)
Withdrawal criteria	1 (0.6)	5 (2.8)	6 (1.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Completed extension	151 (86.8)	122 (69.3)	273 (78.0)
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)
Extension trial set	152 (87.4)	128 (72.7)	280 (80.0)

N: Number of subjects
%: Proportion of randomised subjects

Baseline data

The trial population was generally well balanced with only marginal differences between the two treatment arms in the demographic characteristics. **Table 17** and **Table 18**. The majority of subjects were 'White' (75%) with the second most common race being 'Asian-non-Indian'(16%). 3% of subjects were of hispanic or latino origin, and 97% were of 'Not hispanic or latino' origin. Other baseline characteristics were also similar with the exception of slightly higher mean HbA1cand FPG in the IDeg arm (8.2% and 9.0 mmol/L) than in the IDet arm (8.0% and 8.4mmol/L)). The proportion of subjects with diabetes complications at baseline was very low. Only 4 subjects reported diabetes complications at screening (IDeg: 1 subject with diabetic ketoacidosis; IDet: 3 subjects with diabetic neuropathy). The frequency of concomitant illnesses at screening was low with both treatments and, with the exception of seasonal allergy; no concomitant illnesses were reported in more than 5% of subjects.

The treatment arms were well matched with respect to insulin regimen at screening. The vast majority of subjects (95.7% of randomised subjects) were using basal-bolus therapy, and in both treatment arms, IDet was the most widely used basal insulin followed by insulin glargine (IGlar).

IAsp was the most commonly used bolus insulin. Overall the baseline demographics and diabetes characteristics across the age groups were in line with those of all subjects with the exception of small differences for sex and FPG in children aged 1-5 years in the IDet group. In this group, the male/female distribution was approximately 40:60 as opposed to approximately 56:44 for all IDet subjects, and the mean FPG was 9.2 mmol/L compared to 8.4 mmol/L for all IDet subjects.

Table 17 Demographics and baseline characteristics - summary - full analysis set (abbreviated)

	IDeg OD N (%)	IDet N (%)	Total N (%)
Number of Subjects	174	176	350
Age Group			
N	174 (100.0)	176 (100.0)	350 (100.0)
Adolescents (12-17 yrs)	61 (35.1)	66 (37.5)	127 (36.3)
Children (1-5 yrs)	43 (24.7)	42 (23.9)	85 (24.3)
Children (6-11 yrs)	70 (40.2)	68 (38.6)	138 (39.4)
Sex			
N	174 (100.0)	176 (100.0)	350 (100.0)
Female	78 (44.8)	78 (44.3)	156 (44.6)
Male	96 (55.2)	98 (55.7)	194 (55.4)

N: Number of subjects
%: Percentages are based on N

Table 18 Trial 3561 Baseline and diabetes characteristics - descriptive statistics - full analysis set

	IDeg OD	IDet	Total
Number of Subjects	174	176	350
Age (years)			
N	174	176	350
Mean (SD)	10.0 (4.4)	10.0 (4.4)	10.0 (4.4)
Median	10.2	10.3	10.3
Min ; Max	1.5 ; 18.4[$]	1.8 ; 17.7	1.5 ; 18.4[$]
Height (m)			
N	174	176	350
Mean (SD)	1.37 (0.25)	1.38 (0.25)	1.38 (0.25)
Median	1.39	1.38	1.39
Min ; Max	0.80 ; 1.86	0.82 ; 1.89	0.80 ; 1.89
Body Weight (kg)			
N	174	176	350
Mean (SD)	38.0 (18.7)	37.8 (18.9)	37.9 (18.8)
Median	35.0	32.7	34.8
Min ; Max	11.2 ; 102.2	10.8 ; 95.3	10.8 ; 102.2
BMI (kg/m^2)			
N	174	176	350
Mean (SD)	18.7 (3.6)	18.5 (3.6)	18.6 (3.6)
Median	17.9	17.4	17.6
Min ; Max	12.9 ; 34.5	10.0 ; 30.4	10.0 ; 34.5
Duration of Diabetes (years)			
N	174	176	350
Mean (SD)	3.9 (3.6)	4.0 (3.4)	4.0 (3.5)
Median	2.5	2.9	2.7
Min ; Max	0.3 ; 15.8	0.0 ; 15.0	0.0 ; 15.8
HbA1c (%)			
N	174	176	350
Mean (SD)	8.2 (1.1)	8.0 (1.1)	8.1 (1.1)
Median	8.2	8.0	8.1
Min ; Max	5.5 ; 10.7	5.4 ; 11.1	5.4 ; 11.1
FPG (mmol/L)			
N	157	160	317
Mean (SD)	9.0 (5.2)	8.4 (4.9)	8.7 (5.1)
Median	8.4	7.6	8.2
Min ; Max	0.8 ; 34.4	0.4 ; 25.6	0.4 ; 34.4
FPG (mg/dL)			
N	157	160	317
Mean (SD)	162.1 (94.4)	151.0 (87.7)	156.5 (91.1)
Median	152.1	137.5	147.0
Min ; Max	14.1 ; 620.0	7.0 ; 462.0	7.0 ; 620.0

BMI: Body mass index, N: Number of subjects, SD: Standard deviation
FPG: Fasting plasma glucose [$]All subjects were within the age range 1-<18 years at screening.

Outcomes and estimation

HbA1c

Primary analysis-HbA1c after 26 weeks of treatment

The primary endpoint in Trial 3561 was change from baseline in HbA1cafter 26 weeks of treatment. The result from the 26-week main trial period showed that both IDeg+IAsp and IDet+IAsp effectively improved glycaemic control and non-inferiority between the two treatment arms in terms of lowering

HbA1cwas confirmed as the upper limit of the 95% CI for the estimated treatment difference was ≤0.4%(estimated treatment difference, IDeg –IDet: 0.15%-points $[-0.03;0.32]_{95\%CI}$). Non-inferiority was also confirmed based on the PP analysis set (IDeg –IDet: 0.19 %-points $[0.01;0.37]_{95\%CI}$), and the results of the sensitivity analyses for the primary endpoint, including an analysis based on the repeated measures model, were similar to that of the primary analysis.

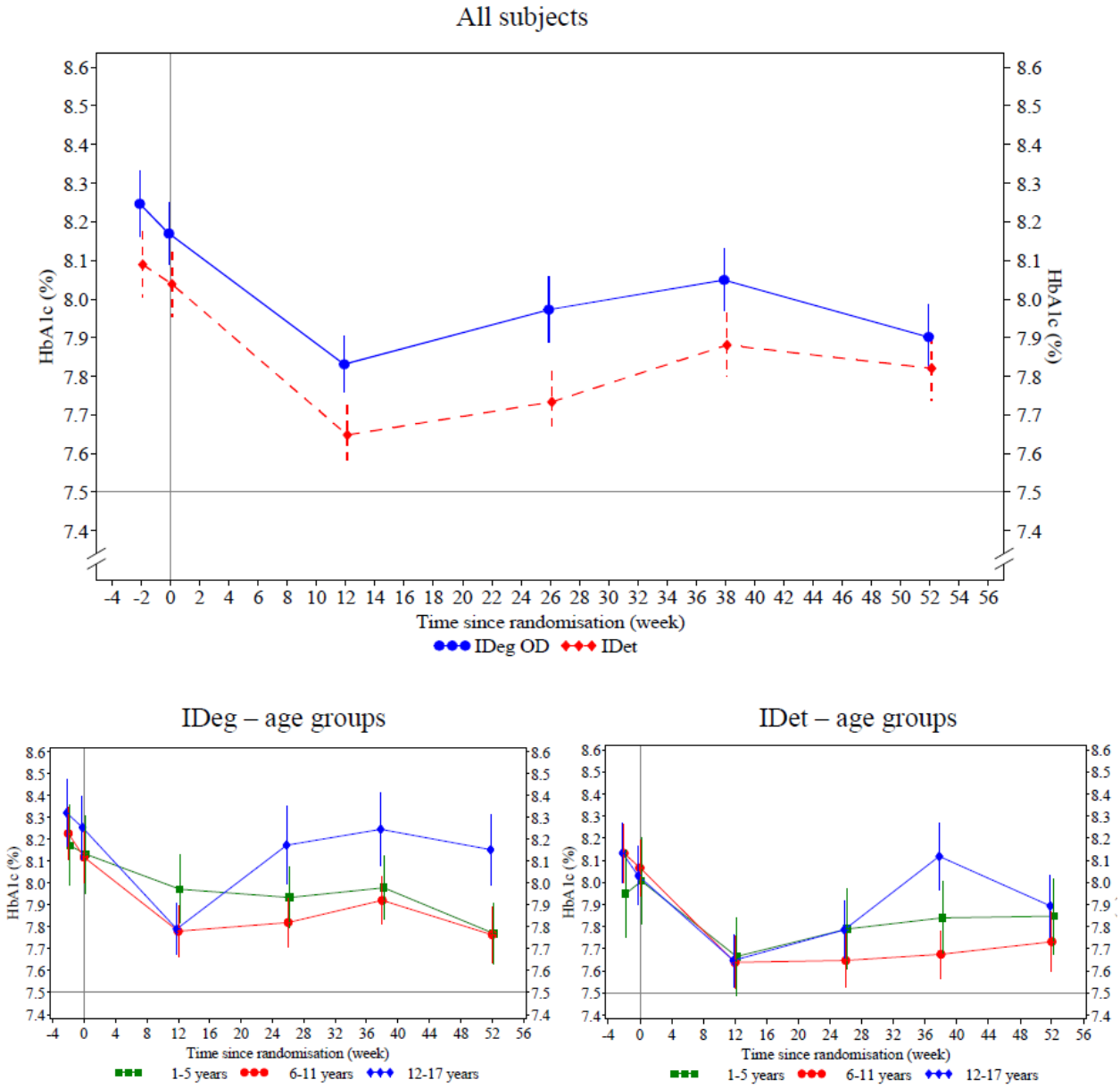
There was an overall reduction in HbA1c from baseline to 26 weeks with both treatments with the observed HbA1c being reduced from 8.2% to 8.0% in the IDeg arm and from 8.0% to 7.7% in the IDet arm. The overall change over time in HbA1c within the 3 age groups was comparable to that seen for all subjects. Thus, in all age groups the observed mean HbA1c was lower after 26 weeks of treatment than at baseline for both treatments.

HbA1c after 52 weeks of treatment

The reduction in HbA1c was maintained after 52 weeks of treatment in both treatment groups indicating that the glycaemic effect was sustained, and at the end of trial, the estimated mean HbA1c was similar for IDeg and IDet with an estimated treatment difference of -0.01 %-points $[-0.20;0.19]_{95\%CI}$). As seen for the 26-week data, the sensitivity analysis using repeated measurements as well as the analyses based on the PP analysis set and the extension trial set, including all subjects who continued in the extension period, supported this result. The observed change from baseline was -0.27 %-point with IDeg and -0.22 %-point with IDet, and the observed mean HbA1c after 52 weeks was 7.9% in the IDeg arm and 7.8% in the IDet arm.

The mean profiles for HbA1c over time were similar with the two treatments, See Figure 8. For both treatments, the initial reduction in HbA1c was followed by a slight increase from Week 12 to 38 before it decreased again towards the end of the trial. The slight increase during the middle period of the trial was primarily driven by the adolescent age groups. Effective glycaemic control in adolescents is particularly challenging due to multiple factors including physiological changes of puberty (increased insulin resistance), and psychosocial factors. This age group is often associated with deterioration in glycaemic control. However, it was notable that in Trial 3561, the observed HbA1c was lower after 52 weeks of treatment than at baseline across all age groups in both the IDeg and the IDet treatment arms.

Figure 8 Trial 3561 Mean HbA1c (%) over 52 weeks – for all subjects (upper panel) and by treatment and age group (lower panel) – full analysis set



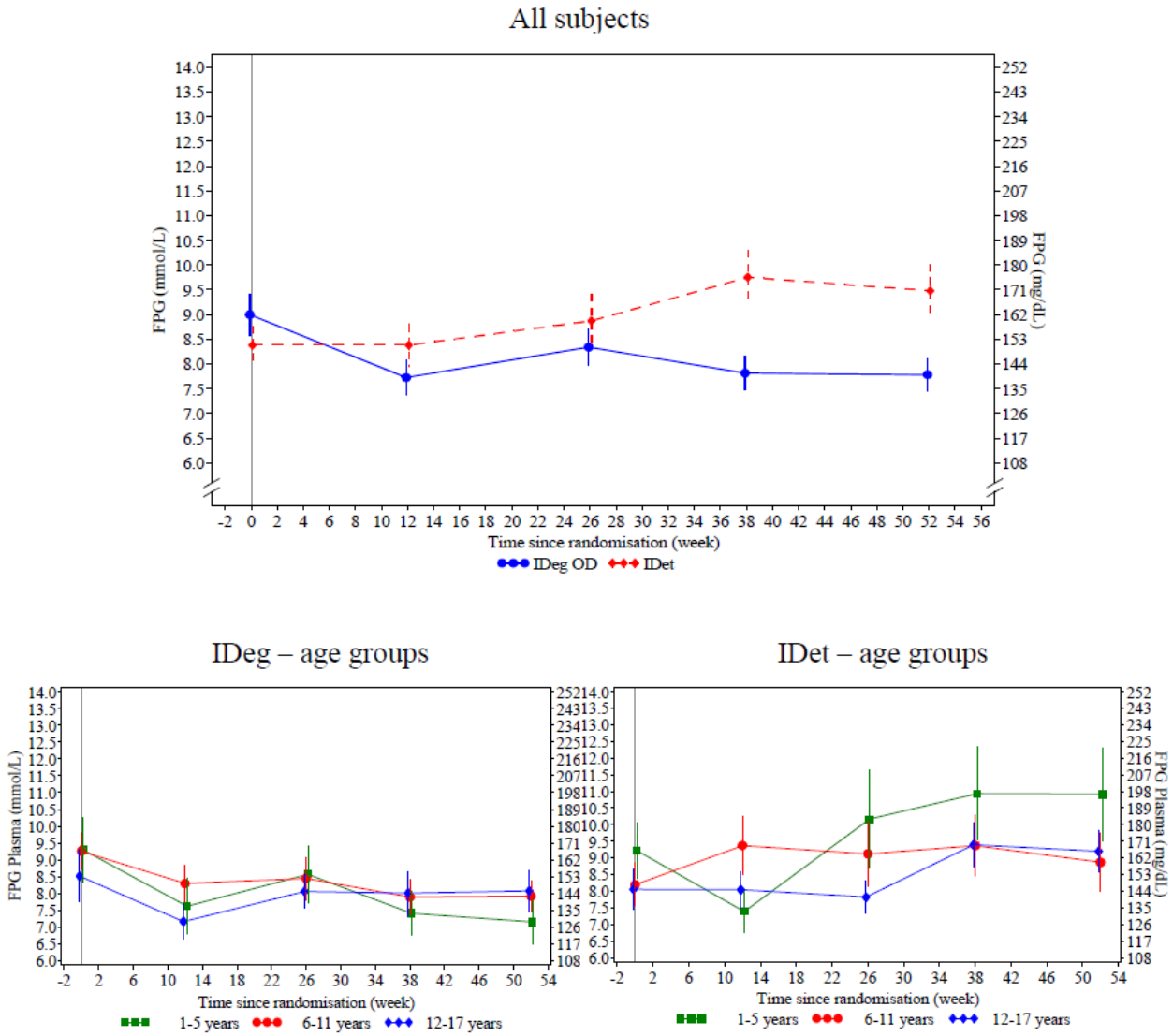
FAS; LOCF imputed data. Error bars ± standard error (mean)

Secondary endpoints

Fasting plasma glucose

During the trial, mean FPG decreased in the IDeg treatment groups and increased in the IDet treatment group, . With IDeg, the observed mean FPG decreased from 9.0 mmol/L at baseline to 7.8 mmol/L after 52 weeks of treatment, whereas it increased in the IDet treatment group from 8.4 mmol/L at baseline to 9.5 mmol/L, and the change from baseline in FPG was statistically significantly different for the two treatments (IDeg-IDet: -1.62mmol/L[-2.84; -0.41]$_{95\%CI}$).The overall change over time in the 3 age groups was comparable to that seen for all subjects in both treatment groups.

