25 June 2015
EMA/CHMP/385608/2015 - adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Levemir

International non-proprietary name: INSULIN DETEMIR

Procedure No. EMEA/H/C/000528/II/0070

Note

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

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List of abbreviations

ADA	American Diabetes Association
ANOVA	analysis of variance
BG	blood glucose
BID	bis in die (twice daily)
BMI	body mass index
CAS	completer analysis set
CGM	continuous glucose monitoring
ETS	extension trial set
FAS	full analysis set
FDA	US Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
IAsp	insulin aspart
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDeg	insulin degludec
IDet	insulin detemir
IG	interstitial glucose
ISPAD	International Society for Pediatric and Adolescent Diabetes
ITT	intent-to-treat
LOCF	last observation carried forward
OD	once daily
NPH	neutral protamine hagedorn
PG	plasma glucose
PIP	Paediatric investigational plan
PK	pharmacokinetic
PP	per-protocol
PYE	patient year(s) of exposure
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SMPG	self-measured plasma glucose
SOC	system organ class
TEAE	treatment emergent adverse events
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 8 December 2014 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 and IIIB

Extension of Indication for Levemir to include new population, i.e. children between 1 and less than 2 years of age; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to update the efficacy and safety information. The Package Leaflet is updated in accordance.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0172/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0172/2014 was completed. The PDCO issued an opinion on compliance for the PIP P/0172/2014.

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 appointed by the CHMP was:

Rapporteur: Jens Heisterberg

Timetable	Actual dates
Submission date	8 December 2014
Start of procedure:	26 December 2014
CHMP Rapporteur Assessment Report	26 February 2015
CHMP comments	16 March 2015
Rapporteur Revised Assessment Report	23 March 2015
Request for supplementary information (RSI)	26 March 2015
CHMP Rapporteur Assessment Report	3 June 2015
CHMP comments	15 June 2015
Rapporteur Revised Assessment Report	25 June 2015
Opinion	25 June 2015

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. Subjects with T1DM require lifelong treatment with insulin. A well-documented rise in the incidence has been noted in many countries, some reporting a disproportionately greater increase in those under the age of 5 years.

Type 2 diabetes mellitus (T2DM) is becoming more common in adolescents, particularly in the peripubertal period, although the disease remains relatively rare apart from some minority populations. Available data, suggest that preadolescent children are unlikely to have T2DM even if obese.

Both T1DM and T2DM are associated with acute and chronic complications. Long-term chronic complications of hyperglycaemia include micro- and macro-vascular complications such as retinopathy, nephropathy, neuropathy and cardiovascular disease. Although such long-term complications are rare in children and adolescents with T1DM, poor metabolic control appears to predispose to the development of co-morbidities later in life. In addition, long-term hyperglycaemia due to poor control or inadequate insulin treatment can also be associated with weight loss, stunted growth and delayed puberty in paediatric subjects. Available data from young patients with T2DM show that the burden of the diabetes-related complications in adolescents with the disease is at least as high as in those with T1DM.

The Diabetes Control and Complications Trial (DCCT) confirmed that intensified long-term glucose control aiming at achieving levels of glycaemia as close to the non-diabetic range as possible reduces both the incidence and the progression of complications occurring in relation to T1DM in adults and adolescents ≥ 13 years of age. The results of the Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that the benefits seen in the DCCT trial in adolescents persisted over the subsequent 4 years after the end of the DCCT trial and further underlined the importance of achieving good glycaemic control in adolescents. The underlying mechanisms responsible for the improvement in outcomes and for the prolonged effects of early intervention remained unclear. However, the phenomenon, referred to as 'metabolic memory' is observed in both T1DM and T2DM. The challenge to obtain good glycaemic control

in the absence of hypoglycaemia is greater in a paediatric population compared to an adult population due to growth, more variable lifestyle, need of assistance with insulin injection and hormonal changes.

Information about insulin treatment in paediatric patients based on randomised clinical trials is limited, particularly in young children.

IDet (Levemir) received a marketing authorisation in Europe on 1 June 2004 for use in adults, and has since been marketed in more than 60 countries worldwide. IDet is approved for treatment of diabetes mellitus as basal insulin in combination with meal-related bolus insulin and oral antidiabetic drugs. IDet is to be administered s.c. OD (once daily) or BID (twice daily). The dose of Levemir should be titrated based on the individual patient's needs.

The labelling was subsequently amended on 29 Mar 2005 to include paediatric subjects ≥ 6 years of age, based on the results of a confirmatory clinical efficacy and safety trial in children and adolescents aged 6-17 years (NN304-1379).On 24 Oct 2011, the labelling was amended to include the use of IDet in children aged 2-5 years, based on data demonstrating that IDet is an equally safe and efficacious treatment option for young children with T1DM, compared with neutral protamine hagedorn (NPH) insulin treatment.

IDet is a representative of the class of long-acting soluble insulin analogues intended to cover the basal insulin requirements of subjects with T1DM or T2DM. IDet has consistently been associated with a lower risk of hypoglycaemia compared to NPH insulin, in particular with regards to minor and nocturnal hypoglycaemic episodes.

The efficacy and safety ofIDet in paediatric subjects have been studied in a long-term therapeutic confirmatory trial, Trial 3561. Trial 3561 was conducted in children/adolescents aged 1 to less than 18 years and provides important information about the use of insulin detemir (IDet) in this population. In addition, a pharmacokinetic (PK) modelling study including data from children/adolescents from 1 to less than 18 years has been conducted.

Trial 3561 has already been assessed by the CHMP within procedure EMEA/H/C/528/P46/49.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

The clinical development programme for IDet in paediatric subjects addressed in this application consists of the following components:

- Therapeutic confirmatory trial – Trial 3561(Study #3 of the IDet paediatric investigational plan [PIP]):

  A 26-week multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of IDeg and IDet in children/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.

- PK modelling study (Study #4 of the IDet PIP):

A modelling study in children/adolescents from 1 to less than 18 years of age, compared to adults, all with T1DM. The modelling study consisted of a population PK analysis based on data from Trials NN304-1222 and 3561. The objective of the analysis was to develop a population PK model for IDet in children younger than 6 years.

- Extrapolation and modelling study (Study #5 of the IDet PIP):

  An extrapolation and modelling study to extend efficacy and safety results in adults with T2DM and in children/adolescents with T1DM to children/adolescents with T2DM. The objective was to support the clinical use of IDet as basal insulin in children/adolescents with T2DM, not sufficiently controlled with non-insulin medicinal products.

GCP

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

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

- Tabular overview of clinical studies

Figure 1 - Trial 3561 – overview of trial design and efficacy endpoints

No. of subjects rand. IDeg/IDet exp. (IDeg/IDet)	Treatment	Trial design	Efficacy endpoints
Main period: 174/176 (174/175) **Extension period:** (152/128)	**Basal/bolus:** *Basal:* IDeg OD[a] or IDet OD/ BID[b] *Bolus:* IAsp in both treatment groups	• T1DM subjects • Age: 1– <18 years • 26 weeks + 26 weeks extension • Parallel group • Open-label • Treat-to-target • Non-inferiority • Stratification in age groups (1–5 years, 6–11 years, 12–17 years)	**Primary endpoint**: • Change in HbA_{1c} (after 26 weeks) **Secondary endpoints:** • Change in HbA_{1c} (52 weeks) • Change in FPG (26 and 52 weeks) • 8-point SMPG (26 and 52 weeks) • 4-point SMPG for dose adjustment (26 and 52 weeks) • Steady state IDeg and IDet plasma concentration (during first 26 weeks)

BID: twice daily; FPG: fasting plasma glucose; IAsp: insulin aspart; IDeg: insulin degludec; IDet: insulin detemir; OD: once daily; SMPG: self-measured plasma glucose; T1DM: type 1 diabetes mellitus;
[a]Administered OD approximately at the same time of the day.
[b]According to IDet labelling.

2.3.2. Pharmacokinetics

See section 2.3.4.

2.3.3. Pharmacodynamics

See section 2.3.4.

2.3.4. PK/PD modelling

Study #4

A population pharmacokinetic (PK) analysis for insulin detemir (IDet) in children from 1 to less than 18 years of age, compared to adults, all with T1DM. This analysis is part of the agreed Paediatric Investigational Plan (PIP) for IDet and constitutes Study #4 (Table 1).

Table 1 Study #4 of the IDet PIP*

Study identifier	Study #4
Type of study, study design	PK modelling study in data from children from 1 to less than 18 years of age, compared to adults, all with T1DM.
Study objective(s)	To model the PK of IDet in children younger than 6 years of age.
Study population	PK data from the rich sampling single-dose PK study NN304-1222 in children older than 6 years and in adults, and PK data from the sparse sampling in study NN1250-3561, which includes children younger than 6 years, will be used to construct the models.
Statistical plan	The PK data from trial NN304-1222 must be used to develop a population PK model, which subsequently will be used to simulate PK following multiple dosing in children younger than 6 years of age. In trial NN1250-3561, the steady state PK of IDet will then be investigated across the different age groups by use of population PK. A sparse sampling strategy with 2-3 samples per subject (on separate visits) will be used and a compartmental model, similar to the one used for trial NN304-1222, will be applied. However, the value of the absorption rate constant in the model may have to be fixed to ensure convergence of the estimation, in which case a value from trial NN304-1222 will be used. Using this base model, an analysis of the influence of relevant covariates (age or age group, body weight, etc.) on CL/F must be carried out. The covariates will be incorporated into the base model using forward inclusion with $p<0.01$. When no more significant effects can be found, the final model will be developed using backward elimination with $p>0.001$. Evaluation of the final model will be performed using goodness-of-fit plots, evaluation of the parameter estimates and their uncertainty (incl. comparison with the results from NN304-1222) and a number of sensitivity analyses, where the sensitivity towards outliers as well as the sensitivity towards changes in the fixed parameter values of the model will be assessed.

*Agreed Paediatric Investigational Plan (PIP) for insulin detemir (IDet), EMEA-000412-PIP01-08-M01.

It was decided to perform a joint population PK analysis based on the combined data set, rather than first performing an analysis on Trial 1222 and then performing an analysis on Trial 3561. The rationale for this was that the joint analysis would be more robust and that it would not be necessary to fix any parameters to ensure convergence of the estimation on Trial 3561. Model development, model evaluation, and simulation of multiple dosing were performed as originally planned.

Objectives

The objective of the analysis was to develop a population PK model for IDet in children younger than 6 years of age to address how steady-state IDet exposure compare between children younger than 6 years of age and other age groups. The model would assess the effect of following covariates on exposure:

- Body weight.
- Age group (small children: 1 to 5 years of age, children: 6 to11 years of age, adolescents: 12 to17 years of age, adults: 18 years and above).

- BMI z-score (age adjusted marker) treated as a categorical covariate (less than -1/between-1 and +1/greater than +1).
- Gender (Male/Female).
- Race (White, Asian Non-Indian, Other).

Methods

Data source

The main (non-extension) part of Trial 3561 was a randomised, multinational, multi-centre, open-labelled, two-arm parallel-group, 26-week, treat to target, safety and efficacy trial, comparing IDet and insulin degludec (IDeg) as basal insulin in combination with insulin aspart (IAsp) as bolus insulin in subjects with T1DM, aged from 1 to less than 18 years.

Trial 1222 was a randomised, single-centre, open-label, two-period cross-over, single-dose trial, investigating the PK properties of IDet and Neutral Protamine Hagedorn (NPH) insulin in children (6-12 years), adolescents (13-17 years) and adults (18 years and above) with T1DM. Only the IDet PK data from this trial was included in the present analysis.

Trial population

In Trial 3561 a total of 350 subjects with T1DM were randomised to either IDet or IDeg, using a 1:1 randomisation scheme. The subjects were recruited from Bulgaria, Finland, France, Germany, Italy, Japan, Netherlands, Republic of Macedonia, Russian Federation, South Africa, United Kingdom, and United States. In brief, the subjects included were male or female subjects with T1DM, aged between 1 and less than 18 years, with an HbA1c up to 11%, who had been on insulin treatment for at least 3 months with a total daily dose of up to 2.0 U/kg.

In Trial 1222 a total of 34 subjects with T1DM (13 children (6-11 years), 10 adolescents (12-17 years), and 11 adults (18 years and above)) were randomised to one of two treatment sequences (IDet/NPH or NPH/IDet). The subjects were all recruited from Germany. The subjects included were male or female subjects with T1DM, aged between 6 and 65 years, with an HbA1c up to 12%, who were on multiple daily injections of insulin with a total daily dose of at least 0.6 U/kg.

Dosing regimen

In Trial 3561 subjects should initially administer IDet according to their pre-trial dosing scheme (once-daily (OD) or twice-daily (BID)), but were allowed to switch from OD to BID dosing during the trial. For OD dosing subjects should administer IDet at approximately the same time of the day every day. For BID dosing, subjects should administer IDet at breakfast and in the evening either at main evening meal or at bedtime. The starting dose for IDet was determined based on the subjects' pre-trial total daily insulin dose, according to a pre-specified procedure. During the trial, titration of the IDet dose(s) was performed once-weekly using a pre-specified titration algorithm. For OD dosing the dose adjustment was based on the lowest of three pre-breakfast self-measured plasma glucose (SMPG) values. For BID dosing the morning and evening dose adjustments were based on the lowest of three pre-dinner, respectively pre-breakfast, SMPG values. The target plasma glucose range was 5.0-8.0 mmol/L. SMPG measurements were performed by the subjects themselves using a glucose meter and test strips calibrated to plasma values.

In Trial 1222 all subjects received a single dose of 0.5 U/kg of IDet on a single occasion.

Blood sampling

In Trial 3561 blood samples were drawn to measure the serum concentration of IDet after 2, 12 and 26 weeks of treatment.

In Trial 1222 blood samples were drawn to measure the serum concentration of IDet at 0 h (predose), ½h, 1h, 2h, 3h, 3½h, 4h, 4½h, 5h, 5½h, 6h, 7h, 8h, 10h, 12h, 16h, 20h, and finally at 24h after administration.

Assay

IDet concentration in serum was determined using a validated IDet specific sandwich enzymelinked immunosorbent assay (ELISA) with a lower limit of quantification (LLOQ) of 25 pmol/L. The same assay was used in both trials (Trial 3561 and Trial 1222).

Data

The data file for the analysis was formatted according to the requirements of NONMEM based on source data sets in SAS format. Data from Trials 3561 and 1222 were combined in one data file. For Trial 3561, all IDet doses taken within three days of blood sampling were included. Data records with missing concentration values and data records with concentration values below the LLOQ excluded from the analysis. Data records with missing, incomplete or ambiguous dosing history were also flagged and excluded. Outliers identified based on graphical data analysis were included in the main analysis, but were flagged and excluded in a subsequent sensitivity analysis.

Population PK analysis

The first order conditional estimation method with interaction (FOCE+I) in NONMEM was used for the analysis. Discrimination between intermediate models was based on NONMEM's objective function value (OFV) as well as standard goodness-of-fit plots. In terms of OFV, changes in this value were assumed to be χ^2-distributed (for nested models), and criteria for inclusion/exclusion of covariate effects were defined accordingly.

Structural model

A one-compartment model with first-order absorption and absorption lag time and with first-order elimination was used to describe the PK. This structural model has previously been found to adequately describe the PK of IDet in trials with frequent blood sampling. The model was parameterised in terms of the following parameters:

- KA (absorption rate constant).
- LAG (absorption lag time).
- CL/F (apparent clearance).
- V/F (apparent volume of distribution).

Variability and residual error models

Between-subject variability (log-normally distributed; without correlation between the parameters) was estimated for CL/F and V/F. No between-subject variability was included for KA and LAG, as it was not possible to obtain reliable estimates of these parameters for the subjects in Trial 3561 due to the low number of data points available for each subject (only three blood samples per subject).

A combined proportional + additive error model was used to describe the residual variability.

Covariate analysis

With the 'base' model in place, an analysis of the influence of covariates on CL/F and V/F was carried out. A forward inclusion, backward elimination approach was applied, where the investigated covariates were included into the base model using forward inclusion with a p-value of 0.01 to yield a 'full' model. When no more significant effects could be found, the final model was developed using backward elimination with a p-value of 0.001.

The covariates investigated on CL/F were body weight, age group, BMI category, gender, and race.

For V/F, only the effect of body weight was investigated.

The covariate effects were included into the base model using the following parameterisations:

$$CL/F_i = TVCL \cdot E_{weight,CL} \cdot E_{age} \cdot E_{BMI} \cdot E_{gender} \cdot E_{race} \cdot \exp(\eta_{i,CL})$$

$$E_{weight,CL} = \left(\frac{\text{Body weight}}{\text{Median body weight}} \right)^{\theta_{wt,CL}}$$

$$E_{age} = \exp(\theta_{\text{Small children}})^{\text{Small children}} \cdot \exp(\theta_{\text{Children}})^{\text{Children}} \cdot \exp(\theta_{\text{Adolescents}})^{\text{Adolescents}}$$

$$E_{BMI} = \exp(\theta_{\text{Less than -1}})^{\text{Less than -1}} \cdot \exp(\theta_{\text{Greater than +1}})^{\text{Greater than +1}}$$

$$E_{gender} = \exp(\theta_{\text{Male}})^{\text{Male}}$$

$$E_{race} = \exp(\theta_{\text{Asian Non-Indian}})^{\text{Asian Non-Indian}} \cdot \exp(\theta_{\text{Other}})^{\text{Other}}$$

$$V/F_i = TVV \cdot E_{weight,V} \cdot \exp(\eta_{i,V})$$

$$E_{weight,V} = \left(\frac{\text{Body weight}}{\text{Median body weight}} \right)^{\theta_{wt,V}}$$

where TVCL and TVV are typical values of CL/F and V/F, i.e. values for a hypothetical reference subject, here defined as a white, female, adult with a BMI z-score between -1 and +1 and a body weight corresponding to the median body weight of the adults in the analysis population. 'Small Children', 'Children', 'Adolescents', 'Less than -1', 'Greater than +1', 'Male', 'Asian Non-Indian', and 'Other' are indicator variables for covariate categories. The various subscripted θ values are the covariate effect parameters estimated in the model.

For the body weight covariate the values used in the model were baseline values, and for the categorical covariates, it was decided to require at least 20 subjects in each category (except for the adult age group category, where only the 9 adults from Trial 1222 were available). The BMI z-scores used to define BMI categories were calculated based on the WHO reference population.

The results of the covariate analysis were presented graphically. The effect of body weight was presented using plots of 24 hour steady-state AUC and C_{max} vs. body weight for a typical subject, showing the median and corresponding 95% confidence interval (CI).

Simulation of PK profiles

Using the final model from the covariate analysis, simulations of IDet concentration profiles at steady-state following multiple dosing were performed and presented graphically for each of the four age groups. The simulations were performed using the estimated population mean parameters from the final model by simulating a profile for a typical individual within each age group.

Summary of key assumptions

The following overall assumptions were made:

- Missing data was assumed to be missing at random and not confounded with exposure levels.
- The PK of IDet was assumed to be at steady-state at the time point, where detailed dosing history recording began
- A one-compartment model with first-order absorption and absorption lag time and with first-order elimination was used to describe the PK of IDet.
- Between-subject variability for apparent clearance (CL/F) and apparent volume of distribution (V/F) in the model was assumed to be log-normally distributed and uncorrelated. Residual variability was assumed to follow a combined proportional + additive error model. Both of these distributional assumptions were justified by reasonable standard goodness-of-fit plots.

Results and discussion

Analysis data

A total of 1058 IDet concentration records from 205 subjects were included in the base data set As a result of data cleaning, 12.8% of the IDet concentration records were excluded. The final data set comprised a total of 923 IDet concentration records from 196 subjects, of whom 166 were from Trial 3561 and 30 were from Trial 1222. Of the 166 subjects from Trial 3561, 39 subjects were below 6 years of age.

Table 2 shows summaries of subject characteristics with regard to gender, race, ethnicity and country for the final data set.

Table 2 Summary of subject characteristics (categorical variables).