Figure 9 Trial 3561 Mean FPG (mmol/L) over 52 weeks - for all subjects (upper panel) and by treatment and age group (lower panel) - full analysis set



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

8-point self-measured plasma glucose profiles

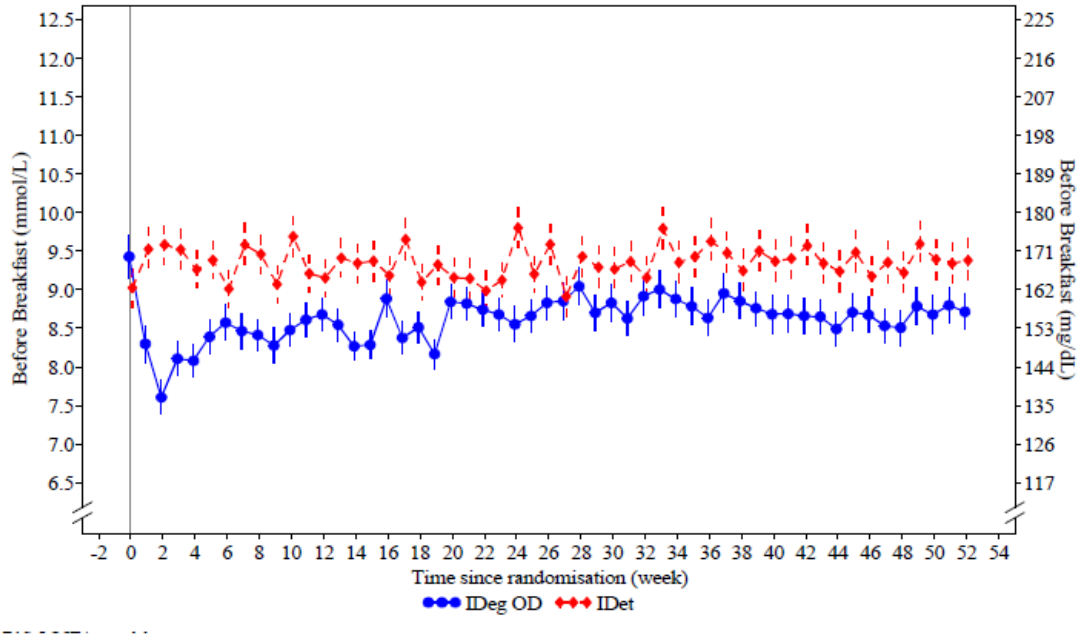
The mean of the 8-point SMPG profile was statistically significantly lower with IDeg compared to IDet after 52 weeks of treatment with an estimated treatment difference(IDeg –IDet) of −0.79mmol/L [−1.32;−0.26] 95% CI.The lower mean reflected the statistically significantly lower SMPG values(IDeg –IDet) at post-breakfast (−1.57 mmol/L [−2.65; −0.49] 95% CI), post-dinner (−1.85 mmol/L [−2.95 ; −0.75]95%CI), and pre-breakfast on the following day (−0.94 mmol/L [−1.77; −0.11] 95% CI). At the remaining time points there were no statistically significant differences.

4-point self-measured plasma glucose for dose adjustment

The 4-point SMPG profiles, which were measured weekly on 3 consecutive days, were used for the titration of the insulin doses. The observed mean pre-breakfast value was higher in the IDeg arm than in the IDet arm at baseline but was lower after one week of treatment and throughout the remaining 52-week treatment period. The mean pre-breakfast SMPG was statistically significantly lower in the

IDeg arm compared to the IDet arm (IDeg – IDet: −0.76mmol/L [−1.46; −0.05] 95% CI) after 52 weeks of treatment. Hence, the result based on self-measured PG values were in accordance with the lower FPG concentrations obtained in the IDeg treatment arm based on central laboratory analyses.

Figure 10 Trial 3561 Mean pre-breakfast self-measured plasma glucose for dose adjustment by treatment week – full analysis set



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

The within-subject variation as determined by the coefficient of variation (%) in pre-breakfast SMPG of the 4-point profiles was similar for the treatment arms after 52 weeks of treatment with an estimated treatment ratio (IDeg/IDet) of 1.04 [0.93; 1.16] 95% CI.

Plasma concentrations of basal insulin

As part of the agreed PIPs for IDeg and IDet, a population PK analysis based on the total IDeg and IDet concentrations was carried out (based on blood samples drawn after 2, 12, and 26 weeks) with the aim to investigate the differences in PK between the three age groups, if any. There was no apparent change in plasma concentrations of IDeg measured at Weeks 2, 12 and 26, whereas the plasma concentrations of IDet increased slightly over time.

Insulin doses over time

Titration algorithms for basal and bolus insulin were provided in the protocol. The same titration algorithm was used for IDeg and IDet, and the algorithm specified the PG target range and the recommended dose adjustments at different PG levels. All subjects were to be individually titrated with the aim of achieving a pre-specified fasting PG target of 5.0-8.0 mmol/L as recommended by the International Society for Paediatric and Adolescent Diabetes (ISPAD) Guidelines. Investigators were in weekly contact with subjects throughout the trial in order to optimise and maintain glycaemic control by individually adjusting insulin doses taking diet, activity level and hypoglycaemic episodes into account. All insulin dose adjustments were done at the discretion of the Investigator. The mean IDeg dose remained relatively constant throughout the trial with the mean daily IDeg dose being 0.37 units/kg at baseline and 0.38 units/kg at the end of the trial. In contrast, the mean daily IDet dose

increased from 0.40 to 0.55 units/kg. The lower mean dose of IDeg compared to IDet may be related to the long duration of IDeg which allows OD dosing in all subjects, whereas IDet could be dosed either OD or BID. The mean daily bolus insulin dose increased slightly during the trial in both treatment groups. From Week 1 to 52, it increased from 0.50 to 0.55 units/kg in the IDeg arm and from 0.52 to 0.58 units/kg in the IDet arm. After 52 weeks of treatment, the ratio of the observed mean basal insulin doses (units/kg) was lower by 30% in the IDeg arm as compared to the IDet arm, whereas the bolus insulin dose ratio was close to 1, indicating that subjects received almost similar doses of IAsp in both the IDeg and IDet treatment arms. Therefore, the total daily dose ratio, which was 18% lower with IDeg than IDet, primarily reflected the lower amount of basal insulin used in the IDeg arm.

The data from Trial 3561 was assessed in the procedure EMEA/H/C/2498/II/11 why these data not were assessed in detail in this procedure.

2.4.3. Discussion of paediatric data on clinical efficacy

The data from study NN5401-3816 (hereafter referred to as study 3816) has been assessed in a recent study report for paediatric studies, P46 005, in June 2015, in accordance with article 46 of regulation (EC) No 1901/2006. In this variation the data from this trial is submitted to support the indication for IDegAsp (Ryzodeg) to treat children and adolescents (aged 1 to less than 18 years) with T1DM. Study 3816 is part of the PIP agreed upon with EMA (PDCO).

Trial 3816 was a 16-week multi-national, multi-centre, open-label, two-arm, parallel group, randomised, treat-to-target, efficacy and safety trial in children and adolescents with T1DM between 1 and 18 years of age.

The primary objective of the trial was to confirm the efficacy of IDegAsp administered OD plus meal-time IAsp for the remaining meals in controlling glycaemia with respect to change from baseline in HbA1c after 16 weeks of treatment. The secondary objective was to compare the efficacy and safety between the two treatment groups. The endpoints chosen are considered adequate and clinically relevant.

The general study design was adequate. A randomised, open-label trial was chosen since the two treatment regimens require different number of daily injections. This is acceptable. Previous studies in adult T1DM patients comparing IDegAsp with IDet showed that HbA1c levels had stabilised after 12 to 16 weeks of treatment. The study duration is therefore considered adequate in the paediatric population. The inclusion and exclusion criteria were adequate. Due to the rise in the incidence of T1DM noted in many countries, with a disproportionately greater increase in children under 5 years, inclusion of the very young age groups (1-18 years) in this trial was required by EMA (PDCO).

The choice of initial dose, comparator and bolus insulin is acceptable. However, nor IDet or IAsp are approved below the age of 2 years, although limited data is available from other clinical trials and no safety concerns have arisen from these data. The inclusion of children > 1 years of age is in line with the PIP for IDegAsp.

The statistical methods were adequate. The chosen non-inferiority margin of 0.4 % is generous as currently a margin of 0.3 % is recommended. However, the chosen non-inferiority margin could serve its purpose for calculating the sample size and the final assessment depends on the actual outcome of the data.

The study included 362 subjects randomised 1:1 to the two treatment groups. Overall 94.5 % of patients completed the study. Withdrawals were evenly distributed between treatments and age groups. The baseline characteristics were generally well balanced between groups. Notably, only one

child below the age of 2 years was included (IDet). Duration of diabetes was slightly longer in the IDegAsp treated group, however, numerically more diabetes complications were reported in the IDet treated group. Both treatments resulted in a reduction of HbA1c compared to baseline (-0.27 % vs -0.23 % for IDegAsp and IDet, respectively) and non-inferiority was demonstrated. The upper limit of the CI was 0.15 % which is well within both the pre-defined non-inferiority margin of 0.4 % and the currently recommended non-inferiority margin of 0.3 %. A similar trend for HbA1c reduction was observed in all age groups irrespective of treatment. Sensitivity analyses were all in line with the primary analysis, thus the outcome appears robust.

The outcome of the secondary endpoints was in line with the primary endpoint. No statistically significant differences were observed between treatments.

The total insulin dose throughout the study was slightly lower in the IDegAsp treated group compared to the IDet treated group. This was due to a lower basal insulin dose in the IDegAsp treated group. The bolus doses were comparable between groups. In both treatment groups, as expected, the highest dose per body weight was observed in the age group 12-17 years. The lower total insulin dose in the IDegAsp group is in line with the findings in study 3561 (see below).

The mean total number of injections per day was lower in the IDegAsp group than in the IDet group for the overall population (3.6 versus 4.9 injections) and for each of the 3 age groups, with similar magnitude of difference between IDegAsp and IDet in each age group. There was wide variation in the daily number of injections used in all age groups and in both treatment arms: from 1 to 5 injections per day in the IDegAsp group and from 1 to 6 injections in the IDet group.

In conclusion, trial 3816 IDegAsp OD+IAsp for the remaining meals was shown to be non-inferior compared to IDet OD or BID+ mealtime IAsp. Comparable glycaemic control was achieved with a lower total insulin dose in the IDegAsp treated group. Both treatments showed sustained efficacy in the paediatric population over 16 weeks.

The results of trial 3561 has already been submitted and assessed with procedure EMEA/H/C/XXXX/LEG/WS/0501, in accordance with Article 46 of the Regulation (EC) No 1901/2006 and in the procedure EMEA/H/C/II/11. The use of IDeg in adolescents and children from the age of 1 year was approved in the EU in January 2015.

Trial 3561 was an open-labelled, randomised (1:1), treat-to-target, safety and efficacy trial comparing IDeg and IDet as basal insulin in combination with IAsp as bolus insulin in subjects with T1DM between 1 and less than 18 years of age. Randomisation was stratified by age groups (1 to less than 6 years; 6 to less than 12 years and 12 to less than 18 years).

The design was similar to the design of the previous therapeutic confirmatory trials with IDeg and standard methods were applied. Statistical methods are acceptable.

In trial 3561, IDeg OD plus meal-time IAsp was non-inferior to IDet OD or BID plus meal-time IAsp in reducing HbA1c after 26 weeks treatment (estimated mean treatment difference, IDeg−IDet: 0.15%-points [−0.03; 0.32] 95% CI). A further improvement in glycaemic control was seen in the IDeg treatment group in the 26-week extension period based on FPG, mean of the 8-point profiles and pre-breakfast SMPG based on 4-point profiles. The mean daily basal insulin dose (units/kg) was lower with IDeg than IDet throughout the trial and remained relatively constant with IDeg, whereas there was an increase over time with IDet. Bolus doses (units/kg) were similar for the two treatments and increased slightly over time with both treatments. Comparable glycaemic control, as assessed by change in HbA1c, was achieved with lower daily insulin doses with IDeg OD + IAsp compared to IDet (OD or BID) + IAsp. Thus, the outcome of study 3561 was in line with the results in study 3816.

2.4.4. Conclusions on the clinical efficacy

In conclusion, trial 3816 has shown that IDegAsp OD+ IAsp for the remaining meals is non-inferior to IDet OD or BID+ bolus IAsp. The supportive study trial 3561 has shown that IDeg OD+ bolus IAsp is non inferior to IDet OD or BID+ bolus IAsp. In addition this supportive study gives data on persistence of efficacy for the IDeg molecule over one year of treatment.

These two confirmatory therapeutic studies include 697 patients which are considered to be sufficient amount of data to support the efficacy of IDegAsp in children.

2.5. Clinical safety

Introduction

The safety profile for IDegAsp has been investigated in the clinical program supporting the marketing authorisation. The results demonstrate that the safety profile of IDeg in patients with T1DM and T2DM as monotherapy or in combination with oral antidiabetic agents is in line with the safety profile of other insulin analogues. The major safety issues are hypoglycaemia, injection site reactions and the potential risk of antibody formation.

2.5.1. Patient exposure Trial 3816

A total of 360 subjects who received at least one dose of trial product were included in the safety analysis set: 181 subjects in the IDegAsp treatment group and 179 subjects in the IDet treatment group. Of those randomised, 94.5% subjects completed 16 weeks of trial treatment. Exposure was similar in the two treatment groups. Mean (SD) exposure was 0.30 (0.03) years with a range of 0.06 to 0.35 years in the IDegAsp group and 0.30 (0.04) years with a range of 0.02 to 0.34 years in the IDet group.

Insulin dose

At randomisation the total daily insulin dose was to be reduced by 20%. Subjects were transferred from pre-trial basal insulin to IDegAsp or IDet aiming for a basal:bolus ratio of between 50:50 and 30:70 with no specific recommendations for basal dose reduction. Daily basal insulin dose relates to the daily dose of IDet or IDeg (70% of the IDegAsp OD dose).

In terms of dosing patterns, the mean total daily insulin dose was lower in the IDegAsp group compared to the IDet group throughout the trial. At week 16, the mean (SD) total daily insulin doses were 0.88 (0.29) vs. 1.01 (0.40) units/kg in the IDegAsp and IDet groups, respectively.

In the IDegAsp treatment group, mean total daily insulin dose per body weight was highest in adolescents throughout the trial; mean dose in children 1-5 years and 6-11 years was similar throughout the trial.

In the IDet treatment group, mean total daily insulin dose per body weight was lowest in children 1-5 years and highest in adolescents 12-17 years throughout the trial.

In the IDet treated group 54.2 % of patients were using IDet BID.

Figure 11 Trial 3816 Total daily insulin dose (actual) in units/kg by treatment week – mean plot – safety analysis set

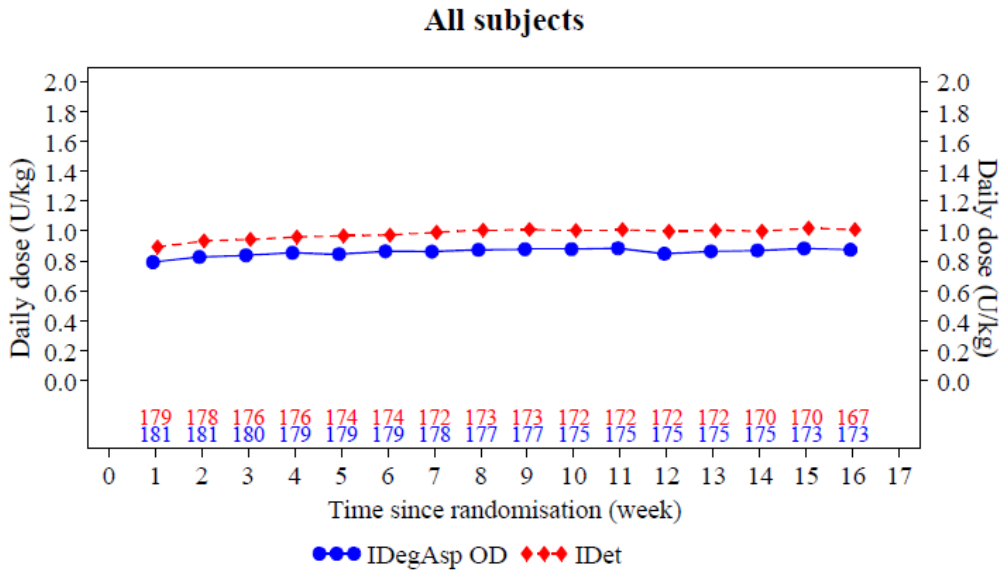
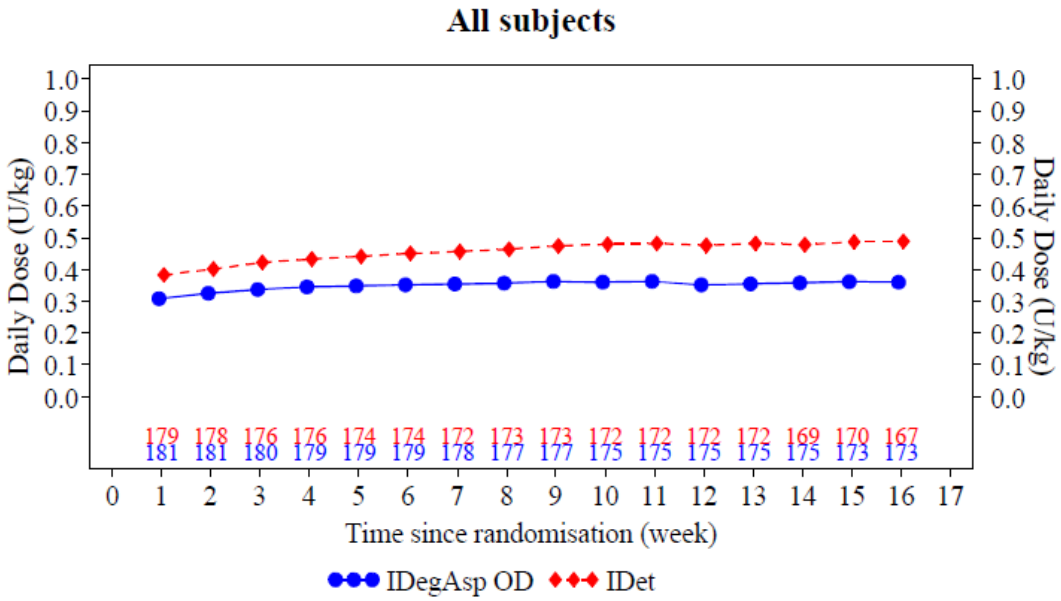


Figure 12 Trial 3816 Daily basal insulin dose (actual) in units/kg by treatment week – mean plot – safety analysis set



2.5.2. Adverse events in Trial 3816

In Trial 3816, the overall rate of AEs was similar in the two treatment groups (915 vs. 853 events per 100 PYE in the IDegAsp and IDet groups, respectively). The majority of events were mild or moderate in severity and were considered as unlikely to be related to the trial products. No deaths were reported. Apart from hypoglycaemia, many of the commonly reported AEs appeared to be related to

infectious diseases as could be expected in this age group. The observed rate of serious adverse events (SAEs) was low in each group, but numerically higher with IDegAsp than with IDet (26 vs. 13 events per 100 PYE, respectively).

The rates of AEs considered possibly or probably related to trial product (IDegAsp or IDet), as judged by the investigator, were 47 vs. 37 events per 100 PYE, respectively, and approximately 75% of all subjects in either treatment group had an outcome of recovered at end of trial.

No unexpected differences between the 3 age groups with respect to type of AEs were observed in the treatment groups. A slightly higher rate of AEs in the IDegAsp treatment group for children 1-5 years was observed.

The most frequent AEs occurring in ≥5% of the subjects are summarised in Table 20. Apart from hypoglycaemic episodes reported on the hypoglycaemic episode form, the most frequently reported AEs (≥5%) in both treatment groups were ‘headache’, ‘nasopharyngitis’, ‘abdominal pain upper’, ‘pyrexia’ and ‘vomiting’

Table 19 Trial 3816 Adverse events – treatment-emergent – summary – safety analysis set

	IDegAsp OD N	(%)	E	R	IDet N	(%)	E	R	Total N	(%)	E	R
Number of Subjects	181				179				360			
Events	141	(77.9)	501	915	134	(74.9)	460	853	275	(76.4)	961	884
Serious												
Yes	11	(6.1)	14	26	7	(3.9)	7	13	18	(5.0)	21	19
No	137	(75.7)	487	889	133	(74.3)	453	840	270	(75.0)	940	865
Severity												
Severe	12	(6.6)	14	26	5	(2.8)	5	9	17	(4.7)	19	17
Moderate	52	(28.7)	96	175	30	(16.8)	58	108	82	(22.8)	154	142
Mild	126	(69.6)	391	714	129	(72.1)	397	736	255	(70.8)	788	725
Relationship to Investigational Product												
Probably	13	(7.2)	16	29	11	(6.1)	13	24	24	(6.7)	29	27
Possibly	10	(5.5)	10	18	6	(3.4)	7	13	16	(4.4)	17	16
Unlikely	136	(75.1)	472	862	129	(72.1)	438	812	265	(73.6)	910	837
Missing	2	(1.1)	3	5	2	(1.1)	2	4	4	(1.1)	5	5
Related to Bolus Insulin												
Probably	9	(5.0)	11	20	7	(3.9)	10	19	16	(4.4)	21	19
Possibly	9	(5.0)	9	16	7	(3.9)	7	13	16	(4.4)	16	15
Unlikely	137	(75.7)	478	873	132	(73.7)	441	818	269	(74.7)	919	846
Missing	2	(1.1)	3	5	2	(1.1)	2	4	4	(1.1)	5	5
Related to Device												
Yes	0	(0.0)	0	0	1	(0.6)	1	2	1	(0.3)	1	1
No	141	(77.9)	498	909	134	(74.9)	457	847	275	(76.4)	955	879
Missing	2	(1.1)	3	5	2	(1.1)	2	4	4	(1.1)	5	5
Outcome												
Recovered/Resolved	137	(75.7)	470	858	133	(74.3)	441	818	270	(75.0)	911	838
Recovering/ Resolving	6	(3.3)	6	11	6	(3.4)	7	13	12	(3.3)	13	12
Recovered/ Resolved with Sequelae	1	(0.6)	1	2	0	(0.0)	0	0	1	(0.3)	1	1
Not Recovered/Not Resolved	20	(11.0)	24	44	10	(5.6)	12	22	30	(8.3)	36	33

N: Number of Subjects
%: Percentage of Subjects
E: Number of Events
R: Event Rate per 100 Patient Years of Exposure
Relationship is based on investigator(s)'s assessment.

Table 20 Trial 3816 Adverse events by system organ class and preferred term – most frequent [≥5%] – treatment emergent – summary – safety analysis set

	IDegAsp OD N	(%)	E	R	IDet N	(%)	E	R	Total N	(%)	E	R
Number of Subjects	181				179				360			
Events	100	(55.2)	242	442	97	(54.2)	243	451	197	(54.7)	485	446
Infections and infestations												
Nasopharyngitis	36	(19.9)	43	79	32	(17.9)	42	78	68	(18.9)	85	78
Upper respiratory tract infection	11	(6.1)	12	22	17	(9.5)	18	33	28	(7.8)	30	28
Influenza	9	(5.0)	10	18	10	(5.6)	12	22	19	(5.3)	22	20
Pharyngitis	3	(1.7)	3	5	10	(5.6)	13	24	13	(3.6)	16	15
Gastrointestinal disorders												
Vomiting	22	(12.2)	25	46	12	(6.7)	13	24	34	(9.4)	38	35
Abdominal pain upper	14	(7.7)	22	40	17	(9.5)	26	48	31	(8.6)	48	44
Abdominal pain	10	(5.5)	13	24	7	(3.9)	13	24	17	(4.7)	26	24
Nervous system disorders												
Headache	23	(12.7)	47	86	32	(17.9)	64	119	55	(15.3)	111	102
Respiratory, thoracic and mediastinal disorders												
Cough	13	(7.2)	16	29	9	(5.0)	9	17	22	(6.1)	25	23
Oropharyngeal pain	9	(5.0)	13	24	13	(7.3)	14	26	22	(6.1)	27	25
General disorders and administration site conditions												
Pyrexia	17	(9.4)	26	47	10	(5.6)	15	28	27	(7.5)	41	38
Metabolism and nutrition disorders												
Hypoglycaemia	11	(6.1)	12	22	3	(1.7)	4	7	14	(3.9)	16	15

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

The overall reporting of adverse events were somewhat higher in the IDegAsp treated group, however, the rate of events deemed to be related to treatment was low and comparable between groups. Apart from hypoglycaemia, the most commonly reported events appears to be related to infectious diseases as could be expected in this age group.

2.5.3. Serious adverse event / deaths / other significant events-trial 3816

The rates of SAEs were low: 14 SAEs reported by 11 (6.1%) subjects in the IDegAsp group and seven SAEs reported by 7 (3.9%) subjects in the IDet group. For IDegAsp, the most frequently reported SAE was hypoglycaemia. One subject in the IDegAsp group was withdrawn from the trial during the 16-week treatment period due to an AE of 'hypoglycaemic seizure'. Additionally, 1 subject in the IDet group withdrew due to hypoglycaemic events judged by the investigator to be related to the trial product reported under 'other' reasons for withdrawal.

Table 21 Trial 3816 Serious adverse events by system organ class and preferred term – treatment emergent - summary - safety analysis set

	IDegAsp OD				IDet				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	181				179				360			
Events	11	(6.1)	14	26	7	(3.9)	7	13	18	(5.0)	21	19
Metabolism and nutrition disorders	6	(3.3)	6	11	3	(1.7)	3	6	9	(2.5)	9	8
Hypoglycaemia	5	(2.8)	5	9	1	(0.6)	1	2	6	(1.7)	6	6
Diabetic ketoacidosis	1	(0.6)	1	2	1	(0.6)	1	2	2	(0.6)	2	2
Hyperglycaemia					1	(0.6)	1	2	1	(0.3)	1	1
Infections and infestations	1	(0.6)	1	2	2	(1.1)	2	4	3	(0.8)	3	3
Viral infection	1	(0.6)	1	2	1	(0.6)	1	2	2	(0.6)	2	2
Laryngitis					1	(0.6)	1	2	1	(0.3)	1	1
Gastrointestinal disorders	2	(1.1)	2	4					2	(0.6)	2	2
Constipation	1	(0.6)	1	2					1	(0.3)	1	1
Gastritis	1	(0.6)	1	2					1	(0.3)	1	1
Injury, poisoning and procedural complications	1	(0.6)	2	4	1	(0.6)	1	2	2	(0.6)	3	3
Fall					1	(0.6)	1	2	1	(0.3)	1	1
Fibula fracture	1	(0.6)	1	2					1	(0.3)	1	1
Tibia fracture	1	(0.6)	1	2					1	(0.3)	1	1
Nervous system disorders	1	(0.6)	1	2	1	(0.6)	1	2	2	(0.6)	2	2
Hypoglycaemic seizure	1	(0.6)	1	2					1	(0.3)	1	1
Loss of consciousness					1	(0.6)	1	2	1	(0.3)	1	1
Congenital, familial and genetic disorders	1	(0.6)	1	2					1	(0.3)	1	1
Developmental glaucoma	1	(0.6)	1	2					1	(0.3)	1	1
Musculoskeletal and connective tissue disorders	1	(0.6)	1	2					1	(0.3)	1	1
Compartment syndrome	1	(0.6)	1	2					1	(0.3)	1	1

N= Number of subjects
%= Percentage of subjects
E= Number of Events
R= Event Rate per 100 Exposure Years

Serious adverse events were few and the most commonly reported event was hypoglycaemia. A hypoglycaemia related event was also the reason for withdrawal of one subject in the IDegAsp treated group. Hypoglycaemia was also the most common reason for dose reductions.

2.5.4. Hypoglycaemic episodes in trial 3816

In the 3816 trial, hypoglycaemic episodes were evaluated based on the International Society for Paediatric and Adolescent Diabetes (ISPAD 2009) classification, See **Figure 3**. (PG ⩽3.9 mmol/L or PG>3.9 mmol/L in conjunction with hypoglycaemic symptoms) and a Novo Nordisk definition of confirmed hypoglycaemic episodes (severe hypoglycaemia and/or those with PG <3.1 mmol/L)

Hypoglycaemia reported as adverse event

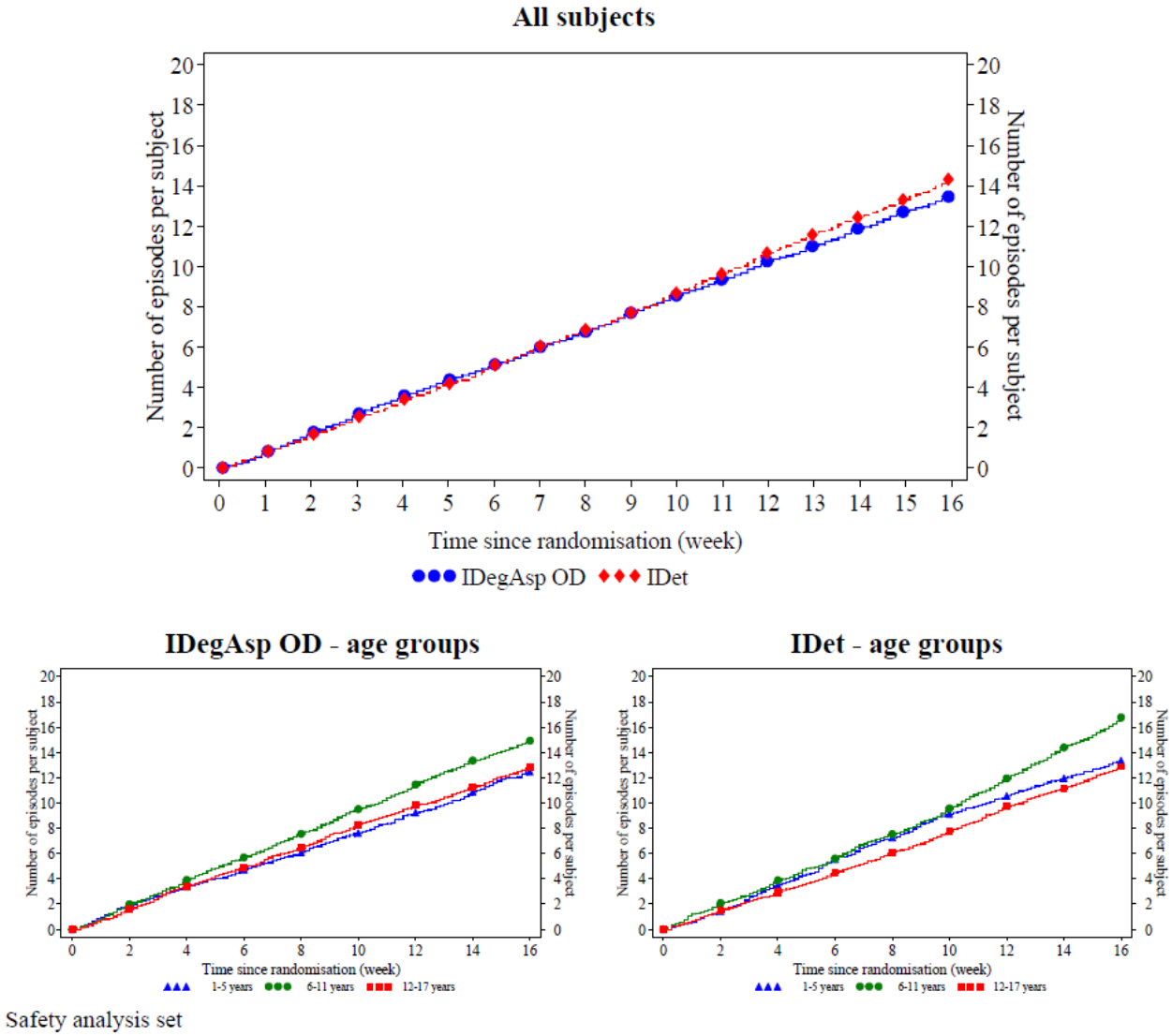
A hypoglycaemic episode was to be reported as an AE if it fulfilled the definition of an SAE or a medical event of special interest (severe hypoglycaemia as per ISPAD definition). Hypoglycaemia was reported as an AE for 11 (6.1%) subjects in the IDegAsp group (12 events) and for 3 (1.7%) subjects in the IDet group (4 events). In addition, hypoglycaemic seizure was reported as an AE for 2 (1.1%) subjects in the IDegAsp group (3 events). Hypoglycaemia-related SAEs (hypoglycaemia and/or hypoglycaemic seizure) were reported for 6 (3.3%) subjects in the IDegAsp group (6 events) and for 1 (0.6%) subject in the IDet group (1 event). In addition, one subject in the IDegAsp group experienced a non-serious AE of hypoglycaemic seizure that led to withdrawal of the subject from the trial.

Table 22 Trial 3816 Hypoglycaemic episodes by classification – treatment emergent – summary - safety analysis set

	IDegAsp OD				IDet			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	181				179			
Confirmed	168	(92.8)	2532	4623	164	(91.6)	2672	4955
ISPAD	178	(98.3)	5833	10651	170	(95.0)	5922	10982
Severe	11	(6.1)	14	26	3	(1.7)	4	7
Documented Sympt.	167	(92.3)	3005	5487	160	(89.4)	3648	6765
Asymptomatic	158	(87.3)	2763	5045	145	(81.0)	2226	4128
Probable Sympt.	2	(1.1)	2	4	4	(2.2)	5	9
Relative	16	(8.8)	49	89	11	(6.1)	39	72
ISPAD Unclassifiable	28	(15.5)	120	219	31	(17.3)	168	312

N: Number of Subjects
%: Percentage of Subjects with the Event
E: Number of Events
R: Event Rate per 100 Patient Year(s) of Exposure
ISPAD: International society for pediatric and adolescent diabetes, Sympt.: Symptomatic
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 PG < 3.1 mmol/L (56mg/dL)

Figure 13 Trial 3816 Confirmed hypoglycaemic episodes – treatment emergent - mean cumulative function (upper panel: all subjects; lower panel: age groups) – safety analysis set



Safety analysis set

The reporting of confirmed hypoglycaemias did not differ between treatment groups with similar proportions reporting an event. In both treatment groups, hypoglycaemias were more common in subjects aged 6-11 years which may reflect greater difficulties in controlling blood glucose in this age group, i.e. during school hours.

Severe hypoglycaemic episodes

The majority of subjects , n=170 (93.9%), had no severe hypoglycaemic episodes neither in the IDegAsp treatment group nor in the IDet treatment group n=176 (98.3%). In the IDegAsp treatment group, 11 subjects (6.1%) reported 14 severe hypoglycaemic episode (Table 24 and **Figure 14**), leading to a rate of 26 episodes per 100 PYE. In the IDet treatment group, 3 subjects (1.7%) reported 4 severe hypoglycaemic episodes leading to a rate of 7 episodes per 100 PYE. There was no statistically significant difference between treatment groups.