Covariate	Category	Trial 3561 N (%)	Trial 1222 N (%)	Total N (%)
Gender	Female	74 (45)	14 (47)	88 (45)
	Male	92 (55)	16 (53)	108 (55)
Race	Asian Non-Indian	30 (18)	-	30 (15)
	Black or African American	5 (3)	-	5 (3)
	Missing	7 (4)	-	7 (4)
	Other	7 (4)	-	7 (4)
	White	117 (70)	30 (100)	147 (75)
Ethnicity	Hispanic or Latino	3 (2)	-	3 (2)
	Not Hispanic or Latino	163 (98)	30 (100)	193 (98)
Country	Bulgaria	16 (10)	-	16 (8)
	Germany	4 (2)	30 (100)	34 (17)
	Finland	7 (4)	-	7 (4)
	France	7 (4)	-	7 (4)
	Great Britain	5 (3)	-	5 (3)
	Italy	8 (5)	-	8 (4)
	Japan	30 (18)	-	30 (15)
	Macedonia	8 (5)	-	8 (4)
	Netherlands	5 (3)	-	5 (3)
	Russia	28 (17)	-	28 (14)
	South Africa	7 (4)	-	7 (4)
	USA	41 (25)	-	41 (21)
Total		166 (85)	30 (15)	196 (100)

Summaries of subject characteristics with regards to age, body weight, and BMI are shown in Table 3. The mean BMI z-score calculated based on the WHO reference population was 0.40 ranging from -5.45 to 2.89, indicating a higher BMI in the present analysis population as compared to the WHO reference population. In order to account for this right-shift of the BMI z-score distribution in the covariate analysis, and to ensure appropriately sized groups when applying the planned splits between groups at BMI z-scores of -1 and 1, all BMI z-scores were adjusted by subtracting 0.5, before dividing the subjects into BMI categories.

Table 3 Summary of subject characteristics (continuous variables).

	Trial 3561 Mean (SD) [Range]	Trial 1222 Mean (SD) [Range]	Total Mean (SD) [Range]
N	166	30	196
Age (years)	10.0 (4.3) [1.8-17.7]	15.6 (6.1) [7.3-39.2]	10.9 (5.0) [1.8-39.2]
Body Weight (kg)	37.7 (18.9) [11.6-95.5]	58.0 (18.5) [24.2-84.1]	40.8 (20.2) [11.6-95.5]
BMI (kg/m^2)	18.4 (3.6) [9.9-30.5]	20.8 (2.7) [16.5-26.9]	18.8 (3.6) [9.9-30.5]
BMI z-score (-)	0.38 (1.15) [-5.45-2.89]	0.50 (0.58) [-0.90-1.46]	0.40 (1.08) [-5.45-2.89]

Graphical analysis

A graphical data analysis was conducted prior to performing the population PK analysis in order to explore trends in the data across covariates and hence obtain initial indications of relevant covariate effects. Using the graphical data analysis, covariate effects identified in the subsequent covariate analysis were also evaluated to see whether they were reflected in obvious data trends.

The data from Trial 1222 was omitted from the graphical data analysis, as the frequently sampled single dose data from this trial would otherwise dominate the sparsely sampled steady-state data from Trial 3561 and prevent meaningful interpretation of the resulting plots.

The graphical data analysis comprised plots of geometric mean and 95% CI for dose-normalised IDet concentration vs. Week No. and vs. time after latest dose stratified by:

- Age group (small children: 1-5 years, children: 6-11 years, adolescents: 12-17 years).
- Body weight (as quartiles).
- BMI z-score treated as a categorical covariate (less than -1/-1 to +1/greater than +1)
- Gender (Male/Female).
- Race (White, Asian Non-Indian, Other).

The dose-normalised IDet concentrations were calculated by dividing the observed concentration values (in pmol/L) by the corresponding doses expressed in absolute amounts (in U).

The dose-normalised IDet concentrations were unchanged throughout the 26 weeks of treatment indicating that the clearance of IDet was constant during this period.

The dose-normalised IDet concentrations decreased with increasing age, so that the three age groups had the following order of IDet exposure: Small children (1-5 years) > children (6-11 years) > adolescents (12-17 years). Likewise, the dose-normalised IDet concentrations decreased with increasing body weight, a finding which may explain the apparent effect of age group. The potentially confounded effects of age group and body weight were subsequently analysed in the population PK covariate analysis.

For the remaining covariates (BMI z-score category, gender and race), no obvious trends in the dose-normalised IDet concentrations were observed.

Population PK analysis

The model used for the population PK analysis was developed in three steps: first a ‘base’ model without covariates was estimated; next a ‘full’ model including all covariate effects significant on a 1% level ($p<0.01$) was developed. Finally, the full model was reduced to the final model by excluding all covariate effects not significant on a 0.1% level ($p>0.001$). Using this stepwise forward inclusion/backward elimination procedure, covariate effects were investigated for both clearance and volume of distribution.

The base model was a one-compartment model with first-order absorption and absorption lag time and with first-order elimination. This model has previously been found to adequately describe the PK of IDet in trials with frequent blood sampling.

During the forward inclusion procedure, body weight was identified as a significant covariate for both clearance and volume of distribution, and these two covariate effects were included in the full model. Age group, BMI category, gender, and race were not significant covariates for clearance and were therefore not included in the full model.

During the backward elimination procedure, body weight was retained for both clearance and volume of distribution. The final model thus consisted of the base model with body weight as a covariate for both

clearance and volume of distribution. The parameter estimates were in good agreement with estimates previously obtained in clinical pharmacology trials with IDet.

The outcome of the covariate analysis was in accordance with the graphical analysis of the data, which showed obvious trends in the exposure data when stratifying by body weight or age group, but no obvious trends when stratifying by BMI category, gender or race. The fact that age group was not a significant covariate in the final model indicates that the apparent trend with age group was mainly driven by differences in body weight between the studied age groups.

The estimated allometric exponents for clearance and volume of distribution in the final model were close to 1 (1.08 [95% CI: 0.851-1.31] for CL/F and 0.932 [95% CI: 0.412-1.45] for V/F). Since exposure is inversely related to clearance (AUC=Dose/(CL/F)), it follows that there is an inverse relationship between exposure and body weight. This is shown in Figure 2 for AUC and C_{max} following a fixed dose of 10U of IDet administered OD to a typical subject. When dosed per kg body weight, the inverse relationship between exposure and body weight is adjusted for, and exposure becomes independent of body weight, as shown in Figure 3 for a dose of 0.4 U of IDet per kg body weight administered OD to a typical subject.

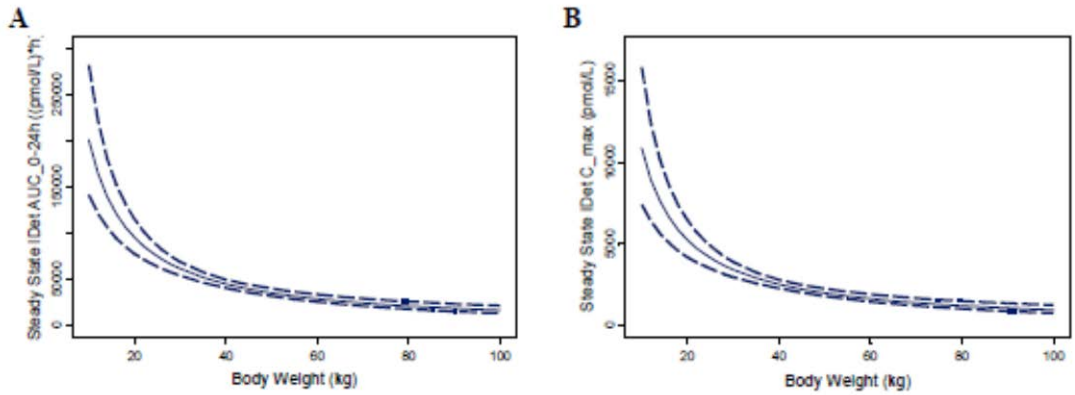


Figure 2 **AUC (A) and C_{max} (B) at steady-state vs. body weight for typical subjects in the weight range 10-100 kg dosed with 10 U of IDet.**
Data are medians with 95% CI obtained from the final model.

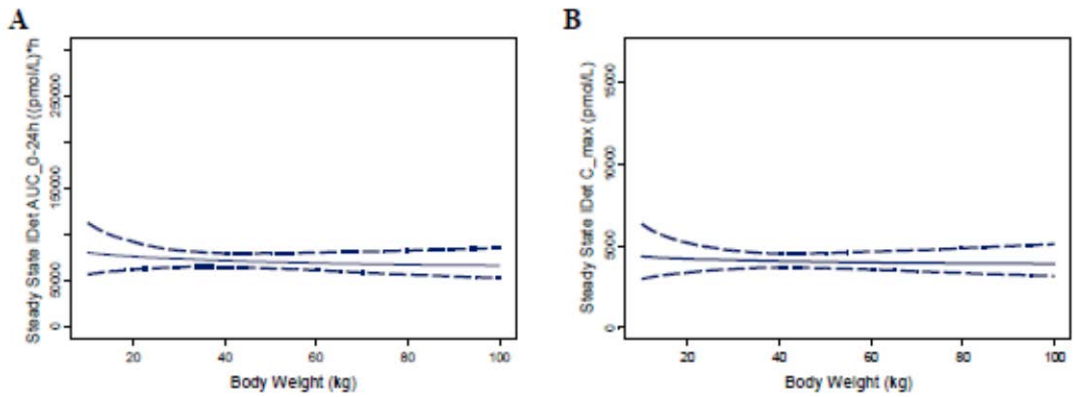


Figure 3 **AUC (A) and C_{max} (B) at steady-state vs. body weight for typical subjects in the weight range 10-100 kg dosed with 0.4 U of IDet per kg body weight.**
Data are medians with 95% CI obtained from the final model.

Likewise, due to the strong correlation between age and body weight, concentration-time profiles are similar across age groups, when IDet is dosed per kg body weight.

This is shown in Figure 4 using model-derived concentration-time profiles for each of the four investigated age groups (1-5 years, 6-11 years, 12-17 years, and 18 years and above), all dosed OD with 0.4 U of IDet per kg body weight. Very similar profiles are predicted for all four age groups.

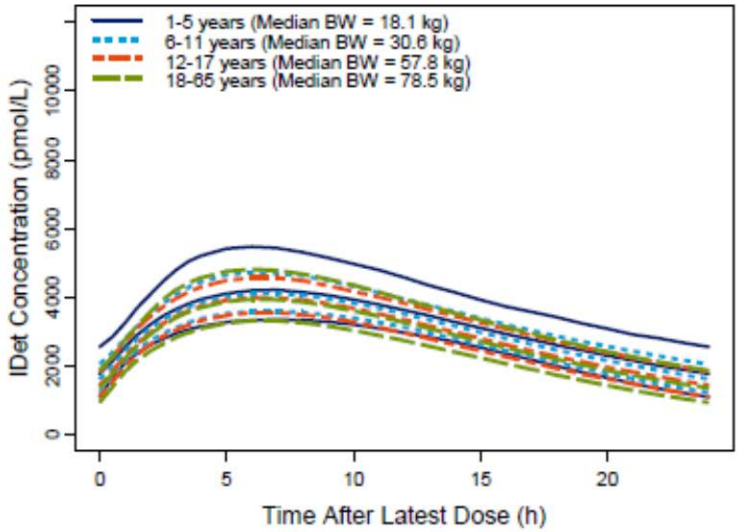


Figure 4 **Model-derived concentration-time profiles over a 24 hour dosing interval at steady-state following once-daily dosing 0.4 U of IDet per kg body weight to a typical subject (based on median body weight (BW)) in four different age groups.**
Data are medians with 95% CI obtained from the final model.

This is in line with the result from Trial 1222, where no statistically significant differences in IDet PK were found among children, adolescents and adults (AUC ratio (children/adults): 1.02 [95% CI: 0.74-1.41], AUC ratio (adolescents/adults): 0.89 [95% CI: 0.65-1.23], Cmax ratio (children/adults) 1.24 [95% CI: 0.86-1.79], Cmax ratio (adolescents/adults) 1.02 [95% CI: 0.71-1.47]).

Model evaluation

The final model was evaluated for descriptive as well as predictive purposes as follows:

- Standard goodness-of-fit plots:
    - The model fit was acceptable and there were no critical trends in the conditional weighted residuals vs. neither IDet concentration nor time. The individual clearance and volume of distribution estimates appeared to follow a normal distribution.
- Evaluation of fixed effect parameter estimates and their uncertainties:
    - The clearance and volume of distribution estimates for a typical subject were 10.6 L/h and 113 L, respectively, and were determined with good precision (relative standard errors (RSEs) of 9% and 16.7%, respectively).
- Assessment of the shrinkage for the random effects:
    - Shrinkage for clearance and volume of distribution were estimated at 5.42% and 50.7%, respectively, indicating that the individual estimates of volume of distribution (but not the estimates of clearance) were biased towards the mean estimate.
- Sensitivity analyses:

- The sensitivity of the model towards outliers identified in the graphical data analysis was investigated by excluding these values and re-estimating the model. Exclusion of outliers had a relatively small influence on parameter estimates. The numerically highest percentage change of +32.4% was seen for the absorption lag time, which changed from 0.0954 h to 0.126 h, which is considered to be an insignificant change, given that the first post-dose sample in Trial 1222 was taken at 0.5 h.
- The sensitivity of the model towards influential observations not identified in the graphical data analysis were investigated by excluding all records giving rise to an absolute conditional weighted residual above 4 or an absolute weighted residual above 4, and re-estimating the model. The model was relatively robust towards exclusion of datawith high residuals. The numerically highest percentage change of +55.3% was seen for the absorption lag time, which changed from 0.0954 h to 0.148 h, which is considered to be an insignificant change, as the first post-dose sample in Trial 1222 was taken at 0.5 h.

- Likelihood profiling for the final model:
  - The confidence intervals obtained by means of likelihood profiling were all in good agreement with the confidence intervals derived from the covariance matrix.
- VPC to assess the applicability of the model for simulation. (Figure 13, Appendix J):
  - The simplified VPC showed that the model was able to reproduce the mean trend in the data set used for estimation and hence suitable for simulation of mean profiles.

The population PK analysis showed that the concentration-time profile in small children (1-5 years) is similar to the concentration-time profiles in children (6-11 years), adolescents (12-17 years) and adults (18 years and above), when IDet is dosed per kg body weight. This result of the joint analysis of Trial 3561 and Trial 1222 is in line with the result from Trial 1222, where no statistically significant differences in IDet PK were found among children, adolescents and adults.

As expected, and as observed for other insulins, body weight was the only significant covariate. Age group was highly correlated with body weight, but was not significant, when body weight was included. BMI z-score, gender and race did not significantly affect exposure.

Study #5

In accordance with the decision of 11 July 2014 (P/0172/2014) on the Paediatric Investigational Plan (PIP) for IDet, a waiver was granted for a clinical trial in children below 10 years of age with T2DM. The binding element (Study #5) concerning children and adolescents with T2DM (Table 1–1) is addressed with this report.

Table 1–1 Study #5 of the IDet PIP

Study identifier	Study #5
Type of study	Extrapolation and modelling study to extend efficacy results in adults with T2DM and children and adolescents with T1DM to children and adolescents with T2DM.
Objectives	To support the clinical use of IDet in children and adolescents with T2DM, not sufficiently controlled with non-insulin medicinal products.
Population	Data from efficacy studies with IDet in adults with T2DM and children and adolescents with T1DM will be analysed and modelled to extrapolate efficacy to children and adolescents with T2DM.
Statistical plan	A combination of model-based extrapolation of self-measured blood glucose[a] and qualitative (non-model-based) extrapolation of trial results on HbA_{1c} and important safety parameters must be used.

Note: From EMA decision (P/0172/2014) on the acceptance of a modification of an agreed PIP for insulin detemir (EMEA-000412-PIP01-08-M01), 11 July 2014.

Abbreviations: EMA = European Medicines Agency; PIP = paediatric investigation plan; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

[a] Pre-breakfast self-measured plasma glucose (SMPG) was measured at home by the subjects/families using the trial-provided blood glucose meter, which was calibrated to plasma values. All glucose measurements made with drawn capillary blood were therefore automatically calibrated to plasma equivalent glucose values.

Extrapolation plan

The extrapolation aims to support the clinical use of IDet as a basal insulin in children and adolescents with T2DM who are not sufficiently controlled with non-insulin medicinal products. Clinical data are available from efficacy and safety trials with IDet in children and adolescents aged 10–17 years and adults with T1DM and in adults with T2DM. Based on these data, the extrapolation approach consisted of a model-based component as well as a more qualitative component:

- The model-based component investigated the dose-response relationship (IDet dose vs. pre-breakfast SMPG levels) in children/adolescents and adults with T1DM. The difference between the 2 populations was then applied to T2DM in order to extrapolate the IDet dose-response relationship from adults with T2DM to children/adolescents with T2DM (illustrated in Table 2–1).
- The qualitative component evaluated key efficacy and safety parameters from the efficacy and safety trials in children/adolescents and adults in context of the estimated dose-response relationships.

Table 2–1 Extrapolation approach

	T1DM	T2DM
Adults	② Trial 3585 (main) and Trial 3725 (extension) 26 weeks + 26 weeks	③ Trial 3785 26 weeks (sub-population: BMI ≥ 30 kg/m^2, insulin naïve and previously treated with metformin only)
Children and adolescents (aged 10–17 years)	① Trial 3561 26 weeks main + 26 weeks extension	④ No clinical trial (dose-response estimate)

The dose-response relationship and the difference between children and adolescents with T1DM and adults with T1DM is estimated (① and ②). This difference is then applied to the estimated dose-response relationship for adults with T2DM (③) as a measure of the dose-relationship in children and adolescents with T2DM (④). The dose-relationships are combined with an evaluation of key efficacy and safety endpoints from the trials for the extrapolation to children and adolescents with T2DM.

Key assumptions

The key assumptions for the extrapolation are:

- The pathogenesis of T1DM is similar in children/adolescents and adults.
- The pathogenesis of T2DM is similar in children/adolescents and adults.
- The difference in dose-response between children/adolescents and adults with T1DM can be used as a predictor for the difference in dose-response between the same age groups with T2DM.
- A subpopulation of adult subjects with T2DM who are insulin naïve, obese (BMI ≥ 30 kg/m2) and on metformin-only therapy are expected to most closely resemble a population of children and adolescents with T2DM for whom intensification with basal insulin treatment would be considered.
- Basal insulin once daily (OD) is usually titrated based on pre-breakfast SMPG values. This was also the case in the trials included in this report. It is acknowledged that overall glycaemic control is impacted by administration of both basal and bolus insulin. Therefore, dose-response relationships could be made between basal, bolus, or total insulin dose and SMPG values. However, for the purpose of the dose-response analysis and the extrapolation to children and adolescents with T2DM (not sufficiently controlled on non-insulin medicinal products), it is assumed that the basal insulin dose is the most relevant.

Rationale for the extrapolation

Although the incidence of T2DM is increasing in the paediatric population, the absolute number of children and adolescents with T2DM is still relatively low. Given that the number of paediatric subjects requiring insulin on a maintenance basis would only be a subset of this population, recruiting an adequate number of subjects to conduct a robust clinical trial would be extremely challenging. Due to these limitations to the conduct of a clinical trial, an extrapolation and modelling study was accepted as an alternative approach to explore the efficacy and safety of IDet in the treatment of children and adolescents with T2DM, as reflected in the Decision of 26 November 2010 (P/0269/2010) on the PIP for IDet. Given the

similarity in pathogenesis of T1DM and T2DM for children/adolescents and adults, the same key clinical efficacy and safety endpoints are applicable when evaluating and extrapolating between the age groups.

Methodology

Clinical trials

Clinical data for children and adolescents with T1DM are available from a paediatric efficacy and safety trial with IDet (Trial 3561); the trial consisted of a 26-week main period with a 26-week extension period. In this trial, subjects were stratified according to age groups (1–5, 6–11 and 12-17 years) in accordance with the EMA Diabetes guideline and the EMA and International Conference on Harmonisation (ICH) guidelines on clinical investigation of medicinal products in the paediatric population. Subjects aged 10–17 years old are used as representative for children and adolescents in this report.

Data are also available from an efficacy and safety trial in adults with T1DM consisting of a 26-week main period (Trial 3585) with a 26-week extension period (Trial 3725). Trials 3561 and 3585/3725 are similar in terms of treatment regimen (basal-bolus), investigational products (insulin degludec [IDeg] and IDet) and participating regions, thus allowing for an evaluation of the difference in efficacy and safety between children/adolescents and adults with T1DM.

To support an extrapolation from adults with T2DM to children and adolescents with T2DM, a subpopulation of adult subjects was defined which most closely resembles young people with T2DM, the majority of whom are obese. Insulin and metformin are currently the only antidiabetic drugs approved for this population in most countries. Therefore, a subpopulation of adult subjects with T2DM was defined as those who were obese (BMI $\geq$ 30 kg/m2), insulin naïve and previously treated with metformin only. The trial that included the largest number of subjects fulfilling these criteria is a 26-week global pivotal trial in previously insulin naïve adults with T2DM (Trial 3785). In this trial, no active basal insulin comparator was given. Instead, IDet was given as basal insulin treatment in combination with metformin to both treatment groups; the only difference between the 2 groups being that subjects in 1 group received dietary consultation by a certified dietician. Subjects in the other group only received basic dietary advice at baseline (referred to as the Control group); see (Table 2–3). In this report, only results for the Control group are described as these data are considered to most closely resemble the daily life situation; however, results for both groups are provided. The results for this subpopulation in Trial 3785 together with the difference in the dose-response relationship between children/adolescents and adults with T1DM form the basis for the extrapolation of efficacy and safety to children/adolescents with T2DM.

In accordance with the primary objective of Trial 3561 in children and adolescents with T1DM, the efficacy evaluation will focus on the first 26 weeks of treatment. The results after 52 weeks of treatment (last observation carried forward [LOCF]) are presented to evaluate persistence of discussion on clinical pharmacology efficacy. The safety evaluation will comprise the full period in all trials (52 weeks in T1DM and 26 weeks in T2DM).

Table 2–2 Data from efficacy trials in T1DM

Trial (wks)	Trial description	Treatment combination	Subject pop.	No. of subjects randomised	Antidiabetic treatment at screening	Rand. (IDeg: IDet)	Stratification
Children and adolescents (10-17 years)* 3561 (26+26 wks)	IDeg OD vs. IDet OD/BID	+IAsp	Insulin treated	IDeg: 61* IDet: 66*	Any basal–bolus regimen	1:1	Age groups: 1-5, 6-11, 12-17 years
Adults 3585/3725 (26+26 wks)	IDeg OD vs. IDet OD/BID#	+IAsp	Insulin treated	IDeg: 303 IDet: 153	Any basal–bolus regimen	2:1	Region: Europe/Japan/ India/South America

A second IDet dose could be added after 8 weeks in case of inadequate glycaemic control
* Children and adolescents 10-17 years of age were a subpopulation in Trial 3561, which included children and adolescents from 1-17 years of age.
Abbreviations: BID = twice daily; OD = once daily; pop = population; rand. = randomisation; wks = weeks

Table 2–3 Data from efficacy trial in T2DM

Trial (wks)	Trial description	Treatment combination	Subject pop.	No. of subjects randomised	Antidiabetes treatment at screening	Rand. (Diet: Control)	Stratification
Adults (with a BMI ≥ 30 kg/m^2 and on metformin only)							
3785 (26 wks)	IDet 100 U/mL OD with dietary intervention (Diet) or IDet 100 U/mL OD without dietary intervention (Control)	+metformin	Insulin-naïve	Diet: 88* Control: 78*	metformin (mandatory) ±SU/glinide, ± α-GI, ±DPP-4I in any combination	1:1	BMI (kg/m^2): 25.0–29.9 30.0–34.9 35.0–39.9 40.0–45.0

* This is the subpopulation of subjects from Trial 3785 with a BMI ≥ 30 kg/m^2 and on metformin only.
Abbreviations: α-GI = α-glucosidase-inhibitor; BID = twice daily; DPP-4I = dipeptidyl peptidase-4 inhibitor; OD = once daily;pop. = population; rand. = randomisation; SU = sulphonylurea; wks = weeks

Dose-response analysis methodology

Two dose-response analyses of pre-breakfast SMPG vs. total daily IDet dose per kg body weight were performed: 1 for children/adolescents and adults with T1DM, and 1 for a selected subpopulation of adults with T2DM (subjects with BMI ≥ 30 kg/m2 and previously treated with metformin only). The overall objective of performing the 2 analyses was to extrapolate the dose-response relationship in adults with T2DM to children and adolescents with T2DM. In order to do this, the dose-response relationship in subjects with T1DM was first analysed with the aim of quantifying the difference between children/adolescents and adults. The estimated difference was subsequently applied to predict the dose-response relationship in children and adolescents with T2DM based on the estimated dose-response relationship from the analysis of the subpopulation of adults with T2DM. For the T1DM analysis, 26-week data from Trial 3561 and Trial 3585 was used. For the T2DM analysis, 26-week data from Trial 3785 was used.

SMPG sampling schedule and recording of dosing history

In all trials, SMPG measurements were performed by the subjects for 3 days prior to each dose titration, i.e., every week for 26 weeks, and for each of these SMPG values the subjects also recorded the basal insulin dose level on the previous day. A glucose meter and test strips calibrated to plasma values were used for the measurements. Therefore, all glucose measurements performed with drawn capillary blood were automatically calibrated to plasma equivalent glucose values.

Data files

The data files for the analyses were formatted according to the requirements of the nonlinear mixed-effects modelling (NONMEM) software based on source data sets in SAS format. The data files contained dosing information (dose amount), pre-breakfast SMPG measurements, and values of covariates to be investigated. For the statistical analyses of the efficacy and safety data from the trials, full analysis sets and safety analysis sets had been defined. For the present analyses, subjects in the safety analysis sets were included in the analysis population. Data records with missing SMPG values were excluded from the analyses. Data records with missing dosing history were also excluded.

Dose-response analyses

The first order conditional estimation method (FOCE) in NONMEM was used for the dose-response analyses. Discrimination between intermediate models was based on NONMEM's objective function value (OFV) as well as standard goodness-of-fit plots. In terms of OFV, changes in this value were assumed to be χ^2-distributed (for nested models), and criteria for inclusion/exclusion of covariate effects were defined accordingly (see below).

Structural models

Linear models with an intercept and a slope parameter were used to describe the relationship between the observed response (pre-breakfast SMPG) and the recorded dose of IDet. Given the large variability in pre-breakfast SMPG and the small changes in dose levels during the 26-weeks of treatment, particularly in Trials 3561 and 3585, it was not meaningful to use more complex models.

Variability and residual error models

Between-subject variability (normally distributed; without correlation between the parameters) was estimated for both the intercept and slope parameters in both analyses. Additive error models were used to describe the residual variability.

Covariate analyses

With the 'base' model in place, analyses of the influence of covariates on the intercept and slope parameters was carried out. A forward inclusion, backward elimination approach was applied, where the investigated covariates were included into the base model using forward inclusion with a p-value of 0.01 to yield a 'full' model. When no more significant effects could be found, the final model was developed using backward elimination with a p-value of 0.001.

T1DM model

For the T1DM analysis, the covariates investigated on the intercept parameter were age group, BMI category, gender, region and dosing regimen. For the slope parameter, only the effect of age group was investigated. The covariate effects were included into the base model using the following parameterisations:

$$\text{Intercept}_i = TV\text{Intercept} + E_{age,\text{Intercept}} + E_{BMI} + E_{gender} + E_{region} + E_{dosing} + \eta_{i,\text{Intercept}}$$

$$E_{age,\text{Intercept}} = \text{Adolescents} \cdot \theta_{\text{Adolescents, Intercept}}$$
$$E_{BMI} = (\text{Less than} -1) \cdot \theta_{\text{Less than -1}} + (\text{Greater than} +1) \cdot \theta_{\text{Greater than +1}}$$
$$E_{gender} = \text{Male} \cdot \theta_{\text{Male}}$$
$$E_{region} = \text{Japan} \cdot \theta_{\text{Japan}} + \text{USA} \cdot \theta_{\text{USA}} + \text{Other} \cdot \theta_{\text{Other}}$$
$$E_{dosing} = \text{BID} \cdot \theta_{\text{BID}} + \text{Switching} \cdot \theta_{\text{Switching}}$$

$$\text{Slope}_i = TV\text{Slope} + E_{age,\text{Slope}} + \eta_{i,\text{Slope}}$$

$$E_{age,\text{Slope}} = \text{Adolescents} \cdot \theta_{\text{Adolescent, Slope}}$$

where typical value (TV) Intercept and TVSlope are the intercept and slope for a hypothetical reference subject, defined as a European, female, adult with a BMI z-score between -1 and +1 using an OD dosing regimen. 'Adolescents', 'Less than -1', 'Greater than +1', 'Male', 'Japan', 'USA', 'Other', 'BID' and 'Switching' are indicator variables for covariate categories. The θ values are the parameters estimated in the model.

T2DM model

For the T2DM analysis, only the effects of gender and region on intercept were investigated. Further stratification by age group or BMI category was not expected to improve the outcome of the analysis, given the stratification already applied by using a selected subpopulation (adult subjects with BMI ≥ 30 kg/m2 and previously treated with metformin only). The covariate effects were included into the base model using the following parameterisation:

$$\text{Intercept}_i = TV\text{Intercept} + E_{gender} + E_{region} + \eta_{i,\text{Intercept}}$$

$$E_{gender} = \text{Male} \cdot \theta_{\text{Male}}$$
$$E_{region} = \text{USA} \cdot \theta_{\text{USA}} + \text{Other} \cdot \theta_{\text{Other}}$$

where TVIntercept is the intercept for a hypothetical reference subject, defined as a European female. 'Male', 'USA', and 'Other' are indicator variables for covariate categories. The θ values are the parameters estimated in the model.

Prediction of dose-response in children and adolescents with T2DM

In order to predict the dose-response relationship for pre-breakfast SMPG in children and adolescents with T2DM, the estimated effects of age group on the intercept and slope parameters in the T1DM model, if statistically significant, were subsequently applied within the T2DM model.

Summary of dose-response analysis assumptions

- All missing data (dosing history and pre-breakfast SMPG) was assumed to be missing at random and not confounded with response level.
- Linear models with an intercept and a slope parameter were used to describe the relationship between dose and response (pre-breakfast SMPG). This was justified by the large variability in pre-breakfast SMPG and the small changes in dose levels during the 26-weeks of treatment, which precluded development of a more complex model.
- Between-subject variability for the intercept and slope parameters in the model was assumed to be normally distributed and uncorrelated. Residual variability was assumed to follow an additive error model. Both of these distributional assumptions were justified by reasonable standard goodness-of-fit plots.

Clinical data (qualitative extrapolation)

Endpoints

A number of key efficacy and safety endpoints were defined for the qualitative extrapolation to facilitate comparisons between the children/adolescent and adult populations:

- Efficacy: HbA_{1c}, FPG, basal insulin dose and bolus insulin dose (T1DM only)
- Safety: Hypoglycaemic episodes and AEs

For efficacy, the primary focus is after 26-weeks of treatment, to allow evaluation of consistency with the 26-week dose-response analyses. Safety is evaluated across the entire treatment periods in the trials (52 weeks in T1DM and 26 weeks in T2DM).

Titration

Insulin dosing guidelines were developed to ensure uniformity between trials and trial sites. Doses were adjusted individually based on SMPG measurements taking into consideration factors such as diet, activity level and hypoglycaemic episodes to achieve glycaemic targets. To optimise and maintain glycaemic control, the investigators were in weekly contact with subjects during the course of the main trials to discuss glycaemic control and hypoglycaemic episodes, and to assist the subjects in adjusting insulin doses. All insulin dose adjustments were done at the discretion of the investigators.

Basal insulin titration

Trials in adult subjects with T1DM or T2DM

For the trials in adults included in this report, the basal insulin dose was to be increased based on the mean of 3 pre-breakfast SMPG values measured on the 3 days prior to visit/phone contacts in OD regimens with IDet or IDeg. In the adult T1DM trial, IDet was allowed to be given either OD or twice-daily (BID). For the IDet BID regimen, the evening dose was to be increased as in the OD regimens, while the morning dose was to be increased based on the mean of 3 pre-dinner SMPG values measured on the 3 days prior to visit/phone contacts. The pre-breakfast SMPG target was 3.9 to <5.0 mmol/L (70 to <90 mg/dL) in T1DM trials and 4.0 to ≤ 5.0 mmol/L (71 to ≤ 90 mg/dL) in the T2DM trial. Doses were to be decreased if any of the pre-meal SMPG values were below target:

Table 2–4 Adjustment of basal insulin doses – adult subjects with T1DM

Pre-breakfast or pre-dinner SMPG		Dose Adjustment
mmol/L	mg/dL	
<3.1	<56	Decrease by 4 U
<3.9	<70	Decrease by 2 U
<5.0	<90	*No adjustment*
<10.0	<180	Increase by 2 U
<15.0	<270	Increase by 4 U
≥15.0	≥270	Increase by 6 U

Guidelines are both for IDet and IDeg; applies to Trial 3585/3725

Abbreviations: SMPG = self-measured plasma glucose

Table 2–5 Adjustment of basal insulin doses – adult subjects with T2DM

Pre-breakfast SMPG		Dose Adjustment
mmol/L	mg/dL	
<3.9	<70	Decrease by 3 U
4.0-5.0	71-90	*No adjustment*
>5.0	>90	Increase by 3 U

Applies to Trial 3785.

Abbreviations: SMPG = self-measured plasma glucose

Trial in children and adolescents with T1DM

The basal insulin dose was to be titrated based on the lowest of 3 pre-breakfast SMPG values measured on the 3 days prior to visit/phone contacts in OD regimens with IDet or IDeg. IDet was allowed to be given OD or BID. For the BID regimen, the evening dose was to be increased as in the OD regimens, while the morning dose was to be adjusted based on the lowest of 3 pre-dinner SMPG values measured on the 3 days prior to visit/phone contacts. The pre-specified target ranges were adopted from the International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines. The pre-breakfast SMPG target was 5.0 to ≤ 8.0 mmol/L (90-145 mg/dL). Doses were to be decreased if any of the pre-meal SMPG values were below target:

Table 2–6 Adjustment of basal insulin doses – children and adolescents with T1DM

Current dose		< 5 U	5-15 U	> 15 U
Pre-breakfast or pre-dinner plasma glucose		Adjustment (U)		
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

Bolus insulin titration

Trials in adult subjects with T1DM

Adjustment of the insulin aspart (IAsp) dose was done based on the mean pre-prandial plasma glucose:

Table 2–7 Adjustment of IAsp doses, adults

Pre-prandial plasma glucose		Adjustment (U)
mmol/l	mg/dl	
< 5.0	< 90	0
< 8.0	< 144	+2
< 10.0	< 180	+3
≥ 10.0	≥ 180	+4

IAsp titration was done once-weekly based on the mean of 3 SMPG values measured prior to the next meal and bedtime on the 3 days prior to visits/phone contacts:

- If the subject ate breakfast, the pre-breakfast IAsp dose was to be titrated according to the mean pre-lunch plasma glucose.
- If the subject ate lunch the pre-lunch IAsp dose was to be titrated according to the mean pre-dinner plasma glucose.
- If the subject ate dinner, the pre-dinner IAsp dose was to be titrated according to the mean bedtime plasma glucose.
- The subjects were allowed to inject an additional bolus dose of IAsp in order to cover an additional main meal.

Trial in children and adolescent subjects with T1DM

IAsp was adjusted according to a sliding scale (see Table 2–8) or following the principles of flexible dosing as described below. The total dose could be divided into 2–4 daily doses.

When using the sliding scale, IAsp titration was done once weekly based on the lowest of 3 SMPG values measured prior to the next meal and bedtime on the 3 days prior to visit/phone contacts:

- 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 2–8 Adjustment of IAsp doses, children and adolescents

Current bolus dose		≤ 5 U	> 5 U
Lowest pre-meal or bedtime plasma glucose		Adjustment (U)	
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

Alternatively, IAsp doses could be adjusted according to the principles of flexible dosing whereby the meal carbohydrate content and pre-prandial plasma glucose value are used to determine bolus insulin doses. Using this method, bolus insulin dose adjustments are conducted multiple times daily in accordance with the insulin:carbohydrate ratio and the plasma glucose correction factor.

Hypoglycaemia

Classification

Hypoglycaemic episodes were classified according to the ADA definition for adults and according to the ISPAD definition for children and adolescents. In this report, the focus is on severe and confirmed hypoglycaemic episodes, overall and during the night (nocturnal), as defined below.

Severe hypoglycaemia

The definition of severe hypoglycaemia differed between the adult trials and the paediatric trial:

- **Adults - Severe hypoglycaemia (ADA):** An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- **Children and adolescents - Severe hypoglycaemia (ISPAD):** 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).

For children and adolescents, the ISPAD definition contains a criterion that could be considered subjective in the sense that it relies on the parents' evaluation of the mental status of the child/adolescent.

Confirmed hypoglycaemia

In normal physiology, symptoms of hypoglycaemia occur at a blood glucose level of approximately < 2.8 mmol/L (50 mg/dL) or plasma glucose level < 3.1 mmol/L (56 mg/dL). Therefore, the MAH has used this cut-off value to define confirmed hypoglycaemia. A confirmed hypoglycaemic episode is defined as:

- An episode with symptoms consistent with hypoglycaemia with confirmation by plasma glucose < 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 value < 3.1 mmol/L (56 mg/dL) or full blood glucose value < 2.8 mmol/L (50 mg/dL).
- Or severe hypoglycaemia.

In Trial 3785 (T2DM), 'confirmed hypoglycaemic episodes' corresponds to the pool of 'minor and severe hypoglycaemic episodes' where 'minor hypoglycaemic episodes' are defined as the 2 first bullets above.

Nocturnal hypoglycaemia

In the adult trials, the nocturnal period has been defined as episodes occurring between 00:01 and 05:59 (both included). For children and adolescents, nocturnal hypoglycaemia was defined as episodes occurring between 23:00 and 07:00 (both included; as agreed with the PDCO). A wider time interval for the nocturnal period in the paediatric trial was defined to reflect the wide range of ages included in the paediatric trial.

Results in T1DM

Dose-response analysis results in T1DM

Analysis data for the T1DM dose-response analysis

The data set for the T1DM dose-response analysis comprised a total of 17,703 SMPG records from 243 subjects treated with IDet. An additional 1,826 SMPG records were available but had to be excluded because appropriate dosing information was not available. One subject was excluded from the analysis on this account. Summaries of characteristics for the subjects in the data set are shown in Table 3–1 (gender, race, ethnicity and country):

Table 3–1 Summary of subject characteristics for the data included in the T1DM dose-response analysis (categorical variables)

Covariate	Category	Children & adolescents (Trial 3561) N (%)	Adults (Trial 3585) N (%)	Total N (%)
Gender	Female	34 (37)	67 (44)	101 (42)
	Male	57 (63)	85 (56)	142 (58)
Race	Asian Indian	-	20 (13)	20 (8)
	Asian Non-Indian	23 (25)	61 (40)	84 (35)
	Black or African American	4 (4)	-	4 (2)
	Missing	3 (3)	-	3 (1)
	Other	2 (2)	1 (1)	3 (1)
	White	59 (65)	70 (46)	129 (53)
Ethnicity	Hispanic or Latino	2 (2)	8 (5)	10 (4)
	Not Hispanic or Latino	89 (98)	144 (95)	233 (96)
Country	Bulgaria	5 (5)	-	5 (2)
	Brazil	-	8 (5)	8 (3)
	Germany	6 (7)	-	6 (2)
	Finland	4 (4)	15 (10)	19 (8)
	France	3 (3)	-	3 (1)
	Great Britain	3 (3)	24 (16)	27 (11)
	India	-	20 (13)	20 (8)
	Italy	2 (2)	12 (8)	14 (6)
	Japan	23 (25)	61 (40)	84 (35)
	Macedonia	3 (3)	12 (8)	15 (6)
	Netherlands	5 (5)	-	5 (2)
	Russia	9 (10)	-	9 (4)
	USA	28 (31)	-	28 (12)
Total		91 (37)	152 (63)	243 (100)

Abbreviations: N: Number of subjects

Table 3–2 (age, body weight, and BMI):

Table 3–2 Summary of subject characteristics for the data included in the T1DM dose-response analysis (continuous variables)

	Children and adolescents (Trial 3561)	Adults (Trial 3585)	Total
	Mean (SD) [Range]	Mean (SD) [Range]	Mean (SD) [Range]
N	91	152	243
Age (years)	13.6 (2.2) [10.0-17.7]	41.7 (14.5) [18.2-80.9]	31.1 (17.8) [10.0-80.9]
Body weight (kg)	51.5 (15.4) [25.6-95.5]	66.8 (13.4) [39.1-97.7]	61.0 (16.0) [25.6-97.7]
BMI (kg/m^2)	20.4 (3.6) [14.3-30.5]	23.7 (3.4) [16.1-33.0]	22.5 (3.8) [14.3-33.0]
BMI z-score (-)	0.41 (0.98) [-2.26-2.60]	0.46 (0.99) [-2.35-2.55]	0.44 (0.99) [-2.35-2.60]

Abbreviations: N: Number of subjects

The country/region distribution was different in the adult subpopulation (from Trial 3585) compared to the child and adolescent subpopulation (from Trial 3561), but this was considered acceptable, as region was investigated as a covariate in the analysis. The mean BMI z-score calculated based on the WHO reference population13,14 was 0.44 ranging from -2.35 to 2.60, indicating a higher BMI in the present analysis population as compared to the WHO reference population. In order to account for this right-shift of the BMI z-score distribution in the covariate analysis, and to ensure appropriately sized groups when applying the planned splits between groups at BMI z-scores of -1 and 1, all BMI z-scores were adjusted by subtracting 0.5 before dividing the subjects into BMI categories.