When evaluating severe hypoglycaemic episodes it is important to note that these were mostly single occurrences in individual subjects. Three (3) subjects in the IDegAsp treatment group reported 2

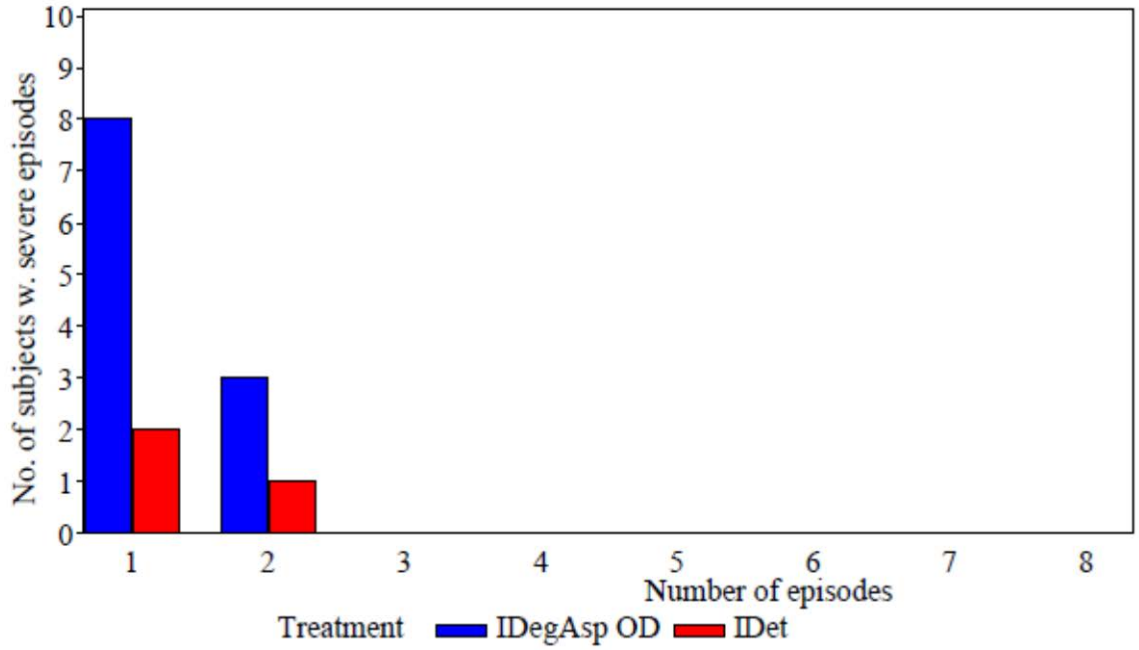
severe hypoglycaemic episodes each (1 of these subjects reported the events within 19 minutes and it was evaluated to be the same episode by the external classifier; see below) and 1 subject in the IDet treatment group reported 2 severe episodes. Two (2) of the episodes in the IDegAsp group and 1 in the IDet group appeared to be related to exercise. The observed rate of severe hypoglycaemic episodes was higher with IDegAsp than with IDet throughout the trial. The majority of the severe hypoglycaemic episodes occurred during daytime (diurnal) in both treatment groups.

Table 23 Trial 3816 Hypoglycaemia SAEs - treatment emergent - summary - safety analysis set

	IDegAsp OD				IDet			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	181				179			
Serious AEs as evaluated by investigator								
Hypoglycaemia	5	(2.8)	5	9	1	(0.6)	1	2
Hypoglycaemia seizure	1	(0.6)	1	2				
Additional Serious AEs as evaluated by sponsor								
Hypoglycaemia	1	(0.6)	1					

N= Number of subjects
%= Percentage of subjects
E= Number of Events
R= Event Rate per 100 Exposure Years

Figure 14 Trial 3816 Distribution of severe hypoglycaemic episodes - subject counts against number of episodes - safety analysis set



The x-axis denotes observed subject counts of severe hypoglycaemic episodes.
The height of a bar (measured on the y-axis) gives the number of patients experiencing a given number of severe hypoglycaemic episodes.
Safety analysis set

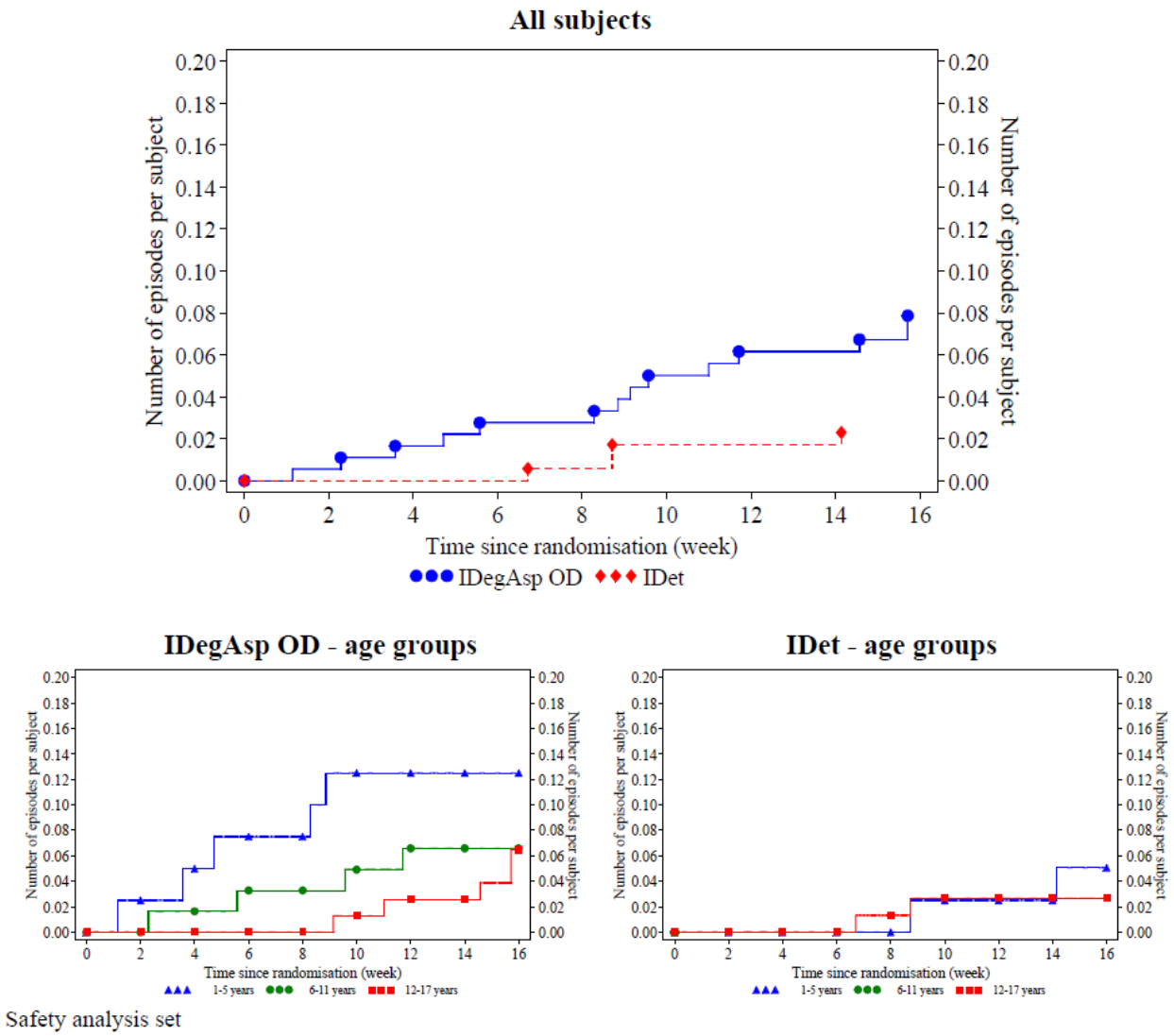
The episodes of severe hypoglycaemia according to ADA and ISPAD were reviewed by an external expert in a blinded manner in order to have a centralised assessment of severe hypoglycaemia classification, in accordance with ISPAD. The classification was based on case narratives and paraclinical findings. Under the external classification, 7 events (in 6 subjects) in IDegAsp treatment group were classified as severe based on the most subjective criterion 'altered mental status and cannot assist in his care'; no events in the IDet treatment group met this criterion. Additionally, 6 events (in 5 subjects) in the IDegAsp treatment group and 4 events (in 3 subjects) in the IDet treatment group involved the child being semiconscious or unconscious, or in a coma ± convulsions (Table 24).

Table 24 Trial 3816 External classified severe hypoglycaemic episodes – treatment emergent - summary - safety analysis set

	IDegAsp OD				IDet			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	181				179			
All reported severe hypoglycaemia	11	(6.1)	14	26	3	(1.7)	4	7
Externally classified episodes	11	(6.1)	14	26	3	(1.7)	4	7
Severe hypoglycaemia	11	(6.1)	13	24	3	(1.7)	4	7
Altered mental status and cannot assist in his care	6	(3.3)	7	13				
Semiconscious or unconscious	3	(1.7)	3	5	2	(1.1)	3	6
Coma ± convulsions	2	(1.1)	3	5	1	(0.6)	1	2
Not severe hypoglycaemia	1	(0.6)	1	2				

N: Number of subjects, %: Percentage of subjects with the event, E: Number of events
R: Event rate per 100 patient year(s) of exposure

Figure 15 Trial 3816 Severe hypoglycaemic episodes - treatment emergent - mean cumulative function (upper panel: all subjects; lower panel: age groups) – safety analysis set



Severe hypoglycaemic episodes across age groups

In the IDegAsp treated group, the number of severe hypoglycaemic episodes was similar between age groups; 5 episodes in 4 subjects were reported in children 1-5 years and in adolescents 12-17 years while 4 episodes in 3 subjects were reported in children 6-11 years (Figure 15). The rate for children 1-5 years was higher compared to other age groups, although it should be noted that the rates are based on few episodes.

In the IDet treated group, two (2) episodes in 2 subjects were reported in children 1-5 years and 2 episodes in 1 subject were reported in adolescents 12-17 years. No episodes were reported in children 6-11 years .

Table 25 Severe hypoglycaemic episodes - treatment emergent - statistical analysis – full analysis set

	FAS	N	Estimate	95% CI
LSMeans, Events per 100 PYE				
IDegAsp OD	182	181	15.71	
IDet	180	179	4.91	
Treatment Ratio				
IDegAsp OD / IDet			3.20	[0.88 ; 11.66]

FAS: Full analysis set, N: Number of subjects contributing to analysis
CI: Confidence interval
PYE: Patient years exposure
The number of events is analysed using a negative binomial regression model using a log-link function and the logarithm of the exposure time (100 years) as offset. The model includes treatment,sex,region and age group as fixed effects.

The Applicant has presented data on severe hypoglycaemias in the lowest age group of children 2-5 year. There is a signal of a potential higher risk for severe hypoglyacemic event but this signal is based on few events in few individuals and should be interpreted with caution. In addition, the hypoglycaemias were seen mostly during daytime and the overall rate of nocturnal hypoglycaemias did not differ between treatments. Notably, a lower rate of nocturnal hypoglycaemias was observed in the youngest age group treated with IDegAsp. Even though a premixed insulin probably not is a suitable treatment for the majority of young children there may be clinical situations where a premixed insulin may offer advantages for a young child for example may be suitable for some children, for example in cases of poor compliance and with the need for fewer injections.

During the procedure the children aged 1 to <2 years in the were excluded from the indication because of for example, small doses of insulin, variable feeding patterns and activity levels and inability of communicating symptoms of hypoglycaemia.

In the IDegAsp treatment group, 5 subjects reported 5 SAEs, severe hypoglycaemia, considered possibly or probably related to IDegAsp.

In the IDet treatment group, 1subject reported 1 SAE (‘loss of consciousness’) considered possibly related to IAsp.

One case with a mix-up between basal and bolus insulin was found.

Nocturnal confirmed hypoglycaemic episodes

The percentages of subjects experiencing nocturnal confirmed hypoglycaemic episodes were similar with IDegAsp (N= 101 [55.8%]) and IDet (N= 106 [59.2%]) as was the observed rates per 100 PYE (577 with IDegAsp and 540 with IDet). No statistically significant difference was observed between the treatment arms (IDegAsp OD/IDet: 1.09 [0.81; 1.48] 95% CI). Approximately 90% of the subjects in both treatment groups reported 4 or fewer nocturnal confirmed hypoglycaemic episodes during the trial.

Nocturnal confirmed hypoglycaemic episodes across age groups

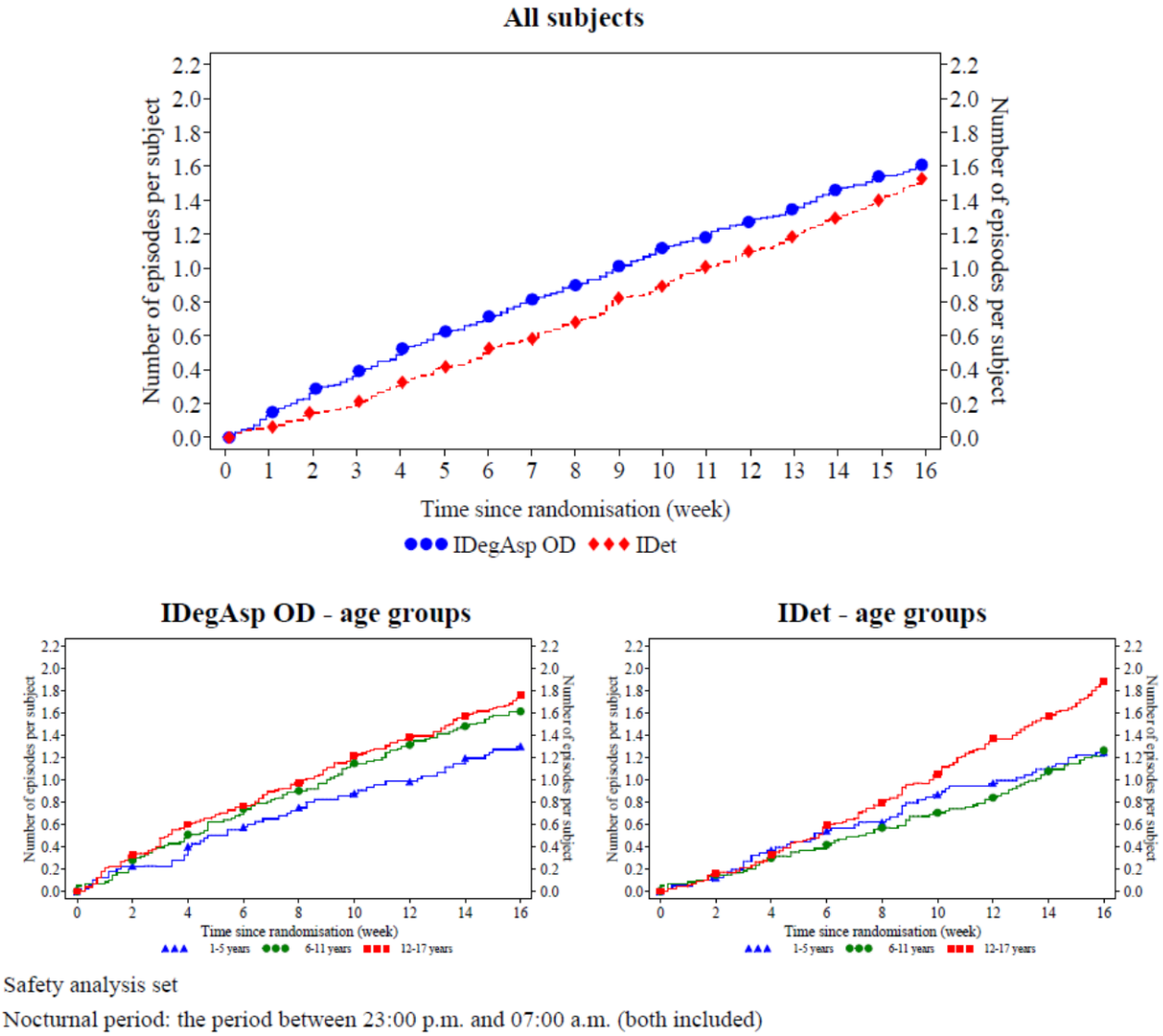
The rate of nocturnal confirmed hypoglycaemic episodes tended to increase with increasing age. Thus, the rate was higher in adolescents 12-17 years as compared to the overall trial population and lower in children 1 to 5 years. The higher rate in adolescents may be attributed to adolescent lifestyle.

Nocturnal severe hypoglycaemic episodes

The number of nocturnal severe hypoglycaemic episodes was low in both treatment groups, which precluded meaningful statistical analysis comparison between treatments.

Two (2) nocturnal severe hypoglycaemic episodes in 1 subject was reported in the IDegAsp treatment group (children 6-11 years) and 2 episodes in 2 subjects was reported in the IDet treatment group (1 subject in children 1-5 years and 1 subject in adolescents 12-17 years).

Figure 16 Trial 3816 Nocturnal confirmed hypoglycaemic episodes – treatment emergent - mean cumulative function (upper panel: all subjects; lower panel: age groups) – safety analysis set



Safety analysis set

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

The overall rate of nocturnal hypoglycaemias did not differ between treatments. Notably, a lower rate of nocturnal hypoglycaemias was observed in the youngest age group treated with IDegAsp.