Graphical analysis of the T1DM dose-response data

A graphical data analysis was conducted prior to performing the T1DM dose-response analysis in order to explore trends in the data across covariates and hence obtain initial indications of relevant covariate effects. The graphical data analysis comprised plots of geometric mean and 95% CI for pre-breakfast SMPG stratified by age group (children/adolescents and adults) and plotted vs. week no., vs. IDet dose, and vs. IDet dose further stratified by:

- BMI z-score treated as a categorical covariate (less than -1/-1 to +1/greater than +1).
- Gender (Male/Female).
- Region (Europe, Japan, USA, Other).
- Dosing regimen (OD, BID, Switching).

To ensure that the graphical data analysis would be maximally informative about the dose-response relationship, the doses for each subject were adjusted by first subtracting the median dose for that subject and then adding the median dose for all subjects in the analysis population. This was necessary, because IDet was titrated individually towards a common plasma glucose target. The amount of IDet required to achieve glycaemic control in a given subject reflects that individual subject's insulin sensitivity and lifestyle in terms of physical activity and nutritional habits, and this amount varies between subjects. When a population of subjects requiring such varying amounts are titrated towards a common plasma glucose target, and when the changes in dose levels are small, a plot of response vs. dose in the population may result in a flat curve, even though there is a clear dose-response relationship for each of the subjects. By applying the dose adjustment, the flat curve is avoided, as the resulting plots show the dose-response relationship for a typical subject.

For both subpopulations, pre-breakfast SMPG values were relatively stable throughout the 26-weeks of treatment, and mean SMPG was approximately 8 mmol/L for the children and adolescents and approximately 6 mmol/L for the adults. As expected, there was an overall decreasing trend in SMPG with increasing IDet dose, although there seemed to be a slight increase at the high end of the dose range. This may be due to the contribution of subjects switching from OD to BID dosing during the trials. These subjects are likely to be more insulin-resistant and therefore have higher pre-breakfast SMPG than the subjects who did not switch, and they will tend to contribute more at the high end of the dose range.

No obvious effects of BMI z-score, gender, region or dosing regimen were observed for SMPG vs. IDet dose in any of the age groups.

T1DM dose-response analysis

The model used for the dose-response analysis was developed in three steps: first a 'base' model without covariates was estimated; next a 'full' model including all covariate effects significant on a 1% level ($p<0.01$) was developed. Finally, the full model was reduced to the final model by excluding all covariate effects not significant on a 0.1% level ($p>0.001$).

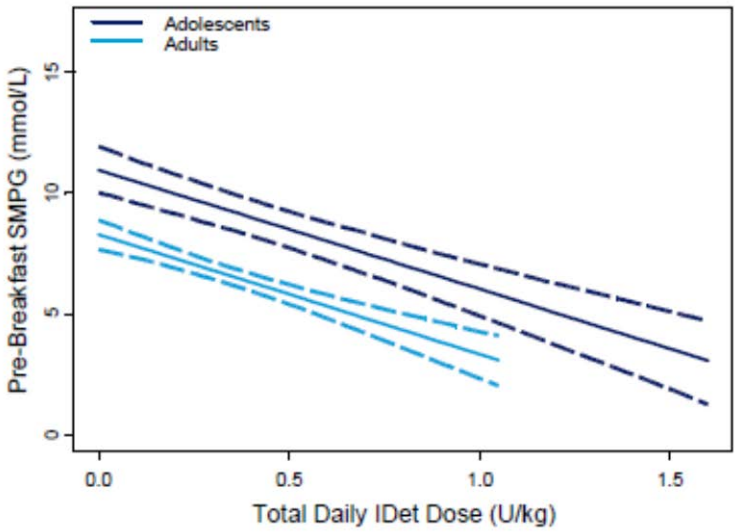
The base model was a linear model with an intercept and a slope parameter relating pre-breakfast SMPG to IDet dose per kg body weight. The model was implemented in such a way that the intercept corresponds to a dose of 0.4 U/kg – a value chosen because it is close to the average basal insulin dose level in adults after 26-weeks of treatment (Table 3–3). Given the large variability in pre-breakfast SMPG and the small changes in dose levels during the 26-weeks of treatment, it was not meaningful to use a more complex model. The estimated slope was negative (-4.7 (mmol/L)/(U/kg)) and statistically significantly different from 0 (CI: [-6.2;-3.2] (mmol/L)/(U/kg)), indicating a clear dose-response relationship with decreasing SMPG with increasing dose for the individual subjects.

During the forward inclusion procedure, age group, dosing regimen and BMI category were identified as covariates for intercept and included in the full model. Gender and region were not significant covariates for intercept and age group was not a significant covariate for slope. During the backward elimination procedure, BMI category was excluded as a covariate for intercept again.

As a result, the final model included age group and dosing regimen as covariates for intercept. Given the relatively small changes in the individual IDet dose levels during the 26-weeks of treatment and the large variability in pre-breakfast SMPG, the model fit was considered acceptable.

There were no critical trends in the weighted residuals vs. SMPG or IDet dose, and the individual intercept and slope estimates appeared to follow a normal distribution. The outcome of the covariate analysis was in accordance with the graphical analysis of the dose-response data, which showed a clear difference in SMPG level between children/adolescents and adults, but no obvious effects of BMI category, gender and region. The graphical analysis showed a less clear trend towards lower SMPG in subjects using an OD dosing regimen, compared to subjects using a BID dosing regimen or subjects switching from OD to BID, but the effect was nevertheless significant in the covariate analysis.

The estimated dose-response relationships are presented in Figure 3–1, which shows that adults typically obtain a 2.7 mmol/L lower pre-breakfast SMPG than children and adolescents at comparable dose levels. Figure 3–1 also shows a typical decrease in pre-breakfast SMPG of approximately 0.5 mmol/L, when the IDet dose is increased by 0.1 U/kg, regardless of age group.



Data is median with 95% CI obtained from the final dose-response model. The median lines have been shown for dose ranges going from zero to dose levels corresponding to a pre-breakfast SMPG value of 3.1 mmol/L. Further extrapolation is not supported by the model. The term 'adolescent' applies to subjects aged 10–17 years.

Abbreviations: SMPG = self-measured plasma glucose

Figure 3–1 Model derived dose-response relationships for a typical adolescent and a typical adult with T1DM

Clinical data in T1DM

Efficacy in T1DM

A dose-response relationship could be established for both age groups (children/adolescents and adults) based on data from clinical trials in T1DM. The results showed that adults typically obtain a lower pre-breakfast SMPG than children and adolescents at comparable dose levels. In other words, children and adolescents would need higher doses to obtain the same level of glycaemic control as adults. Higher basal insulin dose requirements in children/adolescents compared to adults is consistent with the physiologic increase in insulin resistance associated with puberty.

Key endpoints after 26-weeks of treatment from efficacy and safety trials in children and adolescents (Trial 3561) and adults (Trial 3585) confirmed this finding. After 26-weeks of treatment, the mean IDet basal dose was higher in children and adolescents than adults (0.59 vs. 0.41 U/kg); however the mean bolus dose tended to be lower (0.60 vs. 0.64 U/kg) (Table 3–3).

HbA_{1c} levels were higher in children and adolescents than adults (7.8% vs. 7.3%) with IDet after 26-weeks of treatment, but FPG levels were lower (7.9 vs. 9.1 mmol/L) (Table 3–3).

This pattern persisted through the extension period in both trials and the results obtained after 52 weeks of treatment were similar to those after 26-weeks of treatments, except for FPG where the level was higher in children and adolescents than adults (9.0 vs. 8.7 mmol/L) (Table 3–3).

For the extension trial set (i.e., only including subjects entering the extension period), similar results were obtained. Within each trial, the treatment arms were well-matched in terms of demographics and baseline diabetes characteristics. Apart from the dose-response differences, the higher absolute HbA_{1c} levels observed in children and adolescents as compared with adults may also reflect the different titration targets between the 2 groups. As seen with HbA_{1c}, the FPG levels were also higher in children and adolescents compared with adults after 52 weeks of treatment (9.0 vs. 8.7 mmol/L); however, the FPG level was lower after 26-weeks of treatment (7.9 vs. 9.1 mmol/L).

Overall, these results support that children and adolescents need higher doses of IDet than adults to obtain good glycaemic control.

Table 3–3 Efficacy and dose results – T1DM

	Children and adolescents (3561)		Adults (3585/3725)	
	IDeg+IAsp	IDet OD/BID+IAsp	IDeg+IAsp	IDet OD/BID[2]+IAsp
Safety analysis set (N)	88	92	301	152
Basal dose – Week 1	0.43 (0.17)	0.44 (0.20)	0.33 (0.16)	0.32 (0.16)
Basal dose (U/kg) – Week 26	0.44 (0.15)	0.59 (0.30)	0.35 (0.19)	0.41 (0.25)
Basal dose (U/kg) – Week 52[1]	0.45 (0.15)	0.63 (0.35)	N/A	N/A
Basal dose (U/kg) – Week 53[1]	N/A	N/A	0.36 (0.19)	0.44 (0.27)
Bolus dose (U/kg) – Week 1	0.56 (0.22)	0.54 (0.22)	0.42 (0.21)	0.46 (0.22)
Bolus dose (U/kg) – Week 26	0.58 (0.23)	0.60 (0.26)	0.54 (0.40)	0.64 (0.40)
Bolus dose (U/kg) – Week 52[1]	0.63 (0.29)	0.63 (0.25)		
Bolus dose (U/kg) – Week 53[1]	N/A	N/A	0.55 (0.41)	0.63 (0.41)
Full analysis set (N)	88	92	302	153
FPG (mmol/L) – Week 0	8.3 (5.3)	8.4 (4.7)	9.9 (4.0)	9.5 (4.0)
FPG (mmol/L) – Week 26	7.9 (3.9)	7.9 (3.9)	7.1 (3.1)	9.1 (4.1)
FPG (mmol/L) – Week 52[1]	7.5 (4.5)	9.0 (5.0)	N/A	N/A
FPG (mmol/L) – Week 53[1]	N/A	N/A	7.7 (3.6)	8.7 (3.8)
HbA_{1c} (%) – Week 0	8.3 (1.2)	8.2 (1.1)	8.0 (1.0)	8.0 (0.9)
HbA_{1c} (%) – Week 26	8.1 (1.3)	7.8 (1.0)	7.2 (1.0)	7.3 (0.8)
HbA_{1c} (%) – Week 52[1]	7.9 (1.2)	7.9 (1.3)	N/A	N/A
HbA_{1c} (%) – Week 53[1]	N/A	N/A	7.5 (1.1)	7.5 (0.9)

Based on safety analysis set for bolus and basal dose results and full analysis set (FAS) for HbA_{1c} and FPG results.

Dose, FPG and HbA_{1c} are given as mean values and standard deviations are in brackets.

[1] Results for Weeks 52 and 53 are LOCF. For Trial 3585/3725, Week 53 corresponds to 52 weeks of treatment, due to the 1 week wash out period from Weeks 26 to 27.

[2] A second IDet dose could be added after 8 weeks in case of inadequate glycaemic control.

Abbreviations: LOCF = last observation carried forward; N = Number of subjects; N/A = not applicable (not measured).

Hypoglycaemia in T1DM

Confirmed and severe hypoglycaemic episodes are summarised by classification for children and adolescents in Table 3–4 and for adults in Table 3–5.

The rate of confirmed hypoglycaemic episodes for IDet was higher in children and adolescents compared to adults after 52 weeks of treatment (5,547 vs. 3,926 episodes per 100 PYE). This was also observed for IDeg (4,827 vs. 3,778 episodes per 100 PYE; see Table 3–4 and Table 3–5). This difference in rates between the age groups is likely due to the elevated insulin resistance during puberty and irregular or inconsistent exercise and eating habits amongst adolescents.

Few of the hypoglycaemic episodes were severe with comparable rates between children and adolescents and adults with both treatments (29 vs. 28 episodes per 100 PYE for IDet; 42 vs. 23 episodes per 100 PYE for IDeg).

For the extension trial set (i.e., only including subjects that continued in the extension period), the rates of hypoglycaemia tended to be lower than for the safety analysis set (i.e., all subjects exposed), but the between treatment pattern was similar for children and adolescents and adults.

Table 3–4 Hypoglycaemic episodes – children and adolescents (10–17 years) with T1DM – Trial 3561

	IDeg OD				IDet			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	88				92			
Confirmed	87	(98.9)	3983	4827	87	(94.6)	4279	5547
ISPAD Severe	14	(15.9)	35	42	11	(12.0)	22	29

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

Table 3–5 Hypoglycaemic episodes – adults with T1DM – Trial 3585/3725

	IDeg OD				IDet			
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	301				152			
Confirmed	285	(94.7)	10326	3778	141	(92.8)	5269	3926
ADA Severe	42	(14.0)	63	23	18	(11.8)	37	28

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

Nocturnal hypoglycaemic episodes are summarised by classification for children and adolescents in Table 3–6 and for adults in Table 3–7.

The rate of nocturnal confirmed hypoglycaemic episodes was higher for children and adolescents than adults treated with IDet during 52 weeks of treatment (1,049 vs. 481 episodes per 100 PYE).

This was also observed in the IDeg treatment groups (680 vs. 338 episodes per 100 PYE). The low number of severe nocturnal hypoglycaemic episodes makes comparison difficult, but there was no apparent difference between treatments for either age group (Table 3–6 and Table 3–7).

For nocturnal confirmed hypoglycaemic episodes, similar results were obtained with the extension trial set (i.e., only including subjects that continued in the extension period).

Table 3–6 Nocturnal hypoglycaemic episodes – children and adolescents (10–17 years) with T1DM - Trial 3561

	IDeg OD N	(%)	E	R	IDet N	(%)	E	R
Number of Subjects	88				92			
Confirmed	77	(87.5)	561	680	71	(77.2)	809	1049
ISPAD Severe	5	(5.7)	11	13	6	(6.5)	6	8

N: Number of subjects
%: Percentage of subjects with the event
E: Number of events,
R: Event rate per 100 patient year(s) of exposure
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 (56 mg/dL)
Nocturnal period: the period between 23:00 p.m. and 07:00 a.m. (both included)

Cross reference: modified from Appendix B Table 28

Table 3–7 Nocturnal hypoglycaemic episodes – adults with T1DM - Trial 3585/3725

	IDeg OD N	(%)	E	R	IDet N	(%)	E	R
Number of Subjects	301				152			
Confirmed	205	(68.1)	924	338	98	(64.5)	646	481
ADA Severe	16	(5.3)	18	7	6	(3.9)	7	5

N: Number of Subjects
%: Percentage of Subjects with the Event
E: Number of Events
R: Event Rate per 100 Patient Year(s) of Exposure
Confirmed hypoglycaemia: subject unable to treat himself/herself and/or have a recorded PG < 3.1 mmol/L (56 mg/dL)
Nocturnal period: the period between 00:01 and 05:59 a.m. (both included).

Cross reference: modified from Appendix B Table 71

Adverse events in T1DM

AEs for T1DM are summarised in Table 3–8 for children and adolescents and in Table 3–9 for adults. The rate of AEs was higher in children and adolescents than in adults (839 events per 100 PYE vs. 420). Most of the events were non-serious, of mild severity and considered unlikely related to IDet (Table 3–8, Table 3–9). A higher rate of AEs for children and adolescents compared to adults was also observed for the IDeg treatment groups. This rate differential may be attributable to the particular physiological and psychosocial changes experienced during adolescence.3

The most frequently reported AEs by preferred term (>20 events per 100 PYE in the IDet treatment group) were comparable between children/adolescents and adults. Headache, nasopharyngitis, oropharyngeal pain, upper respiratory tract infection, vomiting, upper abdominal pain, blood ketone body increased, and hypoglycaemia were most frequently reported in children and adolescents. In adults, nasopharyngitis, upper respiratory tract infection, headache and hypoglycaemia were the most frequently reported AEs. The separate reporting of hyperglycaemia and measurement of capillary blood ketone levels when plasma glucose exceeded 14.0 mmol/L (250 mg/dL) was specific for the trial in children and adolescents.

None of the ‘blood ketone body increased’ events were reported as serious.

Table 3–8 Adverse events – treatment emergent – summary – children and adolescents (10–17 years) with T1DM - safety analysis set – Trial 3561

	IDeg OD				IDet				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	88				92				180			
Events	83	(94.3)	643	779	85	(92.4)	647	839	168	(93.3)	1290	808
Serious												
Yes	8	(9.1)	10	12	5	(5.4)	5	6	13	(7.2)	15	9
No	83	(94.3)	633	767	85	(92.4)	642	832	168	(93.3)	1275	799
Severity												
Severe	13	(14.8)	19	23	5	(5.4)	12	16	18	(10.0)	31	19
Moderate	32	(36.4)	80	97	24	(26.1)	69	89	56	(31.1)	149	93
Mild	82	(93.2)	544	659	84	(91.3)	565	732	166	(92.2)	1109	695

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.

Cross reference: modified from Appendix B Table 23

Table 3–9 Adverse events – treatment emergent - summary – adults with T1DM - safety analysis set - Trial 3585/3725

	IDeg OD				IDet				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	301				152				453			
Events	248	(82.4)	1255	459	118	(77.6)	564	420	366	(80.8)	1819	446
Serious												
Yes	36	(12.0)	54	20	11	(7.2)	23	17	47	(10.4)	77	19
No	244	(81.1)	1201	439	118	(77.6)	541	403	362	(79.9)	1742	427
Severity												
Severe	42	(14.0)	64	23	20	(13.2)	47	35	62	(13.7)	111	27
Moderate	65	(21.6)	131	48	34	(22.4)	60	45	99	(21.9)	191	47
Mild	234	(77.7)	1060	388	112	(73.7)	457	341	346	(76.4)	1517	372

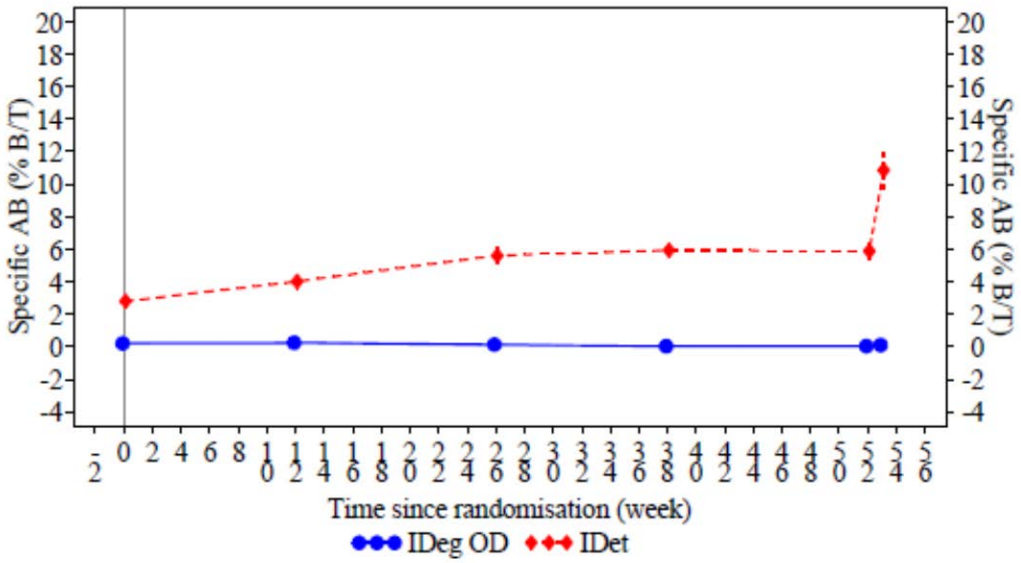
N= Number of Subjects
%= Percentage of Subjects
E= Number of Events
R= Event Rate per 100 Patient Years of Exposure

Cross reference: modified from Appendix B Table 66

Antibodies in T1DM

Antibody levels were measured before, during and after treatment in children/adolescents and in adults with T1DM. Since the investigational product may interfere with the antibody analyses, a 1-week washout period (where investigational product was discontinued and replaced with NPH insulin) was included after end of treatment in both age groups and after 26-weeks of treatment in adults, to improve antibody detection.