Hyperglycaemic episodes and ketosis

According to the protocol, subjects were to report a hyperglycaemic episode whenever a glucose measurement was 14.0 mmol/L (250 mg/dL) or above, and the subject looked/felt ill. Subjects having a hyperglycaemic episode as described were to also measure ketone bodies. The ketone measurement involved an additional finger prick. Ketosis was considered present if blood ketones were higher than 1.5 mmol/L.

The percentages of subjects experiencing hyperglycaemic episodes were similar between IDegAsp (N= 72 [39.8%]) and IDet (N= 73 [40.8%]) treatment groups (**Table 26**) The observed rate of hyperglycaemic episodes per 100 PYE was 1094 with IDegAsp and 833 with IDet.

The percentages of subjects experiencing hyperglycaemic episodes with ketosis (blood ketones > 1.5 mmol/L) were numerically lower with IDegAsp (N= 4 [2.2%]) compared to IDet (N= 8 [4.5%]). The rate per 100 PYE was 11 with IDegAsp and 22 with IDet. There were no statistically significant differences between treatment groups in the rates of hyperglycaemic episodes or hyperglycaemic episodes with ketosis.

In order to assess the hyperglycaemic episodes with ketosis in the trial, it has to be considered that many subjects did not measure ketone bodies as per protocol. Ketone bodies were measured for approximately 74% of hyperglycaemic episodes in the IDegAsp treatment group and for 67% in the IDet treatment group. This imbalance in ketone body measurement among groups would be expected to result in more ketosis episodes identified in the IDegAsp treatment group. However, less episodes of ketosis were reported in the IDegAsp treatment group than in the IDet treatment group (6 episodes in 4 subjects with IDegAsp versus 12 episodes in 8 subjects with IDet), implying that the difference in episodes of ketosis in favour of IDegAsp might have been underestimated.

Regarding subjects experiencing nocturnal hyperglycaemic episodes, the percentages of subjects were similar between IDegAsp (N= 26 [14.4%]) compared to the IDet (N= 30 [16.8%]) treatment group. The respective rates per 100 PYE were 184 with IDegAsp and 98 with IDet (**Table 26**).

Regarding nocturnal hyperglycaemic episodes with ketosis (blood ketones > 1.5 mmol/L), 1 episode in 1 subject was reported with IDegAsp vs 2 episodes in 2 subjects with IDet (**Table 26**). No statistical analysis was performed for nocturnal hyperglycaemic episodes nor for nocturnal hyperglycaemic episodes with ketosis.

Table 26 Hyperglycaemic episodes and episodes of ketosis – treatment emergent – summary - safety analysis set

	IDegAsp OD				IDet			
	N	(%)	E	R	N	(%)	E	R
All hyperglycaemic episodes								
Number of Subjects	181				179			
Hyperglycaemic episodes	72	(39.8)	599	1094	73	(40.8)	449	833
Hyperglycaemia with ketones measured	57	(31.5)	441	805	60	(33.5)	301	558
Hyperglycaemia with ketones (> 1.5 mmol/L)	4	(2.2)	6	11	8	(4.5)	12	22
Nocturnal hyperglycaemic episodes								
Number of Subjects	181				179			
Hyperglycaemic episodes	26	(14.4)	101	184	30	(16.8)	53	98
Hyperglycaemia with ketones measured	21	(11.6)	79	144	17	(9.5)	29	54
Hyperglycaemia with ketones (> 1.5 mmol/L)	1	(0.6)	1	2	2	(1.1)	2	4

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

In conclusion, the proportion of subjects reporting hyperglycaemias did not differ between treatment groups, but more hyperglycaemic events were reported in the IDegAsp treated group. The reporting of hyperglycaemia with ketones was low, with fewer reports in the IDegAsp treated group, even though, as noted by the MAH, more subjects had actually measured ketones in accordance with the protocol in the IDegAsp treated group. Thus, the rate of ketosis in the IDet group may be underestimated.

Hyperglycaemic episodes across age groups

In the IDegAsp treated group, children 6-11 years had higher rate per 100 PYE (1751) of hyperglycaemic episodes compared to children 1-5 years (817) and adolescents 12-17 years (722). The number of hyperglycaemic episodes with ketosis was 3 in children 1-5 years, 1 in children 6-11 years and 2 in adolescents 12-17 years.

The percentage of subjects with nocturnal hyperglycaemic episodes was similar between age groups. The number of nocturnal hyperglycaemic episodes with ketosis was very low for all age groups.

In the IDet treated group, children 1-5 years had a higher rate per 100 PYE (955) of hyperglycaemic episodes compared to children 6-11 years (758) and adolescents 12-17 years (827). The number of hypoglycaemic episodes with ketosis was 4 in children 1-5 years, 3 in children 6-11 years and 5 in adolescents 12-17 years.

The percentage of subjects with nocturnal hyperglycaemic episodes was similar between children 1- 5 years and children 6-11 years and slightly higher for the adolescents 12-17 years. The number of nocturnal hyperglycaemic episodes with ketosis was very low for all age groups.

Vital signs and laboratory findings

No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed for vital signs or laboratory values. Mean SD score for body weight increased in the IDegAsp group from 0.40 at baseline to 0.44 at week 16. No such increase was seen in the IDet group, where there was very little change in mean SD score for body weight. Statistical analysis of change from baseline in weight SD score showed a statistically significant treatment difference; IDegAsp-IDet: 0.07 [0.02; 0.12]95% CI for the change from baseline to week 16.

2.5.5. Adverse events of special interest trial 3816

Medication errors concerning trial products

Eight (8) events of medication error occurred in 7 subjects in the IDegAsp treatment group (1 ‘overdose’ and 7 ‘wrong drug administered’) and 6 events in 6 subjects in the IDet treatment group (2 ‘accidental overdose’, 1 ‘drug dispensing error’ and 3 ‘wrong drug administered’). All of the ‘wrong drug administered’ events were due to mix-up of insulins by the subjects’ carer. In the IDegAsp treatment group, 5 out of the 7 ‘wrong drug administered’ events were due to mix-up between the two trial products, and 2 events (both in the same subject) were due to mix-up between the trial product and the pre-trial insulin. In the IDet treatment group, out of the 3 ‘wrong drug administered’ events, 1 was due to mix-up between the two trial insulins, and 2 were due to mix-up with the pre-trial insulin product. None of the events were reported as SAEs. Most of the events were mild in severity and all subjects recovered from the events.

A review of the SAEs of severe hypoglycaemia revealed one episode that was temporally associated with a mix-up between bolus and basal insulin. Investigators were required to report all medication errors concerning trial products (both serious and non-serious) as MESIs.

Allergic reactions

A total of 9 events of allergic reactions occurred in 6 subjects in the IDegAsp treatment group and 5 events in 4 subjects in the IDet treatment group leading to rates of 16 vs. 9 events per 100 PYE, respectively. This difference was mostly driven by 5 events of 'hypersensitivity' in 2 subjects in the IDegAsp treatment group vs. no events in the IDet treatment group. All of the events were unlikely related to trial product and the dose of trial product did not change because of the events.

Injection site reactions

One (1) event of 'injection site hypertrophy' was reported in 1 subject with IDegAsp and 3 events of injection site reactions (2 events of 'injection site hypertrophy' and 1 event of 'injection site swelling') in 3 subjects were reported with IDet. One (1) event was considered possibly or probably related to IDegAsp or IDet in each treatment group respectively. Additionally, 1 injection site reaction in each treatment group was considered possibly or probably related to IAsp.

None of the injection site reactions were serious. One (1) event of 'injection site hypertrophy' in the IDet treatment group was of moderate severity and 3 events were mild in severity. None of the subjects withdrew due to injection site reactions. Two events of 'injection site swelling' had an outcome of not recovered.

Across age groups, 1 event of 'injection site hypertrophy' in the IDet treatment group was reported in children 1-5 years, no events were reported in children 6-11 years, and the remaining 3 events were reported in adolescents 12-17 years.

Slightly more allergic reactions were reported in the IDegAsp treated group, however, none of the events were considered related to study product and did not result in any discontinuations. Few injection site reactions were reported, which were evenly distributed between treatments.

Discontinuation due to adverse events

One subject in the IDegAsp treatment group was withdrawn from the trial due to an AE ('hypoglycaemic seizure').

In addition, one subject in the IDet treatment group was withdrawn due to hypoglycaemic events judged by the investigator to be related to the trial product.

Adverse events leading to dose reduction

The number of AEs leading to dose reduction of IDegAsp, IDet and/or IAsp was numerically higher with IDegAsp compared with IDet (21 events in 15 subjects in the IDegAsp treatment group and 9 events in 8 subjects in the IDet treatment group, leading to rates of 38 vs. 17 events per 100 PYE, respectively).

Dose reduction due to AEs was most frequently related to events of infection or because of gastrointestinal disorders and events of 'hypoglycaemia'. In both treatment groups most of the events related to dose reduction were reported in the SOC Infections and infestations (6 events in 5 subjects with IDegAsp and 6 events in 6 subjects with IDet, respectively). Insulin adjustments are normally required in connection with infections. The infections themselves may result in a need for higher insulin

doses but the associated symptoms, such as vomiting, decreased appetite and diarrhoea, may cause a need for reducing the dose. Five (5) hypoglycaemia related AEs led to dose reductions in the IDegAsp treatment group compared to 0 events in the IDet treatment group.

Among the AEs leading to dose reduction, 5 subjects reported 5 AEs that were considered possibly or probably related to IDegAsp (3 cases of 'hypoglycaemia', 1 'wrong drug administered' and 1 'overdose') and 1 subject reported 1 AE that was considered probably related to IDet ('accidental overdose'). The AEs considered probably or possibly related to IAsp were 2 events in 2 subjects in the IDegAsp treatment group and no events in the IDet group. In the IDegAsp treatment group 1 event that led to an IDegAsp dose reduction ('hypoglycaemia') was related to both IDegAsp and IAsp.

Adverse events leading to temporary withdrawal of trial product

In total, 3 subjects (0.8%) had 3 AEs leading to temporary withdrawal of trial product; 2 subjects (1.1%) in the IDegAsp treatment group and 1 subject (0.6%) in the IDet treatment group. The events were 'gastroenteritis', 'wrong drug administered' and 'fall', respectively.

All three events were considered unlikely related to trial product and all three subjects recovered or were recovering. The events 'gastroenteritis' and 'wrong drug administered' occurred in the IDegAsp treatment group and 'fall' occurred in the IDet group.

No deaths occurred during the study.

The most common reason for withdrawal or dose reduction was hypoglycaemia.

2.5.6. Clinical safety Supportive trial 3561

Overview of adverse events

The proportion of subjects reporting TEAEs as well as the rate of AEs were comparable in the IDeg and the IDet treatment arms see Table 27. The majority of AEs in both treatment arms were of mild or moderate severity and considered unrelated to basal insulin. No subjects died during the trial, and the rate of serious adverse events (SAEs) was similar in the two treatment groups.

Approximately 97% of all AEs in either treatment arm had an outcome of recovered at end of trial. A total of 3 subjects were withdrawn from the trial due to AEs, all in the IDet treatment arm.

Patient exposure

In total, 174 subjects were exposed to IDeg and 175 subjects were exposed to IDet. The total exposure was higher in the IDeg arm (161.5 years) than in the IDet arm (147.4 years) and in both treatment arms, the mean exposure for an individual subject was close to 1 year. The mean exposure was comparable between the two treatment groups during the main trial period (first 26 weeks), but higher in the IDeg arm than in the IDet arm during the last 26 weeks, reflecting the higher proportion of subjects continuing on IDeg compared to IDet in the extension phase of the trial. Males had a higher total exposure than females (175.3 vs. 133.5 years, respectively) reflecting the higher proportion of males to females exposed to trial products in both treatment arms. The total exposure was distributed similarly across the 3 age groups in the two treatment arms.

Serious adverse event / deaths / other significant events

Deaths and other serious adverse events

No deaths were reported in this trial. The observed rates of SAEs were similar for IDeg and IDet, both overall, across severity and causality categories, and with respect to recovery. Most of the SAEs were considered unlikely related to trial products and with an outcome of 'recovered' at end of trial). The low number of SAEs should be taken into consideration when evaluating the observed rates between treatment groups as these comparisons are based on a low number of subjects with few events.

The majority of the SAEs were related to infections, hypoglycaemia, and hyperglycaemia in both treatment arms and no SAEs were reported by more than 5% of subjects, see Table 27. The rates of SAEs were similar in the SAS and the ETS. Few of the hypoglycaemic events in both treatment arms were associated with seizure (1 episode with IDeg and 4 episodes with IDet) or unconsciousness (1 episode in each treatment arm). It should be noted that a total of 5 AEs related to hypoglycaemic seizure or hypoglycaemic unconsciousness (2 episodes with IDeg and 3 episodes with IDet) were regarded as non-serious by the investigators but as serious by the applicant. As the clinical database reflects the investigator reported data, these events were included as non-serious AEs in the clinical database (tables and listings), but are included as SAEs in the narratives from the safety database.

Table 27 Trial 3561 Treatment emergent serious adverse events by system organ class and preferred term - summary - safety analysis set

	IDeg OD				IDet				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	174				175				349			
Events	18	(10.3)	25	15	16	(9.1)	24	16	34	(9.7)	49	16
Infections and infestations	5	(2.9)	5	3	7	(4.0)	7	5	12	(3.4)	12	4
Appendicitis	1	(0.6)	1	1	2	(1.1)	2	1	3	(0.9)	3	1
Gastroenteritis	1	(0.6)	1	1	2	(1.1)	2	1	3	(0.9)	3	1
Gastroenteritis viral					2	(1.1)	2	1	2	(0.6)	2	1
Bronchitis	1	(0.6)	1	1					1	(0.3)	1	0
Pharyngitis					1	(0.6)	1	1	1	(0.3)	1	0
Respiratory tract infection viral	1	(0.6)	1	1					1	(0.3)	1	0
Urinary tract infection	1	(0.6)	1	1					1	(0.3)	1	0
Metabolism and nutrition disorders	6	(3.4)	9	6	4	(2.3)	4	3	10	(2.9)	13	4
Hypoglycaemia	5	(2.9)	7	4	2	(1.1)	2	1	7	(2.0)	9	3
Ketosis	1	(0.6)	1	1	1	(0.6)	1	1	2	(0.6)	2	1
Dehydration					1	(0.6)	1	1	1	(0.3)	1	0
Diabetic ketoacidosis	1	(0.6)	1	1					1	(0.3)	1	0
Nervous system disorders	4	(2.3)	4	2	5	(2.9)	6	4	9	(2.6)	10	3
Hypoglycaemic seizure	1	(0.6)	1	1	3	(1.7)	4	3	4	(1.1)	5	2
Hypoglycaemic unconsciousness	1	(0.6)	1	1	1	(0.6)	1	1	2	(0.6)	2	1
Convulsion	1	(0.6)	1	1					1	(0.3)	1	0
Headache	1	(0.6)	1	1					1	(0.3)	1	0
Loss of consciousness					1	(0.6)	1	1	1	(0.3)	1	0
Investigations	2	(1.1)	3	2	2	(1.1)	4	3	4	(1.1)	7	2
Blood ketone body increased	1	(0.6)	2	1	2	(1.1)	4	3	3	(0.9)	6	2
Body temperature increased	1	(0.6)	1	1					1	(0.3)	1	0

N= Number of subjects
%= Percentage of subjects
E= Number of Events
R= Event Rate per 100 Exposure Years

Hypoglycaemia

Definitions of hypoglycaemia

Classification of hypoglycaemia was performed in accordance with the definitions of hypoglycaemic episodes from the ISPAD guidelines, which are in line with the principles underlying the American Diabetes Association (ADA) classification. Furthermore, hypoglycaemia was defined according to the applicant's definition of 'confirmed hypoglycaemia'. In normal physiology, hypoglycaemia symptoms occur at a PG level of approximately < 3.1 mmol/L (56 mg/dL), and the applicant has therefore used this cut-off value to define 'confirmed hypoglycaemia'. Hypoglycaemic episodes with time of onset in

the period 23:00-07:00 (both included) were considered nocturnal. In the following sections, hypoglycaemia will be described based on severe hypoglycaemia as well as confirmed hypoglycaemia.

Severe hypoglycaemia – definition

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

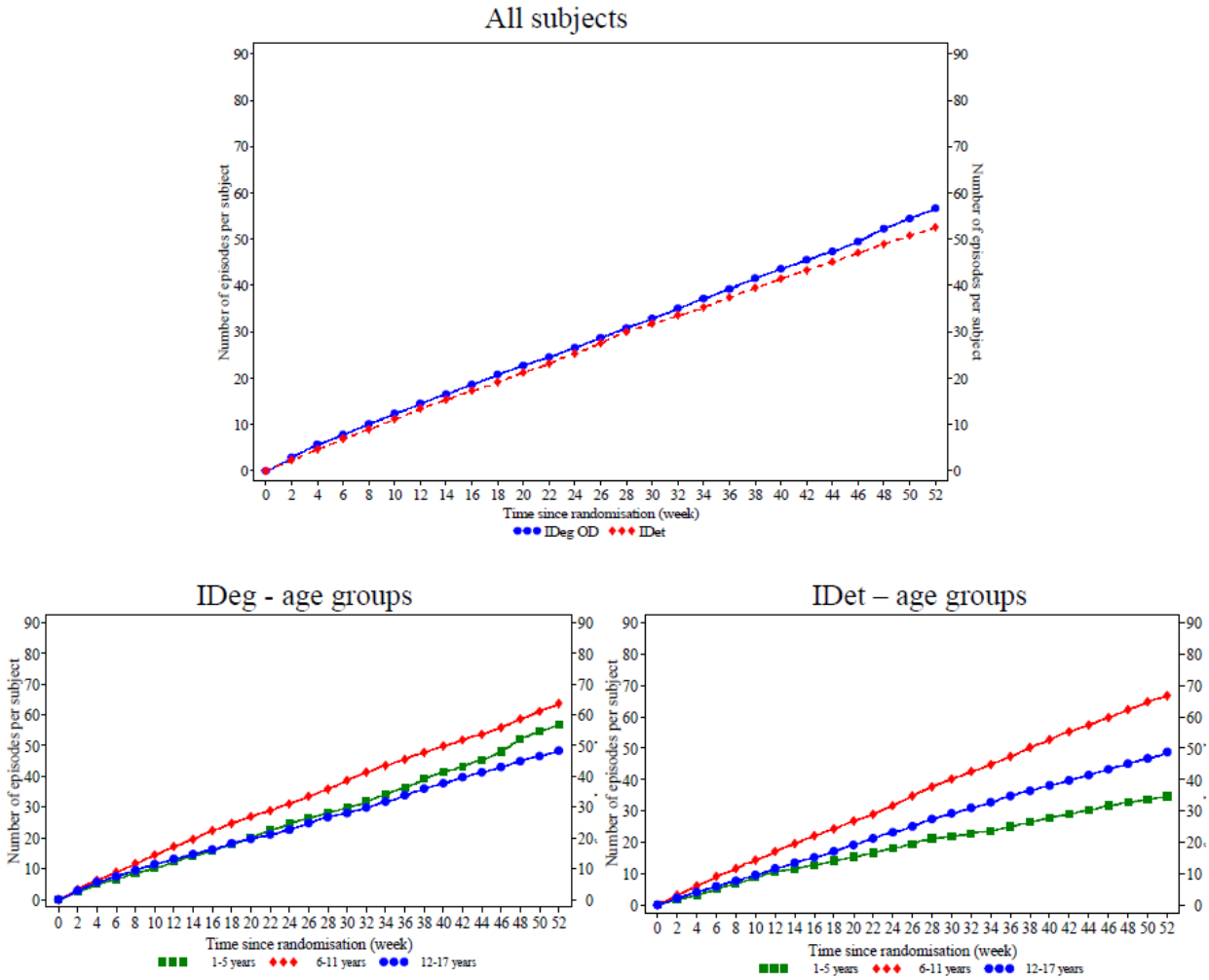
Confirmed hypoglycaemia – definition

- An episode with symptoms consistent with hypoglycaemia with confirmation by PG <3.1 mmol/L (56 mg/dL), or full blood glucose < 2.8 mmol/L (50 mg/dL) and which does not fulfil the requirements for being classified as a severe hypoglycaemic episode,
- Or any asymptomatic PG value < 3.1 mmol/L (56 mg/dL) or full blood glucose value <2.8 mmol/L (50 mg/dL).
- Or severe hypoglycaemia (according to the ISPAD classification see **Figure 3**)

Confirmed hypoglycaemia

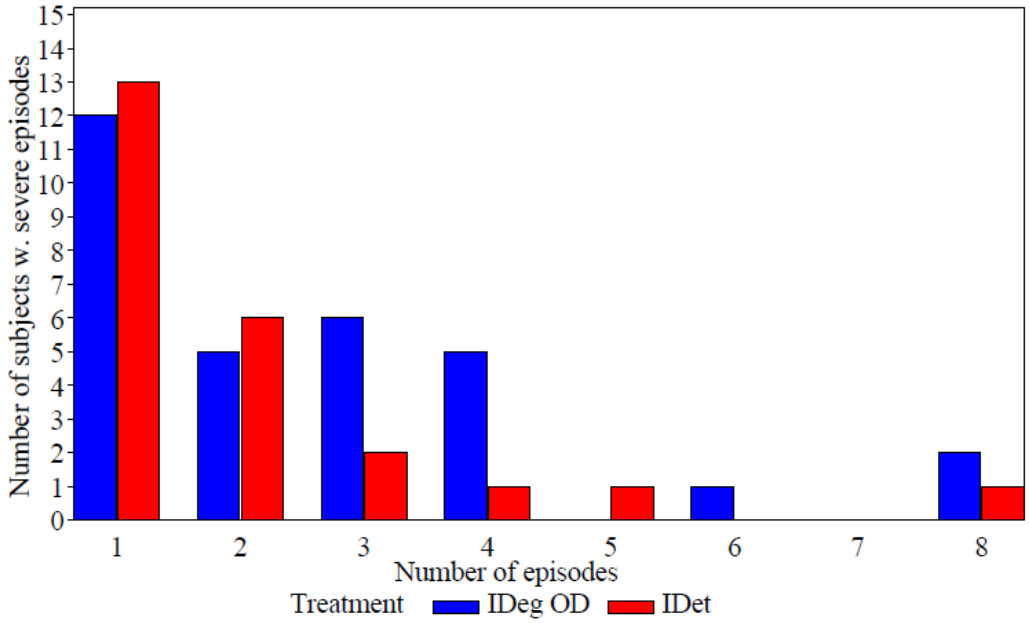
Almost all subjects in the trial experienced confirmed hypoglycaemia (98% of subjects treated with IDeg and and 96% treated with IDet), and the observed rate of confirmed hypoglycaemia was 5771 and 5405 events per 100 PYE in the IDeg and IDet treatment arms, respectively. There was no statistically significant difference between the treatment arms in the rates of confirmed hypoglycaemia (rate ratio IDeg/IDet: 1.11 [0.89; 1.38] 95% CI). A post-hoc analysis of confirmed hypoglycaemia during the maintenance period from 16 weeks of treatment to end of trial led to a similar result (rate ratio IDeg/IDet: 1.05[0.83; 1.32]95%CI), and a post-hoc sensitivity analysis showed that the number of days without confirmed hypoglycaemia was similar with IDeg and IDet treatment (rate ratio IDeg/IDet: 0.99[0.96;1.02]95%CI).

Figure 17 Trial 3561 Confirmed hypoglycaemic episodes – treatment emergent - mean cumulative function – for all subjects (upper panel) and by treatment and age group (lower panel) – safety analysis set



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

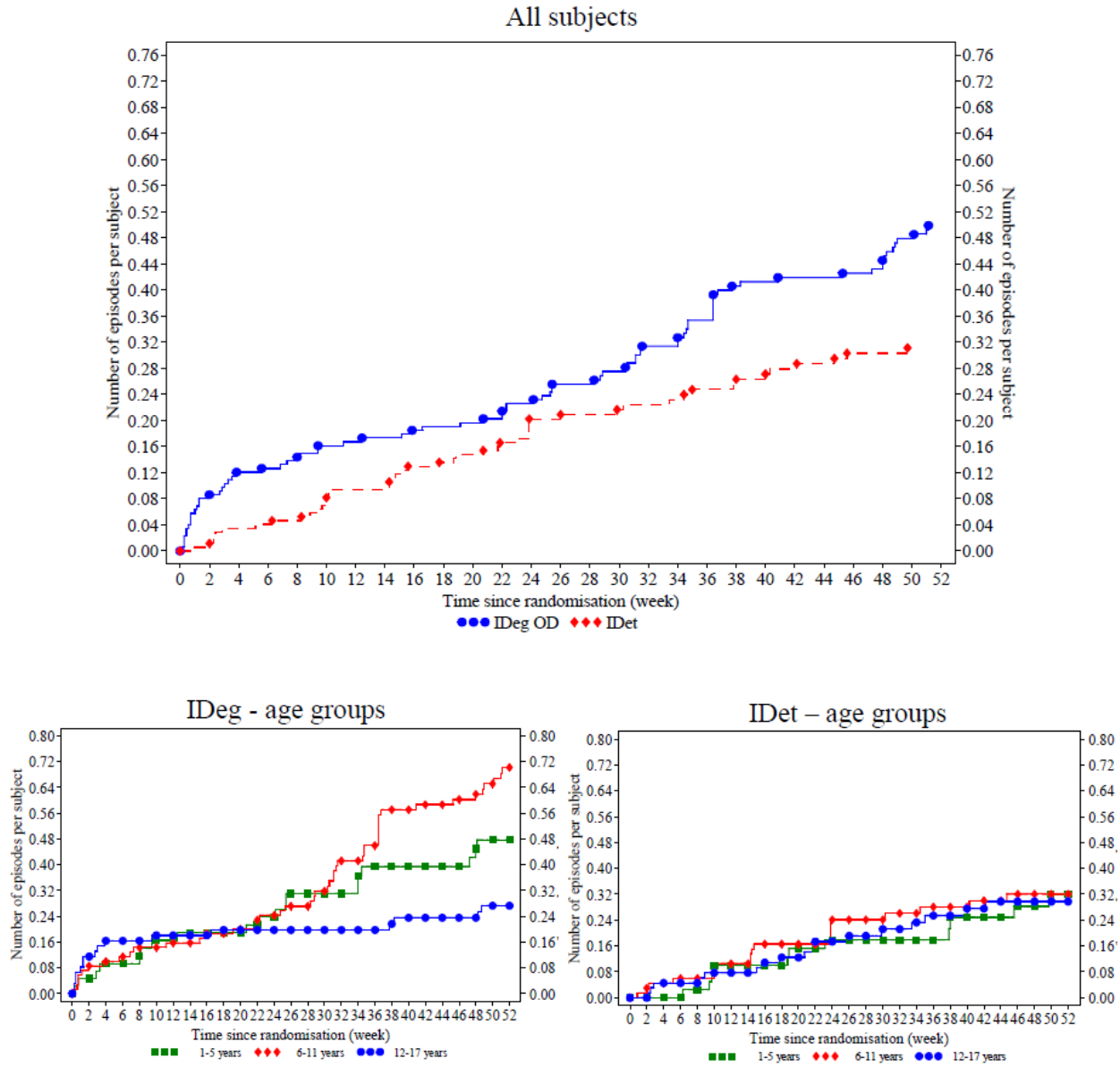
Figure 18 Trial 3561 Distribution of severe hypoglycaemic episodes - subject counts against number of episodes - safety analysis set



Severe hypoglycaemia according to ISPAD definition: The child has altered mental status and cannot assist in his own care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy.

The observed rate of severe hypoglycaemic episodes tended to be higher with IDeg than IDet, especially during the first 4 weeks of treatment. It should be kept in mind that based on the external classification; the observed rates of severe hypoglycaemia were lower in both treatment groups than based on all reported severe hypoglycaemic episodes. The majority of the severe hypoglycaemic episodes (close to 80%) occurred during the daytime in both treatment arms.

Figure 19 Trial 3561 Severe hypoglycaemic episodes - treatment emergent - mean cumulative function – for all subjects (upper panel) and by treatment and age group (lower panel) – safety analysis set



Severe hypoglycaemia according to ISPAD definition: The child has altered mental status and cannot assist in his own care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy.

The higher observed rate in the IDeg arm during the initial 4 weeks of treatment may reflect that the initial weeks of treatment may be associated with an increased risk of hypoglycaemia related to switching to a new insulin product or regimen. In contrast, almost 50% of the subjects in the IDet arm used IDet prior to entering the trial and were familiar with this insulin product. The rate of severe hypoglycaemia differed between the age groups in the IDeg arm, and the higher observed rate of severe hypoglycaemia with IDeg during the last weeks of treatment was primarily driven by children aged 6-11 years. In both treatment groups, children aged 6-11 years also had the highest rate of confirmed hypoglycaemia. Children in this age group go to school and many participate in various physical activities. Thus, it may be particularly challenging to ensure that the insulin dose matches food intake and physical activity, and adult assistance may not be available.

Nocturnal hypoglycaemia Trial 3561

The proportions of subjects with nocturnal hypoglycaemia were similar with IDeg and IDet, while the observed rate of nocturnal confirmed episodes was numerically lower with IDeg compared to IDet, (603 and 760 episodes per 100 PYE, respectively). There was no statistically significant difference between treatment arms (IDeg/IDet: 0.99 $[0.72; 1.34]_{95\%CI}$).The observed rate of nocturnal confirmed hypoglycaemic episodes appeared to be lower with IDeg than IDet during the maintenance period of the trial from 16 weeks of treatment to end of trial. However, there was no statistically significant difference between the treatments in the post-hoc analysis of nocturnal confirmed hypoglycaemic episodes during the maintenance period (rate ratio IDeg/IDet: 0.88 $[0.63; 1.23]_{95\%CI}$). As seen for all confirmed hypoglycaemic episodes, the observed rates of nocturnal confirmed hypoglycaemia differed between the age groups in the IDet arm, which was related to a low observed rate in children aged 1-5 years and to a high observed rate in adolescents.

Hyperglycaemia and hyperglycaemia with ketosis trial 3561

In Trial 3561, the threshold for defining hyperglycaemia was 11.1 mmol/L and subjects with an SMPG > 14 mmol/L (250mg/dL) were to measure blood ketones regardless of symptoms. There were no statistically significant differences between treatment arms in the rate of hyperglycaemic episodes or in the rate of nocturnal (23:00 –07:00, both included) hyperglycaemic episodes; rate ratio IDeg/IDet: 0.97 $[0.84; 1.13]_{95\%CI}$ and 1.17 $[0.92;1.49.]_{95\%CI}$, respectively. In contrast, the rate of hyperglycaemia with ketosis was statistically significantly lower in the IDeg arm compared to the IDet arm (rate ratio IDeg/IDet: 0.41 $[0.22; 0.78]_{95\%CI}$), and the rate of nocturnal episodes of hyperglycaemia with ketosis was numerically lower with IDeg than IDet (10 vs. 18 episodes per 100 PYE) with no statistical analysis being performed due to the small number of episodes. The lower rate of hyperglycaemia with ketosis with IDeg was consistent with the numerically lower rate of 'blood ketone body increased' reported as TEAEs in the IDeg arm than in the IDet arm, and it appeared to be driven by a lower observed rate with IDeg compared to IDet across all age groups. In both treatment arms, the observed rate of hyperglycaemia appeared to be higher in children aged 1-5 years and 6-11 years than in adolescents, whereas the observed rate of hyperglycaemia with ketosis was markedly higher in small children aged 1-5 years compared to the two older age groups. This may possibly be related to the higher rates of infections and infestations observed in the youngest age group.

Post marketing experience

IDegAsp-Ryzodeg - children, adolescents and adults

As of 1 June 2015, Ryzodeg (IDegAsp) had been marketed for use in adults in 6 countries, and the estimated cumulative exposure was 8,173 PYEs based on the assumption of an average daily consumption of 40 units. Cumulatively, a total of 30 ADR reports had been received by the MAH from post-marketing use of Ryzodeg, describing a total of 64 ADRs. In about half of the ADR reports, the subjects experienced more than one ADR, thereby contributing to the total number of 64 ADRs. Most of the ADR reports concerned adults; 6 of the reports were related to use in children and adolescents, all reported from Mexico. In 5 of the 6 reports in paediatric subjects no ADR was reported, only the fact the product had been administered to a child (Ryzodeg is not approved for children in Mexico and therefore the use of the product in this sub-population is considered off label use; reports concerning 'off-label use' are handled as ADRs). The last report related to use in children concerned a non-serious case of blood glucose abnormal. All 64 ADRs were non-serious, except 1 serious event of hypoglycaemia in a 30-year old female; the event was considered due to exercise and lack of food intake. The most frequently reported ADRs in adults were related to hyperglycaemia/increased blood glucose (10 events), injection site reactions (10 events), medication errors (10 events) and

hypoglycaemia (4 events). The ADRs reported for Ryzodeg in the post-marketed setting resemble the AEs reported in clinical trials with IDegAsp in adults, although the rates of the reported events post-marketing were, as expected, lower than those reported in the clinical trials. Based on the estimated exposure from marketed use (8,173 PYEs) the rates of hyperglycaemia/ increased blood glucose, injection site reactions and medication errors were 0.12 events per 100 PYE while the rate of hypoglycaemia was 0.05 events per 100 PYE (3 of the 4 events of hypoglycaemia were reported as severe). In therapeutic confirmatory trials with IDegAsp in adults with T1DM or T2DM the corresponding rates for hyperglycaemia, injection site reactions, medication errors and severe hypoglycaemic episodes were 1.6, 5.1, 5.2 and 26.6 events per 100 PYE, respectively

The bias introduced by under-reporting or differential reporting of events is a known issue related to post-marketing ADR reporting. Based on an evaluation of the ADR cases no concerns were raised.

IDeg-Tresiba - children and adolescents

Information on post-marketing data of IDeg, the basal component of IDegAsp, is considered of value to support the paediatric variation for IDegAsp. IDeg has been approved for the treatment of diabetes mellitus in adults in more than 60 countries, including the EU and Japan. The use of IDeg in adolescents and children from the age of 1 year was approved in the EU in January 2015. As of 4 July 2015, the overall estimated exposure to IDeg was 258,075 PYE, based on the assumption of an average daily consumption of 40 units.