For subjects completing the extension period, the level of IDet specific antibodies remained low during treatment in children/adolescents and adults (Figure 3–2 and Figure 3–3). The increase after end of treatment in both age groups and at Week 27 and Week 54 in adults was due to the improved detection of antibodies after a washout period. For all children/adolescent subjects exposed to IDet (safety analysis set), an increase similar to that in adults was seen at Week 27, due to the washout period for subjects only completing the first 26-weeks of treatment.



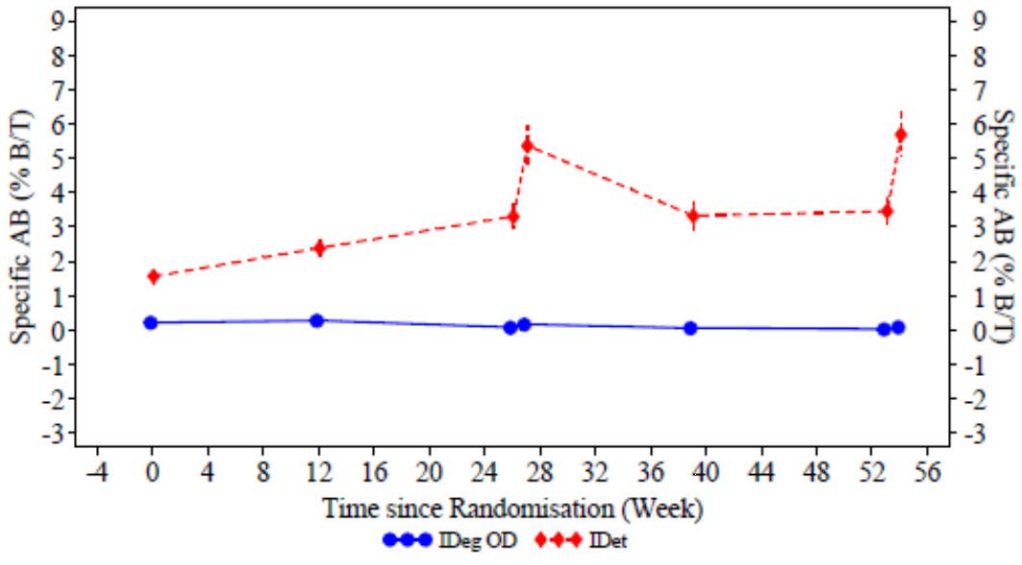
Cross-reference: Appendix B Figure 39

EXT LOCF imputed data

Error bars: +-Standard error (mean)

Abbreviations: LOCF = last observation carried forward; %B/T = antibody binding (% bound/total radioactivity)

Figure 3–2 Insulin Degludec/Detemir specific antibodies (% B/T) – mean plot – children and adolescents (10–17 years) – extension trial set – Trial 3561



Cross-reference: Appendix B Figure 81

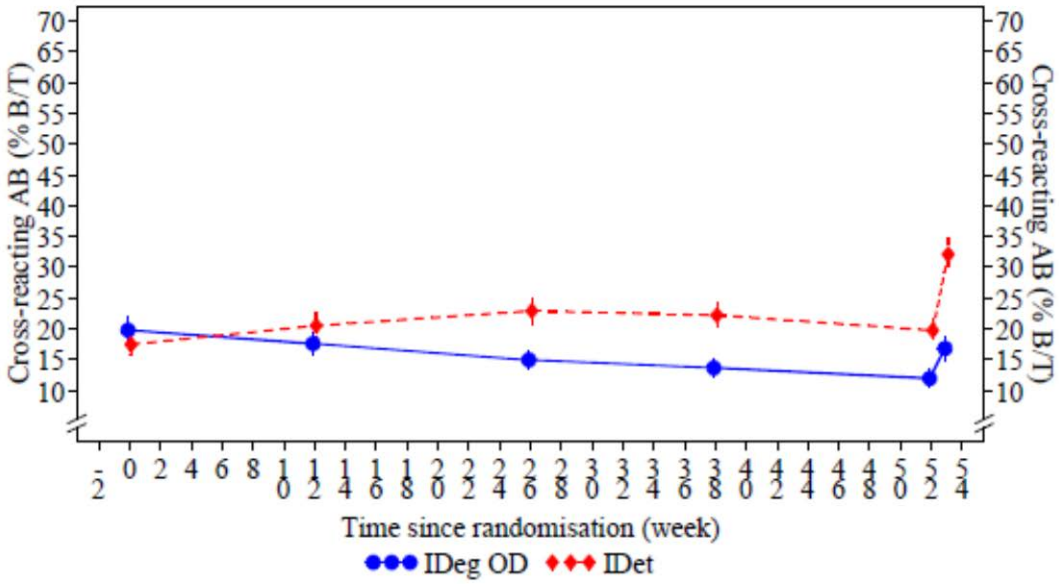
EXT LOCF imputed data

Error bars: +-Standard error (mean)

Abbreviations: LOCF = last observation carried forward; %B/T = antibody binding (% bound/total radioactivity)

Figure 3–3 Insulin Degludec/Detemir specific antibodies (% B/T) – mean plot – adults – extension trial set – Trial 3585/3725

The pattern of cross-reacting insulin antibodies in children and adolescents followed that observed in adults (Figure 3–4, Figure 3–5), except for the increase at Week 27 in adults (due to the washout period during treatment). A similar increase was seen for the safety analysis set in children and adolescents, due to the washout period for subjects only completing the first 26 weeks of treatment. In both age groups, the level of cross-reacting insulin antibodies increased slightly during treatment.



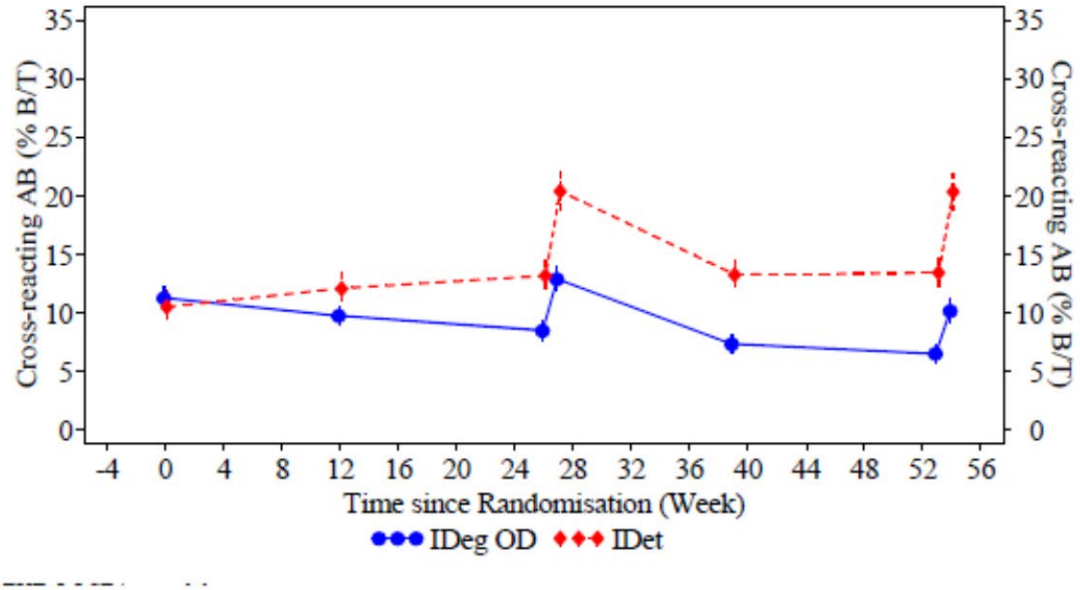
Cross-reference: Appendix B Figure 43

EXT LOCF imputed data

Error bars: +-Standard error (mean)

Abbreviations: LOCF = last observation carried forward; %B/T = antibody binding (% bound/total radioactivity)

Figure 3–4 Cross-reacting antibodies to human insulin (% B/T) – mean plot – children and adolescents (10-17 years) – extension trial set – Trial 3561



Cross-reference: Appendix B Figure 85

EXT LOCF imputed data

Error bars: +-Standard error (mean)

Abbreviations: LOCF = last observation carried forward; %B/T = antibody binding (% bound/total radioactivity)

Figure 3–5 Cross-reacting antibodies to human insulin (% B/T) – mean plot adults – extension trial set – Trial 3585/3725

For both age groups, the levels of antibodies specific to IAsp remained low in both of the IDet and IDeg treatment groups. Accordingly, the pattern of total insulin antibodies (specific antibodies + cross-reacting antibodies) resembled that of the cross-reacting antibodies due to the low levels of specific antibodies.

Results in T2DM

Dose-response analysis results in T2DM

Analysis data for the T2DM dose-response analysis

The data set for the T2DM dose-response analysis comprised a total of 4,776 SMPG records from 73 subjects treated with IDet. One additional SMPG record was available, but had to be excluded because appropriate dosing information was not available. No subjects were excluded from the analysis. Summaries of characteristics for the subjects in the data set are shown in Table 4–1 (gender, race, ethnicity and country) and Table 4–2 (age, body weight, and BMI).

Table 4–1 Summary of subject characteristics for the data included in the T2DM dose-response analysis (categorical variables) (BMI ≥ 30 kg/m^2 on metformin only)

Covariate	Category	N (%)
Gender	Female	38 (52)
	Male	35 (48)
Race	Asian Non-Indian	1 (1)
	Black or African American	7 (10)
	White	65 (89)
Ethnicity	Hispanic or Latino	19 (26)
	Not Hispanic or Latino	54 (74)
Country	Argentina	6 (8)
	Germany	9 (12)
	Spain	1 (1)
	Poland	2 (3)
	Serbia	2 (3)
	Slovenia	1 (1)
	Turkey	1 (1)
	USA	51 (70)
Total		73 (100)

Abbreviations: N = number of subjects; T2DM = type 2 diabetes mellitus

Table 4–2 Summary of subject characteristics for the data included in the T2DM dose-response analysis (continuous variables) (BMI ≥ 30 kg/m^2 and on metformin only)

	Mean (SD) [Range]
N	73
Age (years)	56.8 (11.7) [22.5-83.3]
Body weight (kg)	103.8 (17.3) [69.7-139.0]
BMI (kg/m^2)	37.2 (4.0) [30.0-44.9]

Abbreviations: N = number of subjects; T2DM = type 2 diabetes mellitus

Graphical analysis of the T2DM dose-response data

A graphical data analysis was conducted prior to performing the T2DM dose-response analysis in order to explore trends in the data across covariates and hence obtain initial indications of relevant covariate effects. The graphical data analysis comprised plots of geometric mean and 95% CI for pre-breakfast SMPG vs. Week No., vs. IDet dose, and vs. IDet dose stratified by:

- Gender (Male/Female).
- Region (Europe, USA, Other).

To ensure that the graphical data analysis would be maximally informative about the dose-response relationship, a dose adjustment approach was applied.

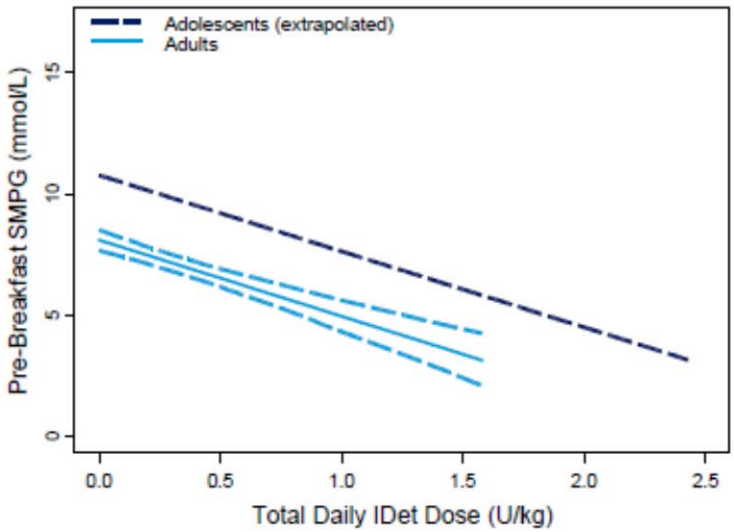
Pre-breakfast SMPG values decreased throughout the 26-weeks of treatment, and mean SMPG after 26-weeks was approximately 5.5 mmol/L. As expected, there was an overall decreasing trend in SMPG with increasing IDet dose. No obvious effects of gender or region were observed for SMPG vs. IDet dose.

T2DM dose-response analysis and extrapolation from adults to children and adolescents

The model used for the T2DM dose-response analysis was developed using the same covariate analysis approach as for the T1DM dose-response analysis. The base model was a linear model with an intercept and a slope parameter relating pre-breakfast SMPG to IDet dose per kg body weight (the model was implemented in such a way that the intercept corresponds to a dose of 0.4 U/kg). During the forward inclusion procedure, no significant covariates were identified. Hence no full model could be developed and the backward elimination procedure was skipped. As a result, the final model was identical to the base model. The model fit was reasonable, there were no critical trends in the weighted residuals vs. SMPG or dose, and the individual intercept and slope estimates appeared to follow a normal distribution.

Furthermore, the outcome of the covariate analysis was in accordance with the graphical analysis of the dose-response data, which showed no obvious effects of gender or region.

The estimated dose-response relationship is presented in Figure 4–1, which shows a typical decrease in pre-breakfast SMPG of approximately 0.3 mmol/L, when the IDet dose is increased by 0.1 U/kg. The extrapolated dose-response relationship in a typical child or adolescent is also included in Figure 4–1. The extrapolated curve was constructed by adding the estimated effect of age group on the intercept parameter in the T1DM model to the intercept parameter in the T2DM model.



Data is median with 95% CI obtained from the final dose-response model for adults and predicted median based on extrapolation for adolescents. The median lines have been shown for dose ranges going from zero to dose levels corresponding to a pre-breakfast SMPG value of 3.1 mmol/L. Further extrapolation is not supported by the model. The term 'adolescent' applies to subjects aged 10 – 17 years.

Figure 4–1 Model derived dose-response relationships for a typical adolescent and a typical adult with T2DM

Clinical data in T2DM

In Trial 3785, IDet was given as basal insulin treatment in combination with metformin to both treatment groups; the only difference between the groups being that subjects in the Diet group received dietary consultation by a certified dietician whereas subjects in the Control group only received basic dietary advices at baseline.

The outcome of this trial showed no differences in efficacy and safety between the 2 groups. Therefore, in this report only results for the Control group are described as these data are considered to most closely resemble the daily life situation; however, results for both groups are provided in this report.

Efficacy in T2DM

As described in Figure 4.1, a dose-response relationship could be established for adults with T2DM. The slope was less steep for T2DM (approximately 0.3 mmol/L decrease in pre-breakfast SMPG with a 0.1 U/kg increase in IDet dose) compared with T1DM (approximately 0.5 mmol/L decrease in pre-breakfast SMPG with a 0.1 U/kg increase in IDet dose). This corresponds to a more gradual decrease in pre-breakfast SMPG with increasing IDet dose for T2DM than in T1DM. Furthermore, based on the extrapolated dose-response relationship for children and adolescents with T2DM, those with T2DM are expected to require higher doses to obtain levels of glycaemic control similar to adults with T2DM.

In Trial 3785, the mean daily basal insulin dose increased throughout the trial and after 26 weeks of treatment, the dose was 1.05 U/kg (Table 4–3). Glycaemic control as measured by HbA1c was improved and decreased from 7.8% at randomisation to 6.8% after 26 weeks. Further, FPG decreased from 9.0 mmol/L at randomisation to 6.2 mmol/L after 26 weeks (Table 4–3).

Taking these dose-response analysis results into consideration, a higher dose level is expected to be needed in children and adolescents than adults to obtain similar glycaemic control. However, as also reflected in subjects with T1DM (see Section 3.2), the level of glycaemic control could be affected by the titration targets, which differ for children/adolescents (ISPAD) and adults (ADA). Due to the less steep slope for adults with T2DM as compared with children/adolescents and adults with T1DM, the relative change in glucose levels for any given dose change is expected to be smaller for children and adolescents with T2DM than those with T1DM.

Table 4–3 Efficacy and dose results – adults with T2DM (BMI ≥ 30 kg/m^2 and on metformin only) – full analysis set

	DIET	Control
N	88	79
Basal Dose – Week 4 (U/kg)	0.34 (0.08)	0.35 (0.07)
Basal Dose – Week 12 (U/kg)	0.67 (0.26)	0.73 (0.22)
Basal Dose – Week 26 (U/kg)	0.94 (0.49)	1.05 (0.51)
FPG (mmol/L) – Randomisation	8.9 (2.3)	9.0 (1.8)
FPG (mmol/L) - Week 12	5.9 (1.6)	5.8 (1.6)
FPG (mmol/L) - Week 26 (LOCF)	6.2 (2.2)	6.2 (1.8)
HbA_{1c} (%) - Randomisation	7.9 (0.8)	7.8 (0.6)
HbA_{1c} (%) - Week 12	7.1 (1.0)	6.9 (0.7)
HbA_{1c} (%) - Week 26 (LOCF)	6.9 (0.9)	6.8 (0.9)

Dose, FPG and HbA_{1c} are given as mean values and standard deviations are in brackets.

Abbreviations: FPG = fasting plasma glucose; LOCF = last observation carried forward; N = number of subjects; T2DM = type 2 diabetes mellitus

Cross reference: modified from Appendix C Tables 3, 6 and 8

Hypoglycaemia in T2DM

In T1DM, hypoglycaemic episodes defined as 'confirmed hypoglycaemic episodes' are evaluated. In Trial 3785, this term was not used. Instead, the pool of 'minor and severe hypoglycaemic episodes' was used, which corresponds to 'confirmed hypoglycaemic episodes'.

The rates of all minor and severe hypoglycaemic episodes and minor and severe nocturnal hypoglycaemic episodes were low. For minor hypoglycaemic episodes the rate was 213 episodes per 100 PYE, and for minor nocturnal hypoglycaemic episodes the rate was 68 episodes per PYE.

Only 1 severe hypoglycaemic episode was reported; this episode was reported as a severe nocturnal episode (Table 4–4 and Table 4–5).

Table 4–4 Hypoglycaemic episodes – adults with T2DM (BMI ≥ 30 kg/m^2 and on metformin only) – safety analysis set

	DIET			Control		
	N	(%)	E	R	N	(%)	E	R
Number of Subjects	88			78			
All episodes	62	(70.5)	856	2290	56	(71.8)	565	1741
Minor	32	(36.4)	142	380	28	(35.9)	69	213
ADA Severe	1	(1.1)	2	5	1	(1.3)	1	3

N: Number of subjects
%: Percentage of subjects
E: Number of episodes
R: Event rate per 100 patient year(s) of exposure
A minor hypoglycaemic episode is defined as either:
- An episode with symptoms consistent with hypoglycaemia with confirmation by a BG value < 2.8 mmol/L (50 mg/dL) or PG < 3.1 mmol/L (56 mg/dL), and which is handled by the subject him/herself, or
- An episode without symptoms with a BG value < 2.8 mmol/L (50 mg/dL) or PG value < 3.1 mmol/L (56 mg/dL), and which is handled by the subject him/herself
Only patients on metformin monotherapy without combination with other OADs are taken into account.

Cross reference: modified from Appendix C Table 15

Table 4–5 Nocturnal hypoglycaemic episodes – adults with T2DM (BMI ≥ 30 kg/m^2 and on metformin only) – safety analysis set

	DIET N	(%)	E	R	Control N	(%)	E	R
Number of Subjects	88				78			
All episodes	27	(30.7)	174	465	27	(34.6)	117	360
Minor	18	(20.5)	57	152	11	(14.1)	22	68
ADA Severe	1	(1.1)	1	3	1	(1.3)	1	3

N: Number of subjects
%: Percentage of subjects
E: Number of episodes
R: Event rate per 100 patient year(s) of exposure
A minor hypoglycaemic episode is defined as either:
- An episode with symptoms consistent with hypoglycaemia with confirmation by a BG value < 2.8 mmol/L (50 mg/dL) or PG < 3.1 mmol/L (56 mg/dL), and which is handled by the subject him/herself, or
- An episode without symptoms with a BG value < 2.8 mmol/L (50 mg/dL) or PG value < 3.1 mmol/L (56 mg/dL), and which is handled by the subject him/herself
Only patients on metformin monotherapy without combination with other OADs are taken into account.

Cross reference: modified from: Appendix C Table 15

Adverse events in T2DM

In Trial 3785, the vast majority of the events were non-serious, of mild or moderate severity and unlikely related to IDet (Table 4–6).

The most frequently reported AEs by preferred term (> 20 events per 100 PYE) were nasopharyngitis, diarrhoea, injection site reaction, back pain, and headache.