As of 1 June 2015, a total of 111 ADR reports had been received by the MAH from postmarketing use in children and adolescents using Tresiba. Most of the ADRs were reported from Brazil, Japan, UK and Mexico. Of the 111 ADR reports, only 51 reports were associated with ADRs (78 events); the remaining 60 reports concerned off-label use with no ADR reported. The majority of the ADRs (49 of the 78 events) occurred in adolescents (aged 12−17 years) while 24 of the events were reported in children aged 6−11 years and 5 events were reported in younger children aged 1−5 years. Approximately 30% of the events were serious (24 of 78 events). Half of the serious ADRs were related to events of hypoglycaemia (12 events); in addition, 4 events of diabetic ketoacidosis were reported. For the remaining serious cases there was no pattern in the reported ADRs. The most frequently reported non-serious ADRs were related to hypoglycaemia (14 events), hyperglycaemia/ increased blood glucose (11 events) and injection site reactions/lipodystrophy (6 events). The ADRs reported for Tresiba in the post-marketing setting resemble the AEs that were reported in the paediatric trial for IDeg (Trial 3561).

2.5.7. Discussion on clinical safety

Trial 3816

The overall reporting of adverse events were somewhat higher in the IDegAsp treated group, however, the rate of events deemed to be related to treatment was low and comparable between groups. Apart from hypoglycaemia, the most commonly reported events appears to be related to infectious diseases as could be expected in this age group. There were no apparent imbalances in the reporting of events by SOC or preferred terms.

Serious adverse events were few and the most commonly reported event was hypoglycaemia. A hypoglycaemia related event was also the reason for withdrawal of one subject in the IDegAsp treated group. Hypoglycaemia was also the most common reason for dose reductions.

Medication errors due to mix-up between trial products and pre-trial products were reported to be equal in both treatment groups. A review of the SAEs of severe hypoglycaemia revealed one episode that was temporally associated with a mix-up between bolus and basal insulin.

Slightly more allergic reactions were reported in the IDegAsp treated group, however, none of the events were considered related to study product and did not result in any discontinuations. Few injection site reactions were reported, which were evenly distributed between treatments.

Hypoglycaemia was only to be reported as an AE if it fulfilled the definition of a SAE or a severe hypoglycaemia as per ISPAD definition. The reporting of hypoglycaemia as AE was higher for IDegAsp than for IDet (6.1 % vs 1.7 %).

The reporting of confirmed hypoglycaemias did not differ between treatment groups with similar proportions reporting an event. In both treatment groups, hypoglycaemias were more common in subjects aged 6-11 years which may reflect greater difficulties in controlling blood glucose in this age group, i.e. during school hours.

Severe hypoglycaemias were rare but more often reported in the IDegAsp treated group. Importantly most of the events occurred in daytime. The number of episodes per subjects was highest in the age group 1-5 years treated with IDegAsp. This finding is in contrast to the findings in trial 3561, where this age group showed the lowest rate of severe hypoglycaemias during the first 16 weeks of the study. The Applicant has presented data on severe hypoglycaemias in the lowest age group of children 2-5 year (n=40). There is a signal of a potential higher risk for severe hypoglycaemic event but this signal is based on few events in few individuals and should be interpreted with caution.

The Applicant has given a detailed description of the severe hypoglycaemias in the IDegIAsp treatment group with children 2-5 years old. There is no clear pattern when these hypoglycaemias occur in relation to dosing time at day or treatments start of the study drug even though the events with severe hypoglycaemia occurred within the first two months of treatment. Therefore it is reasonable to believe that the severe hypoglycaemias in this age group found in Trial 3816 are related to the challenges treating T1DM in small children, and not to IDegIAsp treatment *per se.* Even though a premixed insulin probably not is a suitable treatment for the majority of young children because assessment of hypoglycaemia may be more difficult as young children may have difficulties in communicating symptoms and there may be a need for more frequent adjustment of the bolus dose in the youngest age group as the young child may be less predictable in when accepting a meal or not, However, there may be clinical situations where a premixed insulin may offer advantages for a young child, for example in cases of poor compliance and with the need for fewer injections.

In addition, the hypoglycaemias were seen during daytime and the overall rate of nocturnal hypoglycaemias did not differ between treatments. Notably, a lower rate of nocturnal hypoglycaemias was observed in the youngest age group treated with IDegAsp.

Furthermore, during the procedure the Applicant has suggested to exclude children aged 1 to <2 years in the proposed indication. This is endorsed because of the reasons given i.e small doses of insulin, variable feeding patterns and activity levels and inability of communicating symptoms of hypoglycaemia.

The risk of medication errors as a contributing factor has been discussed and the rate of medication errors was low. A review of the SAEs of severe hypoglycaemia revealed one episode that was temporally associated with a mix-up between bolus and basal insulin.

IDegAsp was to be administered in connection to a main meal without further specification. The Applicant has presented data by age group on hypoglycaemia pattern with relation to the the main meal chosen for administration of Ryzodeg (i.e. with breakfast, lunch or dinner) presented. No clear-

cut pattern was seen. Since the insulin regime in the individual patient always has to be adjusted according to blood glucose level, timing for meals and physical activity this is not surprising.

The rate of nocturnal confirmed hypoglycaemias did not differ between treatment groups andtended to increase with increasing age. Thus, the rate was higher in adolescents 12-17 years as compared to the overall trial population and lower in children 1 to 5 years. The higher rate in adolescents may be attributed to adolescent lifestyle and was seen with both treatments but more pronounced in the IDet treated group. In the IDegIAsp treated group the rate of nocturnal hypoglycaemias was lowest in the youngest age group, but at the same level as in the IDeg treated group.

Only a few severe nocturnal hypoglycaemias (n=4) were reported which were evenly distributed between groups. Notably, no severe nocturnal hypoglycaemias were observed in the youngest age group in the IDeg Asp treated group.

The proportion of subjects reporting hyperglycaemias did not differ between treatment groups, but more hyperglycaemic events were reported in the IDegAsp treated group. This difference was, however, not statistically significant. The reporting of hyperglycaemia with ketones was low, with fewer reports in the IDegAsp treated group. However, as noted by the MAH, more subjects had actually measured ketones in accordance with the protocol in the IDegAsp treated group, thus the rate of ketosis in the IDet group may be underestimated. In the IDegAsp treated group, the highest rate of hyperglycaemias was observed in the age group 6-11 years, whereas in the IDet treated group the highest rate was observed in the age group 1-5 years.

There were no clinically relevant differences observed with regards to vital signs or laboratory values during the study. Mean body weight increased in the IDegAsp treated group, whereas no change was observed in the IDet treated group. This may be related to increased appetite after hypoglycaemic events.

Trial 3561

In terms of safety, no differences overall were observed between IDeg and IDet in terms of TEAEs and the rate of AEs. However, injection site reactions were more frequently reported in the IDeg treatment arm than in the IDet arm (28 events and 17.3 events per 100 PYE with IDeg versus 7 events and 4.7 events per 100 PYE). Altogether 8 subjects reported 12 events which were considered to be possibly or probably related to basal insulin in the IDeg group and 5 subjects reported 6 events in the IDet group. As noted the most obvious reason for this difference is related to the open-label design, i.e. subjects in the IDet group had to have tolerated pre-trial treatment with IDet and subjects in the IDeg group might be more attentive to adverse reactions. Importantly the frequency of the of injection site reactions that were assessed possibly or probably related to IDeg was comparable to the frequency in adults. The MAH monitors injection site reactions from the paediatric population through the routine pharmacovigilance, which is considered adequate.

There was a higher rate of observed severe hypoglycaemia in the IDeg arm compared to the IDet arm. The overall number of episodes of severe hypoglycaemia was higher in the IDeg group than the IDet group and this difference was primarily driven by children aged 6-11 years. The MAH argued that the number of subjects within each age group reporting severe hypoglycaemia was low and too small to conclude upon. This was solved by a wording in the SmPC for Tresiba in section 5.1. The proportions of subjects with nocturnal hypoglycaemia were similar with IDeg and IDet and there was no significant difference in the observed rate of nocturnal confirmed episodes between treatment groups although the rate per 100 PY was lower for IDeg than for IDet (603 and 760 episodes per 100 PYE, respectively). The findings are largely in line with those observed in adult patients with T1DM.

In contrast the rate of hyperglycaemia with ketosis was significantly lower in the IDeg arm compared to the IDet arm.

Insulin antibodies cross-reacting between IDeg or IDet and human insulin decreased slightly with IDeg and increased slightly with IDet, but there was no correlation between cross-reacting antibodies and estimates of glycaemic control. Regarding insulin-specific antibodies the levels were low although slightly higher with IDet than IDeg. Again no correlation between these antibodies and glycaemic parameters were observed.

2.5.8. Conclusions on paediatric data on clinical safety

No unexpected safety concerns have arisen in the main trial 3816 in which IDegAsp was evaluated in the paediatric age group. The overall reporting of adverse events were somewhat higher in the IDegAsp treated group, however, the rate of events deemed to be related to treatment was low and comparable between groups.

Serious adverse events were few and the most commonly reported event was hypoglycaemia. A hypoglycaemia related event was also the reason for withdrawal of one subject in the IDegAsp treated group. Hypoglycaemia was also the most common reason for dose reductions.

The reporting of confirmed hypoglycaemias did not differ between treatment groups with similar proportions reporting an event. In both treatment groups, hypoglycaemias were more common in subjects aged 6-11 years which may reflect greater difficulties in controlling blood glucose in this age range.

The reporting of severe hypoglycaemia was higher for IDegAsp than for IDet (6.1 % vs 1.7 %). Severe hypoglycaemias were most common in the youngest age group which may reflect a greater need for adjustment of the bolus dose as, for example, the young child may be less predictable in when accepting a meal or not. There was no clear pattern when these hypoglycaemias occurred in relation to dosing time at day or treatments start, therefore it is reasonable to believe that the severe hypoglycaemias in this age group are related to the challenges treating T1DM in small children, and not to IDegIAsp treatment *per se.* In addition, a small percentage (5-6%) of the children below the age of six were already treated with a premixed insulin before inclusion in trial 3816 which suggests that there may be a medical need for a premixed insulin for some young children. In conclusion, a premixed insulin is probably not a a suitable treatment for the majority of young children but there may be clinical situations where a premixed insulin may offer advantages for a young child, for example in cases of poor compliance and with the need for fewer injections.

Notably, in the supportive trial 3561, severe hypoglycaemias were very rare in the youngest age group whereas more severe hypoglycaemic events in the 6-11 years age group were found with IDeg compared to IDet. More frequent injection site reactions were found with IDeg compared to IDet which is reflected in the SmPC for IDeg (Tresiba). Both insulin products provided a beneficial efficacious treatment with acceptable safety profiles.

The concerns of treating young children with Ryzodeg are thoroughly described in the SmPC in section 4.2, 4.4 and 4.8. A more detailed study description is made in section 5.1.

2.5.9. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 5 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update:

- "*Regarding the category 4 studies, there is no need to list those in the RMP, and the document could be updated by removing these studies*";
- The text for the routine risk minimisation section of the RMP (in the summary table of risk minimisation measures, section V.3) which relates to the waiver in the paediatric population should be revised, in line with the latest agreed wording in SmPC section 5.1

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

The CHMP endorsed the Risk Management Plan version 5 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Hypoglycaemia • Immunogenicity-related events (allergic reactions)
Important potential risks	• Medication errors due to mix-up between Ryzodeg® and bolus insulin • Immunological events – formation of neutralising insulin antibodies
Missing information	• Pregnant and lactating women • Neonates and infants (<1 year of age) with T1DM and children and adolescents (<18 years of age) with T2DM • Hepatic impairment • Moderate and severe renal impairment • Elderly patients (>75 years) with T1DM • Co-administration of GLP-1 receptor agonists

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies (categories 1-3) for Ryzodeg. Routine pharmacovigilance applies to further characterise the safety concerns.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypoglycaemia	**SmPC** • Section 4.4: Warning text included • Section 4.5: Medicinal products which may change insulin requirements and thereby increase the risk for hypoglycaemia are listed • Section 4.8: Hypoglycaemia is listed as an undesirable effect. In the proposed SmPC, for the indication in children, it is additionally stated that the frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population. • Section 4.9: Warning text included together with instruction on what to do in case of overdose	None
Immunogenicity-related events (allergic reactions)	**SmPC** • Section 4.3: Hypersensitivity is listed as contraindication • Section 4.8: Allergic reactions (hypersensitivity and urticaria) are listed as an undesirable effect. In the proposed SmPC, for the indication in children, it is additionally stated that the frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Medication errors due to mix-up between Ryzodeg® and bolus insulin	Product differentiation strategy includes trade names, label text, colour branding of the carton, container label and cartridge holder, as well as tactile elements on the pen push button. **SmPC** • Section 4.4: Warning text included in order to verify insulin and dose prior to injection. • Section 6.6: Special precautions included for disposal and other handling issues	None
Immunological events – formation of neutralising insulin antibodies	**SmPC** • Section 4.4: Warning text included	None
Pregnant and lactating women	**SmPC** • Section 4.6: Lack of clinical experience described with Ryzodeg® in pregnant women or during breastfeeding. • Section 4.6: Results from nonclinical studies are described in this section.	None
Neonates and infants (<1 year of age) with T1DM, and children and adolescents (<18 years of age) with T2DM	**Proposed SmPC** • Section 4.1: Proposed new indication of Ryzodeg® concerning the treatment of adolescents and children from the age of 1 year with T1DM is included in this section. • Section 4.2: Posology and method of administration for adolescents and children from the age of 1 year with TIDM are only mentioned in this section. • Section 5.1: The following waivers provided by the EMA/PDCO are described (1) neonates and infants from birth to less than 12 months of age with T1DM and children from birth to less than 10 years of age with T2DM; (2) children and adolescents from 10 to less than 18 years of age with T2DM. • Section 5.1: Safety and efficacy of Ryzodeg® have been established in children and adolescents <18 years with TIDM and are described • Section 5.2: Pharmacokinetic properties of Ryzodeg® in children (6–11 years) and adolescents (12–18 years) with TIDM are described. Pharmacokinetics of the insulin degludec component of Ryzodeg® investigated by modelling report is also described in this section.	None
Hepatic impairment	**SmPC** • Section 4.2: Use in patients with hepatic impairment is described in this section. • Section 4.8: No difference in the frequency, type and severity of adverse reactions in patients with hepatic impairment compared to	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the general population is mentioned in this section. • Section 5.2: Pharmacokinetic properties of Ryzodeg® in patients with hepatic impairment are described.	
Moderate and severe renal impairment	**SmPC** • Section 4.2: Use in patients with renal impairment is described in this section. • Section 4.8: No difference in the frequency, type and severity of adverse reactions in patients with renal impairment compared to the general population is mentioned in this section. • Section 5.2: Pharmacokinetic properties of Ryzodeg® in patients with renal impairment are described.	None
Elderly patients (>75 years) with T1DM	**SmPC** • Section 4.2: Use in elderly patients is described in this section. • Section 4.8: No difference in the frequency, type and severity of adverse reactions in elderly patients compared to the general population is mentioned in this section. • Section 5.2: Pharmacokinetic properties of Ryzodeg® in elderly patients are described.	None
Co-administration of GLP-1 receptor agonists	**SmPC** • Section 4.5: Change in insulin requirements if GLP-1 receptor agonists are co-administered is described in this section.	None

2.7. Update of the Product information

As a consequence of this new proposed indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning in 4.4 with regard to Ryzodeg has been added to the product information. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s).

The major changes are listed below. For the complete changes see attached PI.

SmPC

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 2 years.

4.2 Posology and method of administration

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Paediatric population

~~The safety and efficacy of Ryzodeg in children and adolescents below 18 years of age have not been~~

~~established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.~~
Ryzodeg can be used in adolescents and children from the age of 2 years (see section 5.1). When changing from another insulin regimen to Ryzodeg, dose reduction of total insulin needs to be considered on an individual basis, in order to minimise the risk of hypoglycaemia (see section 4.4).

Ryzodeg should be used with special caution in children 2 to 5 years old because data from the clinical trial indicate that there may be a higher risk for severe hypoglycaemia in children in this age group (see sections 4.4, 4.8 and 5.1).

4.4 Special warnings and precautions for use

Hypoglycaemia

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.5, 4.8 and 4.9).
In children, extra care should be taken to match insulin doses with food intake and physical activities in order to minimise the risk of hypoglycaemia. Ryzodeg may be associated with higher occurrence of severe hypoglycaemia compared to a basal-bolus regimen in paediatric population, particularly in children 2 to 5 years old (see section 5.1). For this age group, Ryzodeg should be considered on an individual basis.