Few SAEs were reported (Table 4–6). The SAEs were infrequently reported and none of the preferred terms reported as SAEs occurred in more than 1 subject (including SAEs related to hypoglycaemia).

One death was reported in the Control group. The fatal event of ‘dilated cardiomyopathy’ occurred in a 73-year-old patient and was considered possibly related to trial product by the investigator and unlikely related by the sponsor. The sponsor could not exclude that the patient's underlying diseases or confounding factors may have contributed to the event.

Table 4–6 Summary of treatment emergent AEs – adults with T2DM (BMI≥ 30 kg/m^2 and on metformin only) – safety analysis set

	DIET				Control			
	N	(%)	E	R	N	(%)	E	R
All Subjects	88				78			
Exposure (yr)	37.4				32.5			
All TEAE	58	(65.9)	187	500.2	50	(64.1)	183	563.8
Serious	7	(8.0)	12	32.1	8	(10.3)	9	27.7
Deaths	0				1	(1.3)	1	3.1
Other	7	(8.0)	12	32.1	7	(9.0)	8	24.6
Non-Serious	57	(64.8)	175	468.1	49	(62.8)	174	536.1
Severe	7	(8.0)	10	26.8	7	(9.0)	10	30.8
Moderate	30	(34.1)	59	157.8	24	(30.8)	50	154.0
Mild	47	(53.4)	118	315.7	40	(51.3)	123	379.0
Relation To Trial Product								
Possible	5	(5.7)	7	18.7	5	(6.4)	7	21.6
Probable	13	(14.8)	17	45.5	7	(9.0)	14	43.1
Unlikely	55	(62.5)	163	436.0	48	(61.5)	160	493.0
Unknown	0				1	(1.3)	2	6.2

N= Number of subjects
%= Percentage of subjects
E= Number of events
R= Events/100 Exposure Years
TEAE = treatment emergent adverse event
Only patients on metformin monotherapy without combination with other OADs are taken into account.
Relationship to trial product is based in investigator(s)'s assessment

Cross-reference: Appendix C Table 12

Antibodies in T2DM

In Trial 3785, IDet was given as basal insulin treatment in combination with metformin to both treatment groups. Because an insulin comparator was not included in this trial, antibodies in T2DM are not described here.

Discussion

A dose-response analysis and qualitative extrapolation based on clinical data with IDet in children, adolescents and adults with T1DM and adults with T2DM has been applied to extend efficacy and safety results in these populations to children and adolescents with T2DM.

For T1DM, a dose-response relationship was established with a similar slope for children/adolescents and adults, but indicating that children and adolescents require higher doses of IDet to reach pre-breakfast SMPG levels similar to those seen with adults. This is supported by data from clinical trials with children/adolescents and adults with T1DM. In these trials, children and adolescents had higher dose requirements and less improvement in glycaemic control than their adult counterparts. This is possibly due to multiple factors, including increased insulin resistance during puberty, higher pre-breakfast SMPG titration targets and potentially greater challenges in treatment adherence (including recommendations with respect to diet and exercise) amongst young people as compared with adults. As these general factors are not specific to T1DM, a similar difference is expected between children/adolescents and adults with T2DM. Higher dose requirements are not considered to impact the use of IDet in children and adolescents, as insulin doses are always individually titrated. Apart from this difference in dose requirements, the results for the subpopulation of adult subjects with T2DM (BMI ≥ 30 kg/m2 previously treated with metformin only) indicates that glycaemic control would be similar with IDet in children and adolescents with T2DM. One additional finding was a less steep slope of the dose-response curve for T2DM than for T1DM. This indicates a more gradual reduction in pre-breakfast SMPG with increasing IDet

dose in children and adolescents with T2DM than in those with T1DM, which indicates less risk of hypoglycaemia during dose titration for child and adolescent T2DM patients compared to those with T1DM.

The rate of severe hypoglycaemia was generally low in all populations. The rate of confirmed hypoglycaemic episodes was higher in children and adolescents than adults with T1DM, and this was the case for both IDet and IDeg. Being an adolescent is an independent risk factor for hypoglycaemia, due to – amongst other factors – increased insulin resistance during puberty and more erratic diet and activity behaviours, as also described above. In the subpopulation of adults with T2DM, the rate of minor and severe hypoglycaemic episodes (corresponding to confirmed hypoglycaemic episodes) was lower compared to adults with T1DM. The rate of nocturnal confirmed hypoglycaemic episodes was also higher in children and adolescents than in adults with T1DM for both IDet and IDeg. In the subpopulation of adults with T2DM, the rate of minor and severe nocturnal hypoglycaemic episodes was low and only 1 subject had a severe nocturnal hypoglycaemic episode.

No safety concerns were raised for children and adolescents as compared to adults with T1DM, or for the subpopulation of adults with T2DM, in terms of AEs or antibody profiles. Although a higher rate of AEs for children and adolescents compared to adults was observed, this rate differential may be attributable to the particular physiological and psychosocial changes experienced during adolescence.

The low rates of all minor and severe hypoglycaemic episodes and minor and severe nocturnal hypoglycaemic episodes indicates that in children and adolescents with T2DM, IDet is expected to be associated with similar or lower risk for both overall and nocturnal hypoglycaemia. Nocturnal hypoglycaemia is a specific concern because such episodes are often asymptomatic, difficult to detect and thus a challenge to correct. T2DM confers a degree of protection against hypoglycaemia compared to T1DM because counter-regulatory responses begin at higher blood glucose levels than observed in people without diabetes or in people with T1DM. The benefit-risk profile for IDet in children and adolescents with T2DM is therefore at least as good as for those with T1DM.

An extrapolation and modelling study used data from efficacy trials in adults and in children/adolescents with T1DM (Trials 3585, 3725 and 3561) to extend efficacy results in adults T2DM (Trial 3785) to children and adolescents with T2DM.

Modelling results demonstrated that dose-response relationships could be established for the age groups with T1DM, and that children and adolescents would in general need higher doses than adults to achieve the same level of glycaemic control. Combined with modelling results for adults with T2DM, the dose-response relationship in children and adolescents with T2DM was determined using extrapolation. The extrapolated dose-response relationship clearly indicated that appropriate glycaemic control can be obtained with IDet in children and adolescents with T2DM.

Overall, the results of this study supported the extension of efficacy of IDet in adults with T2DM and children and adolescents with T1DM to children and adolescents with T2DM. No safety concerns in terms of AEs or antibody profiles were raised. This supported the potential to obtain a similar effective glycaemic control with IDet in children and adolescents with T2DM as observed in adults without compromising safety.

2.3.5. Discussion on clinical pharmacology

Population PK

Data from trial NN1250-3561 and NN304-1222 was analysed as pooled data as opposed to the original plan. This approach is justifiable as it likely produced a more robust result. Standard first order estimation method with interaction (FOCE+I) in NONMEN was used. Structurally, a one-compartment model with absorption-lag described the PK adequately. Covariate analysis demonstrated that body weight was a significant covariate for clearance and Vd; however no other covariates were identified. As body-weight correlates strongly to age, no differences are seen in modelled concentration-time profiles of IDet as dosing is based on weight.

The population PK analysis demonstrated that the weight-based dosed concentration-time profile in small children (1-5 years) is comparable to the concentration-time profiles in children (6-11 years), adolescents (12-17 years) and adults (18 years and above). Additionally, in trial NN304-1222, no statistically significant differences in IDet PK were found among children, adolescents and adults.

The population PK analysis based on the two paediatric studies did not focus on the age group of patients aged 1-<2 years.

The model has been subject to adequate model-evaluation and sensitivity analysis. The PoP-PK analysis is thorough and well documented and complies with current guidelines on PoP-PK reporting.

Extrapolation and modelling of efficacy

The applicant presents a quantitative analysis of dose-response associations in adult and in children/adolescents in T1DM and in adults with T2DM. These associations are extrapolated and modelled to account for T2DM in children/adolescent. The approach is technically challenging and inherently implies a number of (mostly plausible) assumptions, but clinical interpretation should be carefully approached. Additionally, a thorough quantitative analysis of adverse reactions is presented.

The approach is overall judged to sufficiently fulfil the purpose of study #5 in the PIP.

For T1DM, a dose-response relationship was established with a similar slope for children/adolescents and adults, but suggesting that higher doses would be required for similar effect in children/adolescents. The steepness of the dose-response curve appeared greater in T2DM. This finding is in accordance with observations in clinical trials. This is plausible due to a number of factors, such as increased insulin resistance, higher pre-breakfast SMPG titration targets and treatment adherence amongst younger people. Such factors are likely an issue in T2DM as well. Results for the subpopulation of adult subjects with T2DM suggest that glycaemic control with IDet in children and adolescents with T2DM is like to be comparable. The reduced steepness of the dose-response curve in T2DM may favour the adverse event profile with respect to hypoglycaemia compared to T1DM subjects.

A higher rate of AE in children/adolescents was observed in T1DM patients, but this is not considered a major issue. Specifically, a low rate of minor and severe (including nocturnal) hypoglycaemic episodes indicates that in children and adolescents with T2DM, IDet is expected to be associated with similar risk. Additionally, T2DM inherently comes with some degree of protection against hypoglycaemia as regulatory responses are activated at higher glucose levels.

Antibody profiles were comparable.

In total, the results from the PoP-PK analysis and the extrapolation study support the efficacy and safety of IDet treatment of T2DM in children and adults to a reasonable extent. It must be stressed though that these findings are strictly supportive in nature, as the approach inherently requires many assumptions.

2.3.6. Conclusions on clinical pharmacology

The applicant has performed a thorough PoP-PK analysis in two clinical trials in children/adolescents between 1 and 18 years of age that complies with guidelines for reporting of population PK. While the amount of data for the youngest age group (1-5 year-old) is very limited, the analysis does not suggest the PK of insulin in this age group to be substantially different from other age groups when dosing IDet per kg body weight. No other predictors of IDet PK were identified.

Furthermore it was noted that the population PK analysis did not focus on the group of patients aged 1-<2 years, which is the topic of the current procedure. Rather it compared small children (1-5 years), children (6-11 years), adolescents (12-17 years) and adults (18 years -). The CHMP requested justification from the MAH how the population PK analysis addresses the specific topic of the current procedure, ie. extending the indication to encompass children aged 1 to <2 years. The MAH has sufficiently addressed the raised concern on the validity of the PoP-PK model for children between 1 and <2 years of age. While the number of actual patients in this age-group studied is very scarce, the interpretation of model and its underlying assumptions are considered acceptable, especially with the proposed warning in section 4.4 of the SmPC.

Additionally, the applicant has provided an extrapolation analysis to support the efficacy of IDet in children and adults with T2DM. This analysis is complex in its nature and inherently subject to many assumptions. Nevertheless, the applicant has to a reasonable extent provided support suggesting that:

- A similar (slope) dose-relationship was seen for children/adolescents and adults in T1DM. Higher doses appear necessary to establish the same level of glycaemic control as in adults.
- A less steep slope of the dose-response curve was seen for T2DM than for T1DM. This indicates a more gradual reduction in pre-breakfast SMPG with increasing IDet dose in children and adolescents with T2DM than in those with T1DM.
- Modelled extrapolation supports a hypothesis of glycaemic control in children/adolescents with T2DM
- No obvious safety issues materialised from a quantitative analysis.

In total, the results from the PoP-PK analysis and the extrapolation study support the efficacy and safety of IDet treatment of T2DM in children and adults to a reasonable extent. It must be stressed though that these findings are strictly supportive in nature, as the approach inherently requires many assumptions.

The PIP as far as clinical pharmacology has been sufficiently addressed.

2.4. Clinical efficacy

2.4.1. Main study

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.

Trial 3561 has already been assessed by the CHMP within procedure EMEA/H/C/528/P46/49. The main conclusions are reflected in the current assessment report.

Summary of main study

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

Table 1 Summary of efficacy for trial 3561

Title: A trial investigating the efficacy and safety of insulin degludec in children and adolescents with type 1 diabetes mellitus (A 26-week, multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of insulin degludec and insulin detemir in children and adolescents 1 to less than 18 years with type 1 diabetes mellitus on a basal-bolus regimen with insulin aspart as bolus insulin, followed by a 26-week extension investigating long term safety).		
Study identifier	Trial ID: NN1250-3561; EudraCT number: 2011-003148-39; Study identifier: NCT01513473. See Trial 3561 (M 5.3.5.1).	
Design	This was a 26-week, open labelled, randomised, multinational, multi-centre, two arm parallel group, treat-to-target, efficacy and safety trial comparing insulin degludec (IDeg) with insulin detemir (IDet) as basal insulin in combination with insulin aspart (IAsp) as bolus insulin in subjects with type 1 diabetes between 1 and less than 18 years of age, followed by a 26-week extension investigating long term safety and immunogenicity. Following screening, eligible subjects were randomised in a 1:1 manner to receive IDet (OD or BID as required) or IDeg OD. Randomisation was stratified according to age group (1 to less than 6 years, 6 to less than 12 years and 12 to less than 18 years of age). Randomised subjects were to attend 8 site visits (including one follow-up visit), and 14 phone contacts. Key visits were at week 0, 12 and 26 where assessments for primary and secondary endpoints were performed. A one week wash-out period with insulin NPH was performed after the last treatment in order to facilitate antibody detection. For selected countries/sites, subjects underwent assessment of their 24-hour interstitial glucose levels with a continuous glucose monitoring (CGM) device. All subjects completing the main trial period (26 weeks of treatment) were invited to continue on their randomised treatment for additional 26 weeks (extension period), for which a new informed consent was obtained. Only results from the main trial period are reported here.	
	Duration of main period:	26 weeks of treatment + 1 week follow-up (trial 3561)
Hypothesis	To demonstrate efficacy of IDeg administered once daily plus mealtime IAsp in controlling glycaemia with respect to change from baseline in HbA1c after 26 weeks of treatment. This is done by comparing the difference in change in HbA1c between IDeg + IAsp and IDet + IAsp to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%. None of the secondary endpoints were analysed as confirmatory endpoints.	

Treatments groups	Insulin degludec (IDeg) + insulin aspart (IAsp)		A total of 174 subjects were randomised to IDeg dosed OD as basal insulin treatment + IAsp as mealtime insulin. The total treatment duration was 26 weeks.
	Insulin detemir (IDet) + insulin aspart (IAsp)		A total of 176 subjects were randomised to IDet dosed OD or BID according to approved labelling + IAsp as mealtime insulin. The total treatment duration was 26 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	Supportive secondary endpoint	Change from baseline in FPG after 26 weeks of treatment	Change from baseline in FPG after 26 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Mean of the 8-point profiles after 26 weeks of treatment	Mean of the 8-point SMPG profiles after 26 weeks of treatment was compared between treatment groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Fluctuation in the 8-point profiles after 26 weeks of treatment	Fluctuation in the 8-point SMPG profiles after 26 weeks of treatment was compared between treatment groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Prandial PG increment from 8-point SMPG profiles after 26 weeks of treatment	8-point SMPG meal increments after 26 weeks of treatment was compared between treatments groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Mean PG before breakfast from 4-point SMPG profiles after 26 weeks of treatment	4-point SMPG mean plasma glucose before and after 26 weeks of treatment was compared between treatment groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Within-subject variability as measured by CV% after 26 weeks of treatment	Within-subject variability as measured by CV% in SMPG after 26 weeks of treatment was compared between treatment groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.

Database lock	13-March-2013		
Results and Analysis			
Analysis description	**Primary analysis and key supportive secondary endpoints**		
Analysis population and time point description	The FAS (n=350) included all randomised subjects. The PP analysis set (n = 338) included subjects without any major protocol violations that may have affected the primary endpoint. The SAS (n=349) included all subjects receiving at least one dose of the investigational product or its comparator. Analyses of efficacy endpoints were based on the FAS, while the safety endpoints were summarised using the SAS. The population consisted of male and female paediatric subjects with type 1 diabetes mellitus with a mean age of 10.0 years (ranging from 1.5 to 18.4 years[a]), mean duration of diabetes of 4.0 years (ranging from 0.0 to 15.8 years), mean HbA_{1c} of 8.1% and mean BMI of 18.6 kg/m^2. The time point duration for all analyses was 26 weeks. A total of 95.7% of the subjects in both treatment groups were treated with a basal-bolus insulin regimen pre-trial. Of these 46.3% of the subjects were treated with IDet pre-trial. A total of 97.7% of subjects in the IDeg group and 93.8% of subjects in the IDet group completed the trial. [a]All subjects were in the age range 1 - <18 years at screening.		
Statistical methods	Change from baseline in HbA_{1c}, and FPG at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, sex, region, and age as fixed factors and baseline HbA_{1c} or FPG as covariates, respectively. Mean and fluctuation in the 8-point profile (SMPG), prandial PG increments and mean before breakfast in the 4-point profile after 26 weeks of treatment were analysed separately using ANOVA with treatment, sex and region and age group as fixed factors and the relevant baseline value as covariate. Fluctuation in the 8-point profile (SMPG) was logarithmically transformed before being analysed. Within-subject variability (CV%) for a treatment was calculated from the corresponding residual variance estimated from a linear mixed model analysing the logarithmically transformed pre-breakfast SMPG values as repeated measures. The model included treatment, sex, region and age as fixed factors, and subject as random factor.		
Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**IDet**
	Number of subjects (FAS)	174	176
	Change from baseline in HbA_{1c} after 26 weeks of treatment, mean % (SD)	-0.20 (0.95)	-0.31 (0.89)
	HbA_{1c} at baseline, mean % (SD)	8.2 (1.1)	8.0 (1.1)
	HbA_{1c} at end of trial, mean % (SD)	8.0 (1.1)	7.7 (1.0)
	Change from baseline in FPG after 26 weeks of treatment, mean mmol/L (SD)	-0.67 (5.99)	0.50 (8.37)

	Mean of the 8-point profiles after 26 weeks of treatment, mean (SD) mmol/L	9.6 (2.5)	9.9 (2.6)
	Fluctuation in in the 8-point profiles after 26 weeks of treatment, geometric mean mmol/L	2.1	2.1
	Prandial PG increment at main evening meal (from 8-point SMPG profile) after 26 weeks of treatment, mean (SD) mmol/L	0.2 (5.8)	-0.3 (5.7)
	Mean plasma glucose before breakfast from 4-point SMPG profile after 26 weeks of treatment, mean (SD) mmol/L	8.8 (2.9)	9.6 (3.4)
	Within-subject variability in SMPG after 26 weeks of treatment, CV%	39.79	39.83
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	0.15
		95% CI	[-0.03; 0.32][†]
	Supportive secondary endpoint: Change from baseline in FPG after 26 weeks of treatment, mmol/L	Comparison groups	IDeg – IDet
		Treatment contrast	-0.42
		95% CI	[-1.65; 0.81]
	Supportive secondary endpoint: SMPG measurements (8-point profiles); mean of the 8-point profiles after 26 weeks of treatment, mmol/L	Comparison groups	IDeg – IDet
		Treatment contrast	-0.41
		95% CI	[-0.93; 0.11]
	Supportive secondary endpoint: SMPG measurements (8-point profiles); fluctuation in the 8-point profiles after 26 weeks of treatment, mmol/L	Comparison groups	IDeg – IDet
		Treatment contrast	0.99
		95% CI	[0.89; 1.10]
	Supportive secondary endpoint: SMPG measurements (8-point profiles); prandial PG increment at main evening meal from 8 point SMPG profile at end of treatment, mmol/L	Comparison groups	IDeg – IDet
		Treatment contrast	0.58
		95% CI	[-0.67; 1.82]
	Supportive secondary endpoint: SMPG measurements (4-point profiles for dose adjustment); mean	Comparison groups	IDeg – IDet
		Treatment contrast	-0.87

	plasma glucose before breakfast after 26 weeks of treatment	95% CI	[-0.53; -0.22]
	Supportive secondary endpoint: Within-subject variability (CV%) in SMPG after 26 weeks of treatment	Comparison groups	IDeg/IDet
		Treatment ratio	1.00
		95% CI	[0.88; 1.12]
Notes	ANOVA: analysis of variance; 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; IDeg: insulin degludec; OAD, oral anti-diabetic treatment, OD: once daily, PG: plasma glucose; PP: per protocol; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose; T1DM: type 1 diabetes.		

Table 2- Summary of efficacy for trial 3561-ext

Title: A trial investigating the efficacy and safety of insulin degludec in children and adolescents with type 1 diabetes mellitus (A 26-week, multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of insulin degludec and insulin detemir in children and adolescents 1 to less than 18 years with type 1 diabetes mellitus on a basal-bolus regimen with insulin aspart as bolus insulin, followed by a 26-week extension investigating long term safety).		
Study identifier	Trial ID: NN1250-3561; EudraCT number: 2011-003148-39; Study identifier: NCT01513473. See Trial 3561 ext (M 5.3.5.1).	
Design	This was a 26-week, open labelled, randomised, multinational, multi-centre, two arm parallel group, treat-to-target, efficacy and safety trial comparing insulin degludec (IDeg) with insulin detemir (IDet) as basal insulin in combination with insulin aspart (IAsp) as bolus insulin in subjects with type 1 diabetes mellitus (T1DM) between 1 and less than 18 years of age, followed by a 26-week extension investigating long term safety and immunogenicity. Following screening, eligible subjects were randomised in a 1:1 manner to receive IDet (OD or BID as required) or IDeg OD. Randomisation was stratified according to age group (1 to less than 6 years, 6 to less than 12 years and 12 to less than 18 years of age). All subjects were titrated according to the insulin titration guideline, i.e. individually for IDeg, IDet and IAsp. A one week wash-out period with insulin NPH was performed after the last treatment in order to facilitate antibody detection. During the 52 weeks, randomised subjects were to attend 14 site visits (including one follow-up visit), and 40 phone contacts. Key visits were at weeks 0, 12, 26, 38 and 52 where assessments for primary and secondary endpoints were performed. All subjects completing the main trial period (26 weeks of treatment) were invited to continue on their randomised treatment in the extension trial (a further 26 weeks), for which a new informed consent was obtained. Data from the entire 52 weeks trial period (26 weeks in the main trial period and 26 weeks in the extension trial period) are presented here.	
	Duration of main period:	26 weeks of treatment+ 1 week follow-up
	Duration of extension period:	26 weeks of treatment + 1 week follow-up
	Duration of extended trial	52 weeks of treatment + 1 week follow-up

Hypothesis	To demonstrate efficacy of IDeg administered once daily plus mealtime IAsp in controlling glycaemia with respect to change from baseline in HbA1c after 26 weeks of treatment. This is done by comparing the difference in change in HbA1c between IDeg + IAsp and IDet + IAsp to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%. None of the secondary endpoints were analysed as confirmatory endpoints.		
Treatments groups	Insulin degludec (IDeg) + insulin aspart (IAsp)		A total of 174 subjects were randomised to IDeg dosed OD as basal insulin treatment + IAsp as mealtime insulin. The total treatment duration was 52 weeks.
	Insulin detemir (IDet) + insulin aspart (IAsp)		A total of 176 subjects were randomised to IDet dosed OD or BID according to approved labelling + IAsp as mealtime insulin. The total treatment duration was 52 weeks.
Endpoints and definitions	Primary endpoint	Change from baseline in HbA_{1c} (%) after 26 weeks of treatment	See Hypothesis.
	Supportive secondary endpoint	Change from baseline in HbA_{1c} (%) after 52 weeks of treatment	Change from baseline in HbA_{1c} after 52 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	Change from baseline in FPG (central lab-measured) after 52 weeks of treatment	Change from baseline in FPG after 52 weeks of treatment was compared between treatment groups and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Mean of the 8-point profiles after 52 weeks of treatment	Mean of the 8-point SMPG profiles after 52 weeks of treatment was compared between treatment groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Fluctuation in the 8-point profiles after 52 weeks of treatment	Fluctuation in the 8-point SMPG profiles after 52 weeks of treatment was compared between treatment groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Prandial PG increment from 8-point SMPG profile after 52 weeks of treatment	8-point SMPG meal increments after 52 weeks of treatment was compared between treatments groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.

	Supportive secondary endpoint	SMPG measurements: Mean PG before breakfast from 4-point SMPG profile after 52 weeks of treatment	4-point SMPG mean plasma glucose before and after 26 weeks of treatment was compared between treatment groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.
	Supportive secondary endpoint	SMPG measurements: Within-subject variability as measured by CV% after 52 weeks of treatment	Within-subject variability as measured by CV% in SMPG after 26 weeks of treatment was compared between treatment groups, both in combination with IAsp and assessed by statistical analysis as part of the efficacy evaluation.
Database lock	03-September-2014		
Results and Analysis			
Analysis description	**Primary Analysis and Key Supportive Secondary Endpoints**		
Analysis population and time point description	The FAS (n=350) included all randomised subjects. The PP analysis set (n=338) included subjects without any major protocol violations that may have affected the primary endpoint. The SAS (n=349) included all subjects receiving at least one dose of the investigational product. Analyses of efficacy endpoints were based on the FAS, while the safety endpoints were summarised using the SAS. The population consisted of male and female paediatric subjects with type 1 diabetes mellitus with a mean age of 10.0 years (ranging from 1.5 to 18.4 years[a]), mean duration of diabetes of 4.0 years (ranging from 0.0 to 15.8 years), mean HbA_{1c} of 8.1% and mean BMI of 18.6 kg/m^2. The time point duration for all analyses was 52 weeks. A total of 95.7% of the subjects in both treatment groups were treated with a basal-bolus insulin regimen pre-trial. Of these 46.3% of the subjects were treated with IDet pre-trial. A total of 86.8% of subjects in the IDeg group and 69.3% of subjects in the IDet group completed the extended trial. [a]All subjects were in the age range 1 - <18 years at screening.		
Statistical methods	Change from baseline in HbA_{1c} and FPG at end of treatment was analysed using an analysis of variance (ANOVA) model with treatment, sex, region, and age as fixed factors and baseline HbA_{1c} or FPG as covariates, respectively. Mean and fluctuation in the 8-point profile (SMPG), prandial PG increments and mean before breakfast in the 4-point profile after 26 weeks of treatment were analysed separately using ANOVA with treatment, sex and region and age group as fixed factors and the relevant baseline value as covariate. Fluctuation in the 8-point profile (SMPG) was logarithmically transformed before being analysed. Within-subject variability (CV%) for a treatment was calculated from the corresponding residual variance estimated from a linear mixed model analysing the logarithmically transformed pre-breakfast SMPG values as repeated measures. The model included treatment, sex, region and age group as fixed factors, and subject as random factor.		

Descriptive statistics and estimate variability	**Treatment group**	**IDeg**	**IDet**
	Number of subjects (FAS)	174	176
	Change from baseline in HbA_{1c} after 52 weeks of treatment, mean % (SD)	-0.27 (1.07)	-0.22 (1.03)
	HbA_{1c} at baseline, mean % (SD)	8.2 (1.1)	8.0 (1.1)
	HbA_{1c} at end of trial, mean % (SD)	7.9 (1.1)	7.8 (1.1)
	Change from baseline in FPG after 52 weeks of treatment, mean mmol/L (SD)	-1.29 (6.53)	1.10 (8.24)
	Mean of the 8-point profiles after 52 weeks of treatment, mean (SD) mmol/L	9.4 (2.4)	10.1 (2.8)
	Fluctuation in in the 8-point profiles after 52 weeks of treatment, geometric mean mmol/L	2.0	2.1
	Prandial PG increment at main evening meal (from 8-point SMPG profile) after 52 weeks of treatment, mean (SD) mmol/L	0.1 (5.1)	0.4 (5.8)
	Mean plasma glucose before breakfast from 4-point SMPG profile after 52 weeks, mean (SD) mmol/L	8.7 (3.1)	9.4 (3.7)
	Within-subject variability in SMPG after 52 weeks of treatment, CV%	33.71	32.36
Effect estimate per comparison	Primary endpoint: Change from baseline in HbA_{1c} (%-point) after 26 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	-0.15
		95% CI	[-0.03; 0.32]
	Supportive secondary endpoint: Change from baseline in HbA_{1c} (%-point) after 52 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	-0.01
		95% CI	[-0.20; 0.19]
	Supportive secondary endpoint: Change from baseline in FPG after 52 weeks of treatment, mmol/L	Comparison groups	IDeg – IDet
		Treatment contrast	-1.62
		95% CI	[-2.84; -0.41]
	Supportive secondary endpoint: SMPG measurements (8-point profiles); mean of the 8-point profiles after 52 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	-0.79
		95% CI	[-1.32; -0.26]

	Supportive secondary endpoint: SMPG measurements (8-point profiles); fluctuation in the 8-point profiles after 52 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	0.95
		95% CI	[0.86; 1.05]
	Supportive secondary endpoint: SMPG measurements (8-point profiles); prandial PG increment at main evening meal from 8 point SMPG profile at end of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	-0.92
		95% CI	[-2.14; 0.30]
	Supportive secondary endpoint: SMPG measurements (4-point profiles); mean PG before breakfast after 52 weeks of treatment	Comparison groups	IDeg – IDet
		Treatment contrast	-0.76
		95% CI	[-1.46; -0.05]
	Supportive secondary endpoint: Within-subject variability (CV%) in SMPG after 52 weeks of treatment	Comparison groups	IDeg/IDet
		Treatment ratio	1.04
		95% CI	[0.93; 1.16]
Notes	ANCOVA: analysis of variance; BMI: body mass index; CI: confidence interval; FAS: full analysis set; FPG: fasting plasma glucose; HbA_{1c}: glycosylated haemoglobin A1c; IAsp: insulin aspart; IDet: insulin detemir; IDeg: insulin degludec; OAD, oral anti-diabetic treatment, OD: once daily, PG: plasma glucose; PP: per protocol; SAS: safety analysis set; SD: standard deviation; SMPG: self-measured plasma glucose; T1DM: type 1 diabetes.		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

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 including the choice of the non-inferiority margin of 0.4% are acceptable. The current “Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus” mentions 0.3% as an acceptable non-inferiority margin for HbA1c; however a margin of 0.4% has been widely used and accepted, also in the pivotal studies supporting the licensing of IDeg. Furthermore, the margin of 0.4% was chosen in agreement with the EMA prior to the introduction of the current Guidelines published on14 May 2012 and the protocol was finalised/approved on 01 Sep 2011.

The choice of the comparator, IDet, is acknowledged as IDet has been proved to be safe and it is a widely used insulin. Although IDet has not been approved for the use in children below the age of 2 years, the PIP decision for IDet includes a waiver for children less than 1 year with T1DM. The present study aimed to include children down to 1 year and is thus expected to provide supporting data in the age group 1-2 years for IDet.

Efficacy data and additional analyses

Recruitment procedures and numbers analysed were acceptable. Completion rates were high with no major differences between groups. More subjects in the IDet group compared to the IDeg group did not continue to the extension phase. The MAHs explanation for this difference, that subjects in this group were treated with an already marketed product, was endorsed. The MAH has performed comparison between subjects discontinuing the trial after the main 26-week period and subjects entering the extension phase. Descriptive data indicated a poorer glycaemic response to the treatment in subjects not continuing to the extension phase compared to those subjects who continued. However, data of glycaemic control after 52 weeks were similar when comparing the full analysis set with the extension trial set.

Baseline data were fairly balanced with no major differences between the study groups.

Regarding the primary endpoint, change in HbA1c after 26 weeks, non-inferiority between the two treatment arms was demonstrated as the upper limit of the 95% CI for the estimated treatment difference was ≤0.4% (0.15 %-points [-0.03; 0.32]95%CI). This was confirmed in the PP analysis set and based on sensitivity analyses for the primary endpoint. The results within the three age groups were comparable to the results seen for all subjects.

Thus the study demonstrates that IDeg was as efficacious as IDet in terms of reducing HbA1c when applying a non-inferiority margin of 0.4%, after 26 weeks of treatment and at the end of the full 52-week treatment period with both treatments approaching the target HbA1c of <7.5%.

Regarding the slight increase in HbA1c observed in the age group 6-11 years after 12 weeks there was no obvious explanation. Fluctuations were also observed in the other age groups during the trial, especially among adolescents. As noted by the MAH this was not unexpected. Importantly, HbA_{1c} was lower after 52 weeks of treatment compared to baseline across all age groups with both treatments.

After 52 weeks of treatment fasting plasma glucose concentrations, 8-point self-measured plasma glucose profiles and pre-breakfast SMPG were significantly lower with IDeg compared to IDet. Regarding insulin dose subjects treated with IDeg required less total as well as basal insulin compared with subjects treated with IDet.

2.4.3. Conclusions on the clinical efficacy

After 52 weeks of treatment with IDeg and IDet in this paediatric population the glycaemic control improved in both groups with similar HbA1c levels in the two groups and lower FPG in the IDeg arm. This glycaemic control was achieved with fewer daily IDeg units compared to IDet.

2.5. Clinical safety

Introduction

The evaluation of safety is based on the safety data from Trial 3561 and results from the extrapolation and modelling study (Study 5).

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 patient-years) than in the IDet arm (147.4 patient-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 three age groups in the two treatment arms.

Adverse events

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 1 below. 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.

Table 1 - Adverse events - treatment-emergent - summary - safety analysis set

	IDeg OD N	(%)	E	R	IDet N	(%)	E	R
Number of Subjects	174				175			
Events	161	(92.5)	1462	906	157	(89.7)	1266	859
Serious								
Yes	18	(10.3)	25	15	16	(9.1)	24	16
No	160	(92.0)	1437	890	157	(89.7)	1242	843
Severity								
Severe	23	(13.2)	34	21	12	(6.9)	21	14
Moderate	72	(41.4)	177	110	51	(29.1)	136	92
Mild	159	(91.4)	1251	775	155	(88.6)	1108	752
Missing	0	(0.0)	0	0	1	(0.6)	1	1
Related to Investigational Product								
Probably	26	(14.9)	32	20	22	(12.6)	28	19
Possibly	30	(17.2)	80	50	31	(17.7)	57	39
Unlikely	157	(90.2)	1336	827	156	(89.1)	1175	797
Missing	13	(7.5)	14	9	6	(3.4)	6	4
Related to Bolus Insulin								
Probably	27	(15.5)	42	26	19	(10.9)	28	19
Possibly	33	(19.0)	86	53	31	(17.7)	67	45
Unlikely	157	(90.2)	1328	823	156	(89.1)	1170	794
Missing	6	(3.4)	6	4	1	(0.6)	1	1
Related to Device								
Yes	2	(1.1)	2	1	1	(0.6)	2	1
No	160	(92.0)	1454	901	157	(89.7)	1263	857
Missing	6	(3.4)	6	4	1	(0.6)	1	1
Outcome								
Recovered	159	(91.4)	1423	881	156	(89.1)	1231	835
Recovering	9	(5.2)	14	9	7	(4.0)	8	5
Not Recovered	13	(7.5)	22	14	20	(11.4)	23	16
Unknown	2	(1.1)	3	2	2	(1.1)	4	3

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.

Common adverse events

The most frequently reported preferred terms (PTs) in both treatment arms were 'nasopharyngitis', 'headache' and 'increased blood ketone levels' with event rates of 103, 74 and 70 events per 100PYE, respectively, followed by 'upper respiratory tract infections', 'pyrexia' and 'hypoglycaemia'(event rates of 37, 34 and 33 events per 100 PYE).

In the IDeg arm, the overall observed rate of AEs was higher in children aged 1 to 5 years than the mean rate in the overall population treated with IDeg. The higher rates were scattered across several SOCs, with the highest rates observed in relation to 'infections and infestations', 'respiratory disorders' and 'gastrointestinal disorders' which are all common SOCs for AEs in the general paediatric population.

In the IDet arm, the rate of AEs was fairly similar across the three age groups and reflected the rate in the overall population treated with IDet.

Differences of interest between treatments were observed for the rates of 'hypoglycaemia' and 'blood ketone body increased'.

Adverse events related to hypoglycaemia

Hypoglycaemia was only reported as an AE if it fulfilled the definition of an SAE or a MESI (severe hypoglycaemia). The observed rates of AEs for 'hypoglycaemic seizure' and 'hypoglycaemic unconsciousness' were low and similar between the two treatment arms, whereas the observed rate of AEs related to 'hypoglycaemia' was higher in the IDeg arm than in the IDet arm. Relatively few of these events were reported as SAEs, suggesting that the majority of the hypoglycaemic episodes were recorded as AEs because severe hypoglycaemia was defined as a MESI according to the protocol. Furthermore, it should be noted that a broad definition of severe hypoglycaemia based on the ISPAD guidelines was used in this trial. About 1/3 of the AEs related to hypoglycaemia were reported as severe AEs by the investigator. A higher proportion of the hypoglycaemia related AEs were considered possibly or probably related to the bolus insulin, IAsp, than to IDeg or IDet, whereas the number of severe hypoglycaemia related AEs considered possibly or probably related to basal or bolus insulin were low and similar in the IDeg and IDet arm.

AEs related to increased blood ketone bodies

The observed rate of 'blood ketone body increased' was lower with IDeg than IDet (50 vs. 92 events per 100 PYE). According to the protocol, subjects with an SMPG recording >14 mmol/L were to measure capillary blood ketones and elevated blood ketone levels >1.5 mmol/L were to be recorded as MESIs. Although high levels of ketones may also originate in the absence of hyperglycaemia in relation to e.g. gastrointestinal illness or vomiting, most of the elevated blood ketone bodies recorded as AEs were probably related to cases of hyperglycaemia with self-measurement of ketones. All episodes of 'blood ketone body increased' were of mild or moderate severity except for one severe episode in the IDet arm. The number and rate of 'blood ketone body increased' judged by the investigator to be possibly or probably related to basal insulin were numerically lower with IDeg than IDet (17 vs. 36 events corresponding to 11 vs. 24 events per 100 PYE) and none of these related events were severe or reported as SAEs. The number and rate considered possibly or probably related to bolus insulin were 19 vs. 34 events with IDeg and IDet, corresponding to 12 vs. 23 events per 100 PYE. In addition to the events of 'blood ketone body increased' described above, subjects in the IDeg and IDet treatment groups reported 8 and 2 other AEs related to hyperglycaemia.

Three of these events were reported as SAEs: 1 event of 'diabetic ketoacidosis' in the IDeg group and 1 'ketosis' event in each treatment group.

Allergic reactions

The rates of allergic reactions were similar between IDeg and IDet treatment groups (21.7 and 17.6 events per 100 PYE). The events were related to skin disorders, seasonal allergies and multiple allergies. None of these events were severe or reported as SAEs, and none of the AEs led to withdrawal from the trial.

Two subjects reported 5 allergic reactions which were assessed as possibly or probably related to IDeg by the investigator while none of the allergic reactions were assessed as possibly or probably related to IDet

Injection site reactions and events of lipodystrophy

Injection site reactions were reported in a relatively small proportion of subjects (18 vs. 6 subjects in the IDeg and IDet arm). These events were more frequently reported in the IDeg arm than in the IDet arm

(28 events vs. 7 events) across a range of preferred terms. None of the injection site reactions were serious and none of the AEs led to withdrawal. All events were mild in severity, except for 5 events of moderate severity (2 subjects with 3 events in the IDeg arm and 1 subject with 2 events in the IDet arm). Possible or probable relation to the investigational medicinal product was reported for 12 events in 8 subjects treated with IDeg, and for 6 events in 5 subjects treated with IDet. Injection site reactions considered possibly or probably related to bolus insulin were reported by 9 subjects (11 events) with IDeg and 2 subjects (3 events) with IDet.

The frequency of injection site reaction in children/adolescents that were assessed as possibly or probably related to IDet (2.9% of subjects) was within the frequency category 'common'(1-10%), and therefore the current label text remains appropriate.

The rates of events of lipodystrophy in the trial were similar for IDeg and IDet (5 subjects with 5 events vs. 5 subjects with 7 events). No subjects were withdrawn from the trial due to lipodystrophy. All of the events of lipodystrophy were non-serious and with the exception of 3 moderate events, all events were of mild severity. All events were recovered at the end of the trial except for 3 'not recovered' events (1 with IDeg and 2 with IDet). Three events in each treatment group were considered possibly or probably related to the investigational medicinal product, and 4 of these 6 events were in addition judged to be possibly or probably related to bolus insulin. The percentage of subjects experiencing events of lipodystrophy assessed as possibly or probably related to IDet was 1.1% which is comparable with the frequency category 'uncommon' in the current label text.

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, please refer to table below. 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.

Table 2 - Serious adverse events – treatment-emergent - summary - safety analysis set

	IDeg OD N	(%)	E	R	IDet N	(%)	E	R
Number of Subjects	174				175			
Events	18	(10.3)	25	15	16	(9.1)	24	16
Severity								
Severe	9	(5.2)	14	9	7	(4.0)	9	6
Moderate	8	(4.6)	8	5	9	(5.1)	11	7
Mild	3	(1.7)	3	2	3	(1.7)	4	3
Related to Investigational Product								
Probably	4	(2.3)	4	2	2	(1.1)	2	1
Possibly	3	(1.7)	4	2	2	(1.1)	3	2
Unlikely	11	(6.3)	17	11	12	(6.9)	19	13
Related to Bolus Insulin								
Probably	3	(1.7)	3	2	1	(0.6)	1	1
Possibly	2	(1.1)	3	2	3	(1.7)	3	2
Unlikely	13	(7.5)	19	12	13	(7.4)	20	14
Related to Device								
No	18	(10.3)	25	15	16	(9.1)	24	16
Outcome								
Recovered	18	(10.3)	25	15	15	(8.6)	23	16
Recovering	0	(0.0)	0	0	1	(0.6)	1	1

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.