4.8 Undesirable effects

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Paediatric population

Ryzodeg has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties (see section 5.2). Safety and efficacy have been demonstrated in a trial in children aged 2 to less than 18 years. The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population with the exception of a signal of higher occurrence of severe hypoglycaemia compared to a basal-bolus regimen in paediatric population, particularly in children 2 to 5 years old (see section 4.2, 4.4 and 5.1).
~~Safety and efficacy have not been investigated in children and adolescents.~~

5.1 Pharmacodynamic properties

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Paediatric population

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The efficacy and safety of Ryzodeg has been studied in a randomised controlled clinical trial in children and adolescents with diabetes mellitus type 1 for a period of 16 weeks (n=362). Patients in the Ryzodeg arm included 40 exposed children aged 2-5 years, 61 children aged 6-11 years and 80 adolescents aged 12-17 years. Ryzodeg dosed once daily with the main meal plus insulin aspart for the remaining meals showed similar reduction in HbA_{1c} at week 16 and no differences in FPG and SMPG compared to comparator insulin detemir dosed once or twice daily plus mealtime insulin aspart. At week 16, the mean total daily insulin dose was 0.88 vs. 1.01 units/kg in the Ryzodeg and insulin detemir arms, respectively. The rates (events per patient-year of exposure) of confirmed hypoglycaemia (ISPAD 2009 definition: 46.23 vs 49.55) and nocturnal confirmed hypoglycaemia (5.77 vs 5.40) were comparable with Ryzodeg versus insulin detemir whereas the rate of severe hypoglycaemia (0.26 vs 0.07) was higher in the Ryzodeg arm although the difference was not statistically significant. Few severe hypoglycaemic episodes were reported in each group; the observed rate of severe hypoglycaemia within the Ryzodeg arm was higher for subjects aged 2-5 years compared to subjects aged 6-11 years or 12-17 years (0.42 vs 0.21 and 0.21 respectively). Efficacy

and safety evaluation for adolescent patients with type 2 diabetes mellitus has been made using data from adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. This assessment supports the use of Ryzodeg in adolescent patients with type 2 diabetes mellitus.

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2.7.1. User consultation

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

- the changes to the patient leaflet are not significant (ref. Guideline on the readability of the labelling and package leaflet of medicinal products for human use, January 2009)
- a user consultation was recently made for the degludec family during the marketing authorization application approved in January 2013 (ref. Summary of Readability and Bridging Strategy for the Degludec family of leaflets, September 2011, eCTD seq. 0000)
- the proposed wording is similar to the wording for Levemir (insulin detemir, Novo Nordisk) which was user tested in May 2011 (ref. Levemir InnoLet, Levemir FlexPen, Levemir FlexTouch and Levemir Penfill)

3. Benefit-Risk Balance

Mixed insulin containing insulins with different pharmacokinetic profiles (basal and bolus insulin) have been available for many years but have mostly been used in T2 DM in adults. There is one mixed insulin (InsAsp/InsAsp protamine) approved from 10 years of age. Although currently the ISPAD guideline does not recommend the use of premixed insulins in the paediatric population, the guidelines acknowledge that premixed insulins may be useful to reduce the number of injections to improve compliance and/or adherence to the regimen, especially in prepubertal children.

Beneficial effects

The MAH has submitted data from the 16 week therapeutic confirmatory Trial 3816 to support an indication for IDegAsp (Ryzodeg) in T1DM in children and adolescents from the age of 1 to 18 years. Ryzodeg is approved in the adult population since January 2013.

Trial 3816 was a 16-week multi-national, multi-centre, open-label, two-arm, parallel group, randomised, treat-to-target, efficacy and safety trial in children and adolescents with T1DM between 1 and 18 years of age. The comparator was IDet (Levemir).

In the IDegAsp arm there were 40 children aged 2-5 years, 61 children aged 6-11 years and 80 adolescents aged 12-17 years. There was no child below the age of 2 in the IDegAsp arm. One child <2 years was included in the IDet treated group.

Both treatments resulted in a reduction of HbA1c compared to baseline (-0.27 % vs -0.23 % for IDegAsp and IDet, respectively) and non-inferiority was demonstrated. The upper limit of the CI was 0.15 % which is well within both the pre-defined non-inferiority margin of 0.4 % and the currently recommended non-inferiority margin of 0.3 %. A similar trend for HbA1c reduction was observed in all age groups irrespective of treatment. Sensitivity analyses were all in line with the primary analysis, thus the outcome appears robust.

The outcome of the secondary endpoints was in line with the primary endpoint. No statistically significant differences were observed between treatments.

The total insulin dose throughout the study was slightly lower in the IDegAsp treated group compared to the IDet treated group. This was due to a lower basal insulin dose in the IDegAsp treated group. The bolus doses were comparable between groups. In both treatment groups, as expected, the highest dose per body weight was observed in the age group 12-17 years. In the IDet treatment arm 54.2 % of patients were using IDet BID.

The Applicant has presented data that points to that a lower number of injections is needed in the IDegAsp group compared to the IDet+IAsp group. This may be advantageous to improve compliance and/or adherence, as acknowledged in current guidelines (ISPAD; International Society for Paediatric and Adolescent Diabetes), particularly in some clinical situations in the paediatric setting, for example during school time.

Results from the supportive study, trial 3561, have shown that IDeg OD+ bolus IAsp is non inferior to IDet OD or BID+ bolus IAsp.

Uncertainty in the knowledge about the beneficial effects

The number of patients in the youngest age group (2-5 years of age) was small. There is, however, no reason to believe that the effect in that age group would be different from that in the entire group.. The requirements with regards to recruitment set out in the PIP have been fulfilled.

Risks and unfavourable effects

The overall reporting of adverse events in study 3816 were somewhat higher in the IDegAsp treated group, however, the rate of events deemed to be related to treatment was low and comparable between groups.

Serious adverse events were few and the most commonly reported event was hypoglycaemia. The reporting of confirmed hypoglycaemias did not differ between treatment groups with similar proportions reporting an event. In both treatment groups, hypoglycaemias were more common in subjects aged 6-11 years.

Confirmed hypoglycaemia

Almost all subjects in the trial experienced episodes of confirmed hypoglycaemia (98% of subjects treated with IDeg and 96% treated with IDet), and the observed rate of confirmed hypoglycaemia was 5771 and 5405 events per 100 PYE in the IDeg and IDet treatment arms, respectively. There was no difference between the treatment arms in the rates of confirmed hypoglycaemia (rate ratio IDeg/IDet: 1.11 [0.89; 1.38]95%CI).

Although few events, the reporting of severe hypoglycaemia was higher for IDegAsp than for IDet (6.1 % vs 1.7 %).

For children aged 2−5 years, the observed rates of severe hypoglycaemia were 42 vs. 16 episodes per 100 PYE in the IDegAsp and IDet groups, respectively (5 events in 4 subjects in the IDegAsp group vs. 2 events in 2 subjects in the IDet group).

Nocturnal confirmed hypoglycaemic episodes

The percentages of subjects experiencing nocturnal confirmed hypoglycaemic episodes were similar with IDegAsp (N= 101 [55.8%]) and IDet (N= 106 [59.2%]) as was the observed rates per 100 PYE

(577 with IDegAsp and 540 with IDet). No difference was observed between the treatment arms (IDegAsp OD/IDet: 1.09 [0.81; 1.48]95%CI). Approximately 90% of the subjects in both treatment groups reported 4 or fewer nocturnal confirmed hypoglycaemic episodes during the trial.

Hyperglycaemia

The proportion of subjects reporting hyperglycaemias did not differ between treatment groups. The reporting of hyperglycaemia with ketones was low. In the IDegAsp treated group, the highest rate of hyperglycaemias was observed in the age group 6-11 years, whereas in the IDet treated group the highest rate was observed in the age group 1-5 years.

The frequency of injection site reactions was low.

In the supportive trial 3561 more frequent injection sites reactions and more severe hypoglycaemic events in the 6-11 years age group was found with IDeg compared to IDet. This is reflected in the SmPC for Tresiba.

Uncertainty in the knowledge about the unfavourable effects

The data indicates that there may be a higher risk for severe hypoglycaemia in children below the age of 6 years. This is described in the relevant sections of the SmPC.
The Applicant has presented data concerning the cases with severe hypoglycaemia. One case with a mix-up between basal and bolus insulin was found.

Benefit-Risk Balance

Discussion on the importance of favourable and unfavourable effects

Study 3816 was an adequately designed study in subjects with T1DM, aged 1-18 years. The data shows that IDegAsp OD+ IAsp for the remaining meals is non-inferior to IDet OD or BID+ bolus IAsp with respect to lowering of HbA1c. The supportive study trial 3561 has shown that IDeg OD+ bolus IAsp is non inferior to IDet OD or BID+ bolus IAsp. These two confirmatory therapeutic studies include 697 patients which are considered to be sufficient amount of data. Therefore, the studies demonstrate the efficacy and support the indication for Ryzodeg.

The overall safety profile of IDegAsp appears comparable to that of IDet in this population and no new safety concerns arise from the data submitted. Hypoglycaemias were seen mostly during daytime and the overall rate of nocturnal hypoglycaemias did not differ between treatment groups. A lower rate of nocturnal hypoglycaemias was observed in the youngest age group treated with IDegAsp. However, there was a slightly higher number of severe hypoglycaemia in the IDegAsp treatment group, with the finding being more pronounced in the youngest age group (below the age of 6). However, this finding with respect to increased risk of severe hypoglycaemia is based on few events in few individuals and therefore needs to be interpreted with caution. To address this, additional text for the sections 4.2, 4.4 and 5.1 of the SmPC, which state that Ryzodeg should be considered on an individual basis particularly in children aged 2-5 years old because there may be a higher risk for severe hypoglycaemia, has been included in the SmPC. As an additional pecaution, the SmPC includes recommendations to lower the dose when switching to Ryzodeg (IDegAsp).

Although premixed insulins (fixed ratio of basal and bolus insulin) are not recommended in the current ISPAD guideline for treatment of children and adolescents with T1DM, since they remove the flexibility to adjust the doses of the separate insulin types, they may be advantageous in certain situations: to improve compliance and/or adherence, as acknowledged in current guidelines, particularly in some clinical situations in the paediatric setting, for example during school time. This is also in line with the view of a focus group with external paediatric diabetes experts put together by the MAH.

Even though the submitted data supports a positive benefit/risk balance for Ryzodeg in children above the age of 2 and in adolescents, it is recognized that this may not be the preferred treatment option for a large fraction of this population. The MAH has in the response to the second RSI presented data showing that a small percentage of the children below the age of six were already treated with a premixed insulin before inclusion in trial 3816. This also suggests that there may be an unmet medical need for premixed insulin in young children in a small proportion of the target population.

In the current application, only data from children and adolescents with type 1 diabetes has been presented. However, as was previously already concluded similarly for insulin degludec (Tresiba), it is considered that efficacy and safety in children and adolescents with type 2 diabetes can be extrapolated from studies with IDegAsp with patients of the same age range with type 1 diabetes and from studies with IDegAsp of adults with type 2 diabetes. Furthermore, the PK/PD-relationship for Ryzodeg is not expected to be different in children and adolescents with type 2 diabetes. Insulin requirements may be higher in this population, but as IDegAsp needs to be individually titrated in any case, this is not of concern. Further, there is no indication that the safety profile would be markedly different in this population than in adult patients with type 2 diabetes. As hypoglycaemia is less common in type 2 diabetes than in type 1, this is considered to be at least equally manageable in these patients.

During the procedure the Applicant has suggested to exclude children aged 1 to <2 years in the proposed indication. This is endorsed because of the relatively small doses of insulin injected, variable feeding patterns and activity levels and the inability to communicate symptoms of hypoglycaemia in these very young children.

Effects Table

Effects Table for Ryzodeg in the use in children and adolescents 2-18 years based on data from Trial 3816 (NN5401-3816) and supportive data from Trial 3561 (NN1250-3561).

Effect	Short Description	Unit	Treatment IDegAsp OD with a main meal + bolus IAsp for the remaining meals	Control IDet OD or twice daily (BID) + bolus IAsp at all meals	Uncertainties/ Strength of evidence	References
Favourable Effects						
Response Trial 3816	Change from baseline in HbA1c after 16 weeks of treatment.	%	Baseline 8% End of treatment 7.9	Baseline 8% End of treatment 7.8	Open study design Non-inferiority to comparator was demonstrated	Fig 4

Effect	Short Description	Unit	Treatment IDegAsp OD with a main meal + bolus IAsp for the remaining meals	Control IDet OD or twice daily (BID) + bolus IAsp at all meals	Uncertainties/ Strength of evidence	References
Secondary	Change (mean) from baseline in FPG after 16 weeks of treatment	mmol/l	−0.3 mmol/L	−0.1 mmol/L	No statistical difference between the two different treatments was shown.	Fig 5
Secondary	SMPG measurements (8-point profiles)	mmol/l	No statistically significant different was seen between the treatment arms in any of the secondary endpoints	No statistically significant different was seen between the treatment arms in any of the secondary endpoints	Supports that IDegAsp OD+IAsp for the remaining meals is non-inferior to IDet or BID+ mealtime IAsp	Fig 6
Trial 3561 Primary endpoint	Change from baseline in HbA1c after 26 weeks of treatment	(%)	Baseline 8.2 After 26 weeks 8.0	Baseline 8.0 After 26 weeks 7.7	Non-inferiority to comparator was demonstrated	Table 18
Unfavourable Effects						
Confirmed hypoglycaemias	PG ⩽3.9 mmol/L or PG>3.9 mmol/L in conjunction with hypoglycaemic symptoms		No difference between treatment groups	No difference between treatment groups		Fig 13
Severe hypoglycaemic episodes All ages	altered mental status and cannot assist in his care	episodes per 100 PYE	13	0	No statistical significant difference.	Table 24
Severe hypoglycaemic	altered mental status and cannot assist in	episodes per 100 PYE	42	16		see also section “Confirmed Hyoglycaemia”

Effect	Short Description	Unit	Treatment IDegAsp OD with a main meal + bolus IAsp for the remaining meals	Control IDet OD or twice daily (BID) + bolus IAsp at all meals	Uncertainties/ Strength of evidence	References
episodes Below 6 years	his care					in section 3
Nocturnal confirmed hypoglycaemic episodes		episodes per 100 PYE	No difference between treatment groups	No difference between treatment groups	No statistical significant difference.	Fig 16

Benefit-risk balance

The data from the submitted studies support a positive benefit/risk balance for the use of Ryzodeg in children and adolescents with diabetes. The studies demonstrated the efficacy in non-inferiority trials. A lower number of injections may be advantageous in certain situations to improve compliance and/or adherence. Although Ryzodeg may not represent the treatment of choice for all children, it represents an additional option, to broaden the range of approved treatment options available for all age groups to meet the needs of individual patients, taking into account differences in life circumstances. The use of Ryzodeg in the youngest age group should be made with caution and be based on an individual assessment by the treating physician and when discussing the pros and cons with different insulin regimes with the patients and caregivers. These cautionary considerations are adequately described in the SmPC as guidance for the prescriber.

In conclusion, the benefit-risk balance for the treatment of diabetes in children from the age of 2 years and adolescents is considered to be positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by a majority of 27 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of Indication to include treatment of diabetes mellitus in paediatric population from 2 years of age for Ryzodeg; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the QRD template version 10.0.

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0034/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

The divergent position to the majority recommendation is appended to this report.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include treatment of diabetes mellitus in paediatric population from 2 years of age for Ryzodeg; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the QRD template version 10.0.

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

Summary

Please refer to the published Assessment Report Ryzodeg H-2499-II-17-AR.

Appendix

Divergent position dated 23 June 2016

Divergent position expressed by CHMP members:

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the variation to the terms of the marketing authorisation of Ryzodeg for the following reasons:

An indication in children from 2 years to less than 6 years is not supported based on:

Safety issues: The data provided include an increased number of severe hypoglycaemic events observed in the study population with the study drug (26/100 pty versus 7/100 pty), with an even higher frequency in the younger children (< 6 years). More hypoglycaemic events are reported during daytime. No SMBG data are reported at night and therefore it cannot be excluded that severe nocturnal hypoglycaemia is underreported. The data depend on the parents, either waking up due to observed noise, which will not always be the case (1), or waking up for checks.

Therefore the risk that an increase in hypoglycaemia during the night may occur cannot be excluded. Based on the data -and the lack of data- and on potential long term consequences of these hypoglycaemic events in this age group, the drug should not be used in children less than 6 years old.

Furthermore: Current international treatment guidelines (CPCG 2014) recommend that physiological insulin replacement should be given to children of all age groups and the upcoming chapter specifically addressing management of diabetes in pre-schoolers confirms this (2). This is not compatible with a fixed dose insulin combination as this cannot be considered as a meal adjusted insulin administration (3). When using a fixed dose, life-style and food intake must be adjusted to insulin dose.

Therefore, a positive benefit/risk has not been demonstrated in that population.

(1) Matyka KA et al. Cognitive function and mood after profound nocturnal hypoglycaemia in prepubertal children with conventional insulin treatment for diabetes. Arch Dis Child 1999 Aug;81(2):138-42.

(2) Danne T et al. Insulin treatment in children and adolescents with diabetes. Pediatric Diabetes 2014: 15 (Suppl. 20): 115–134.

(3) Neu et al. Classifying insulin regimens--difficulties and proposal for comprehensive new definitions. Pediatr Diabetes. 2015;16(6):402-6

London, 23 June 2016

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Agnes Gyurasics

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Jean-Louis Robert

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Jacqueline Genoux-Hames