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, please refer to table 3. 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 MAH. 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 were included as SAEs in the narratives from the safety database.

Table 3 - Treatment emergent serious adverse events by system organ class and preferred term - summary - safety analysis set

	IDeg OD N	(%)	E	R	IDet N	(%)	E	R	Total 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

Within each of the age groups, the number of subjects reporting SAEs was low. In both treatment arms, the observed rate of SAEs was higher in children aged 1 to 5 years than in older subjects.

Most of the events were single episodes in a single subject. Infections and 'blood ketone body increased' occurred more frequently in the youngest age group of both treatment arms.

Other significant adverse events

Adverse events leading to dose reduction

A total of 3 subjects were withdrawn from the trial due to AEs, all from the IDet arm. One subject was withdrawn due to 'hypoglycaemic seizure', one due to 'anxiety disorder' and one due to 'wrong dose administered'. The 3 subjects were 5, 11 and 13 years. The anxiety disorder was regarded as unlikely

related to basal insulin while the two other events were judged as having a probable or possible relation to trial product. The rate of withdrawal due to AEs was low and did not give rise to any safety concerns.

Medication errors concerning trial products

Medication errors were defined as MESIs. The proportion of subjects experiencing medication errors as well as the associated rates were similar in the IDeg and IDet treatment arms (8 and 9 per 100 PYE, respectively), as was the rate of events considered probably or possibly related to trial product (3 and 4 events per 100 PYE, respectively). Most of the events were of mild severity and subjects recovered from all events. Two of the events were reported as SAEs (both in the IDeg arm). The most common AE related to medication error was 'wrong drug administered' (6 events per 100 PYE in each treatment arm). These cases represented mix-ups between basal and bolus insulin. A total of 18 events were reported, with 9 events in each treatment arm. In 11 of the cases bolus insulin was administered instead of basal insulin and in 7 cases basal insulin was administered instead of bolus insulin. Six of these events were followed by hypoglycaemia, 2 cases in the IDeg arm and 4 cases in the IDet arm, including one event of severe hypoglycaemia. Most of the mix-ups were reported from the US during the initial part of the trial due to the use of similar coloured NovoPen Junior devices for basal and bolus insulin. Few mix-up cases were reported after introduction of different colour NovoPen Junior pens to be used for basal and bolus insulin. One event of 'accidental overdose' was reported in the IDeg arm compared to 5 events in the IDet arm.

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 MAH 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 MAH 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 above)

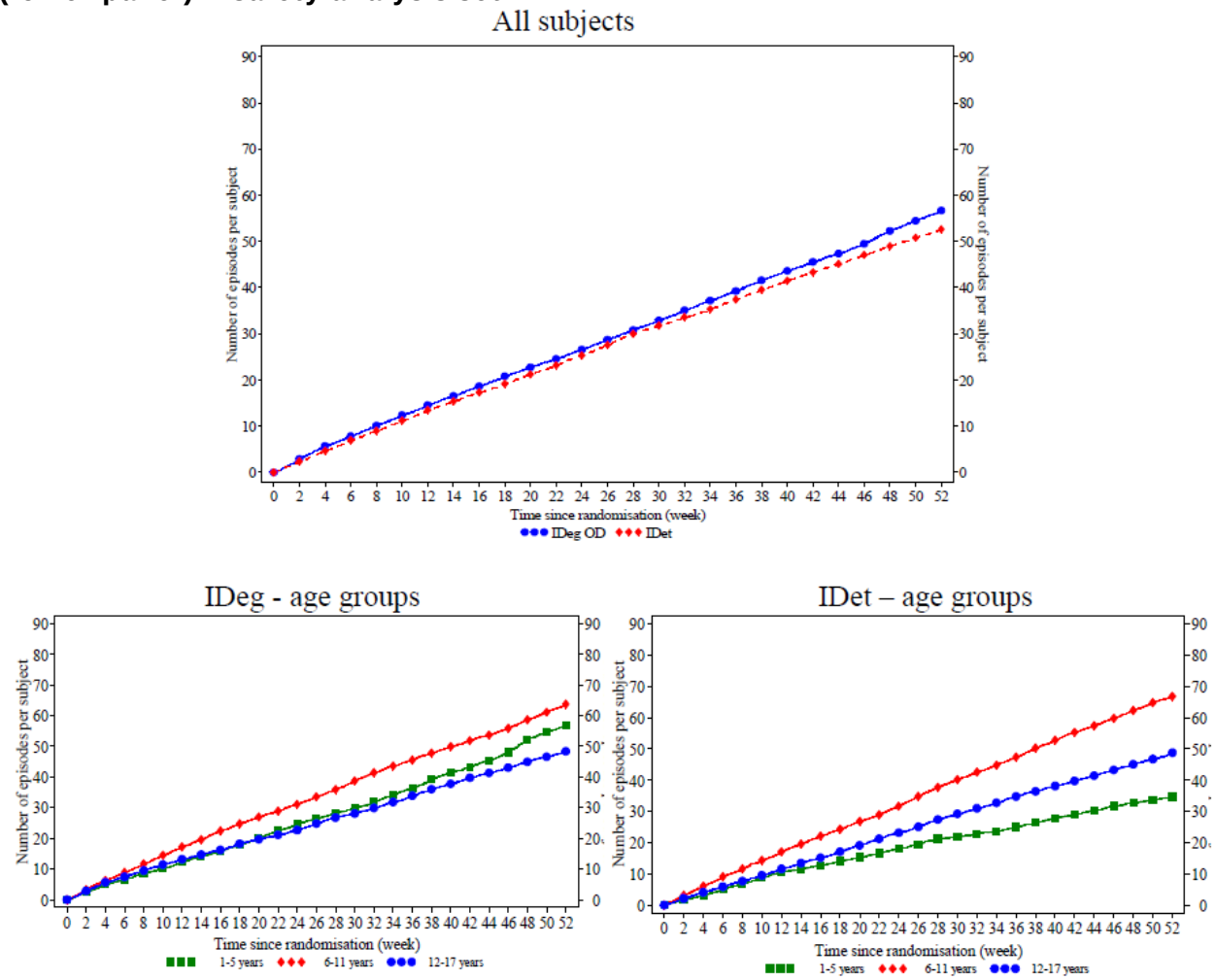
Confirmed hypoglycaemia

The rate of confirmed hypoglycaemia was similar for IDeg and IDet (estimated rate ratio IDeg/IDet: 1.11 [0.89; 1.38]95%CI) with the observed rate of confirmed hypoglycaemia being 5771 and 5405 events per 100 PYE in the IDeg and IDet treatment arms.

Confirmed hypoglycaemia over time is shown in figure 1 below. The majority of the confirmed hypoglycaemic episodes occurred during daytime in both treatment arms. Overall, the results observed across the age groups were in accordance with those seen for all subjects; though for IDet, the rate of confirmed hypoglycaemia was lower for children aged 1-5 years compared to the two other age groups.

In both treatment groups, children aged 6-11 years 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.

Figure 1- Confirmed hypoglycaemic episodes – treatment emergent - mean cumulative function – for all subjects (upper panel) and by treatment and age group (lower panel) – safety analysis set



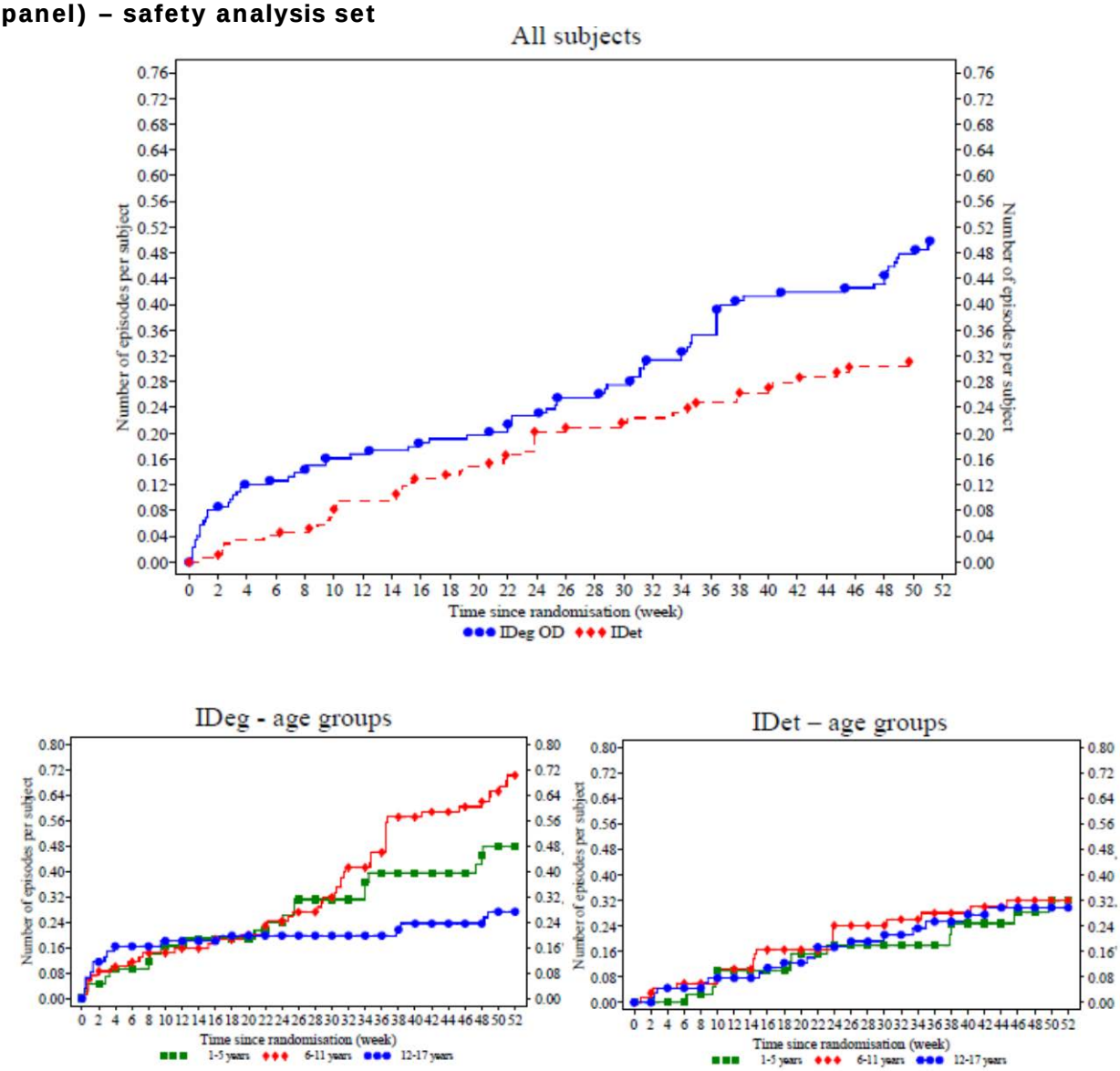
Confirmed hypoglycaemia was defined as hypoglycaemic episodes confirmed by plasma glucose < 3.1 mmol/L or severe (according ISPAD definition).

Severe hypoglycaemic episodes

ISPAD defined severe hypoglycaemic episodes were reported by 18% of subjects in the IDeg arm and 14% in the IDet arm with a total of 82 events and 48 events, respectively. The observed rate of severe hypoglycaemia episodes was higher in the IDeg arm than in the IDet arm (51 vs. 33 episodes per 100 PYE), but there was no statistically significant difference between the treatment arms (estimated rate ratio (IDeg/IDet): 1.30 [0.64; 2.64]95%CI. The majority of the severe hypoglycaemic episodes (approximately 80%) occurred during the daytime in both treatment arms. In the majority of cases (close to 80%), bolus insulin was the last insulin administered prior to the event. All episodes of severe hypoglycaemia were evaluated in a blinded manner by an independent external expert. This pre-specified evaluation is presented in the sub-section 'Severe hypoglycaemia classified by external blinded expert' below.

The observed rate of severe hypoglycaemic episodes was higher with IDeg than IDet during the first 4 weeks of treatment as well as during the extension period of the trial, please refer to figure 3 below. The difference between treatments during the extension period of the trial, (Figure 2) may be related to the difference in rates of confirmed and severe hypoglycaemia observed between the two treatment groups for subjects who did not continue in the extension period after completing the main trial. However, the observed rates of severe hypoglycaemic episodes during the first 26 weeks of treatment were higher with IDeg than with IDet (51 vs. 40 severe episodes). The differences were not statistically significant.

Figure 2: Severe hypoglycaemic episodes - treatment emergent - mean cumulative function – for all subjects (upper panel) and by treatment and age group (lower panel) – safety analysis set

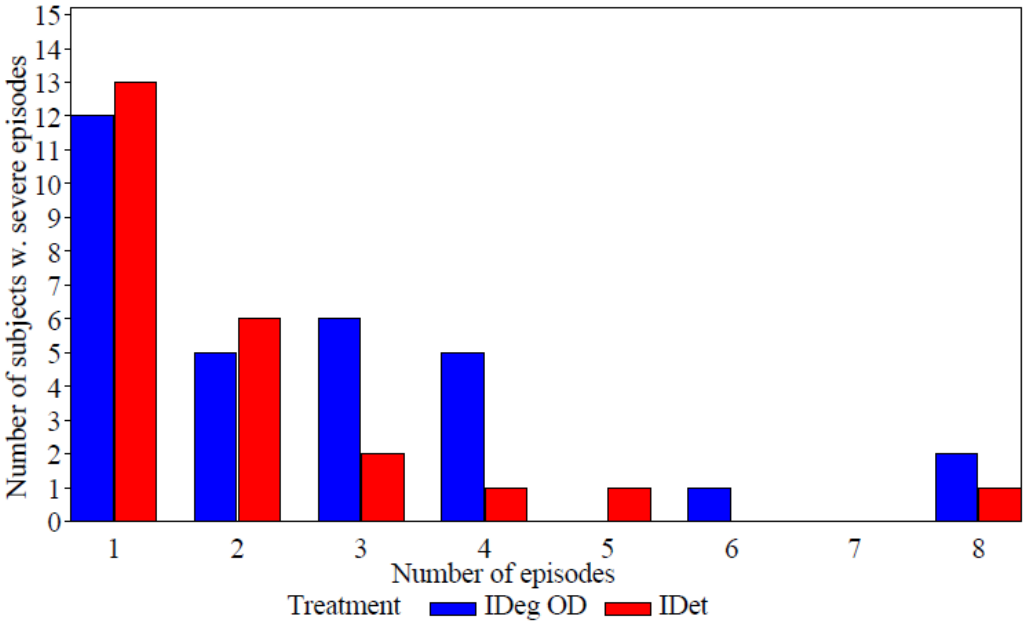


Severe hypoglycaemia according to ISPAD definition: The child has altered mental status and cannot assist in his own care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy.

Cross-reference: Summary 2.7.4, Figure 2-3

When evaluating the severe hypoglycaemic events, it is important to note that these were distributed unevenly between subjects. 30 subjects (8.6%) reported 2 or more severe hypoglycaemia episodes of which 11 (3.1%) subjects reported 4 or more severe episodes (8 subjects treated with IDeg and 3 subjects treated with IDet), see Figure 3. In the IDeg group, these 8 subjects (4.6%) accounted for more than half of all reported severe hypoglycaemia (42 out of 82 episodes; 51%). The 3 subjects (1.7%) treated with IDet accounted for 17 episodes (35%). The majority of subjects in both treatment groups did not experience severe hypoglycaemia (143 [82%] vs. 151[86%] subjects in the IDeg arm and IDet arm, respectively). Furthermore, the percentage of days without severe hypoglycaemia was similar (99.9%) for the two treatment arms in accordance with the results.

Figure 3 - 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.

Severe hypoglycaemia classified by external blinded expert

The ISPAD definition of severe hypoglycaemia is very broad and includes a subjective element: 'The child has altered mental status and cannot assist in his own care,..' and determining whether an episode fulfils the definition can be challenging, especially for episodes involving young children. Due to this challenge, an independent, external paediatric endocrinologist conducted a blinded pre-specified classification of all reported episodes of severe hypoglycaemia. Based on the external classification, the observed rates of severe hypoglycaemia were lower in both treatment arms (38 and 26 events per 100 PYE in the IDeg and IDet arms) compared to the observed rates for all reported episodes of severe hypoglycaemia. It is also important to note that the classification criterion most commonly met was 'altered mental status and cannot assist in his own care' and that the difference between the treatment groups was driven by this criterion. The number of episodes associated with being 'semiconscious or unconscious' or 'coma ± convulsions' was low and similar in the IDeg and IDet arms, with no statistically significant difference between the two treatments, see tables 4 and 5 below .

Due to differences in trial design, including different criteria for severe hypoglycaemia, the rates of severe hypoglycaemia reported in this trial should not be directly compared to rates of severe hypoglycaemia in other published randomised clinical trials in paediatric subjects with T1DM.

In those trials, a more narrow definition of severe hypoglycaemia was used, which did not include the criterion 'altered mental status and cannot assist in his care'.

Table 4: External classified severe hypoglycaemic episodes – treatment-emergent - summary - safety analysis set

	IDeg OD N	(%)	E	R	IDet N	(%)	E	R
Number of Subjects	174				175			
All reported severe hypoglycaemia	31	(17.8)	82	51	24	(13.7)	48	33
Externally classified episodes	31	(17.8)	82	51	24	(13.7)	48	33
Severe hypoglycaemia	28	(16.1)	61	38	22	(12.6)	38	26
Altered mental status and cannot assist in his care	21	(12.1)	46	28	11	(6.3)	18	12
Semiconscious or unconscious	7	(4.0)	7	4	6	(3.4)	10	7
Coma ± convulsions	6	(3.4)	8	5	7	(4.0)	10	7
Not severe hypoglycaemia	5	(2.9)	13	8	5	(2.9)	8	5
Not possible to classify	5	(2.9)	8	5	1	(0.6)	2	1

N: Number of subjects, %: Percentage of subjects with the event, E: Number of events,
R: Event rate per 100 patient years of exposure
Severe hypoglycaemia according to ISPAD definition: 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)

Table 5: External classified severe hypoglycaemic episodes – semiconscious or unconscious or coma ± convulsions – treatment emergent – Post hoc analysis – safety analysis set

	FAS	N	Estimate	95% CI
LSMeans; episodes per 100 PYE				
IDeg OD	174	174	9.95	
IDet	175	175	15.94	
Treatment rate ratio				
IDeg / IDet			0.62	[0.24; 1.60]

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

Cross-reference: Summary 2.7.4, Table 2-20

The percentage of days without severe hypoglycaemia was similar (99.9%) for the two treatment arms. This was in accordance with the results for confirmed episodes, and indicated that subjects in the IDeg arm reported more severe hypoglycaemic episodes within a short interval of time. Around 10% of subjects reported two or more severe hypoglycaemia episodes (see Figure), and the evaluation of severe hypoglycaemia was impacted by a few subjects reporting several episodes, some within a relatively short time interval. In some cases subjects recorded low levels of plasma glucose less than 1 hour apart and reported these as separate hypoglycaemic episodes. When a hypoglycaemic episode occurs, parents will often recheck the blood glucose level shortly after treating the episode to ensure that the blood glucose level is increasing. If the blood glucose level remained low, likely reflecting inadequate time for blood glucose to rise in response to treatment, this was sometimes reported as a distinct hypoglycaemia episode although it most likely represented the same episode.

ISPAD defined severe hypoglycaemia across age groups

The overall frequency of severe hypoglycaemia within each age group was low and the overall hypoglycaemia evaluation was based upon a low number of subjects with relatively few episodes.

Therefore comparison between age groups should be made with caution. Few cases of severe hypoglycaemia in few subjects influence such a comparison markedly.

The observed rate of ISPAD defined severe hypoglycaemia differed between age groups in the IDeg arm with a higher observed rate of severe hypoglycaemia in children aged 6-11 years than in the other age groups. For IDet, the observed rate of severe hypoglycaemia was similar for all three age groups, please refer to table 6 below.

Table 6– Severe hypoglycaemic episodes – treatment emergent, all subjects and by age group – safety analysis set

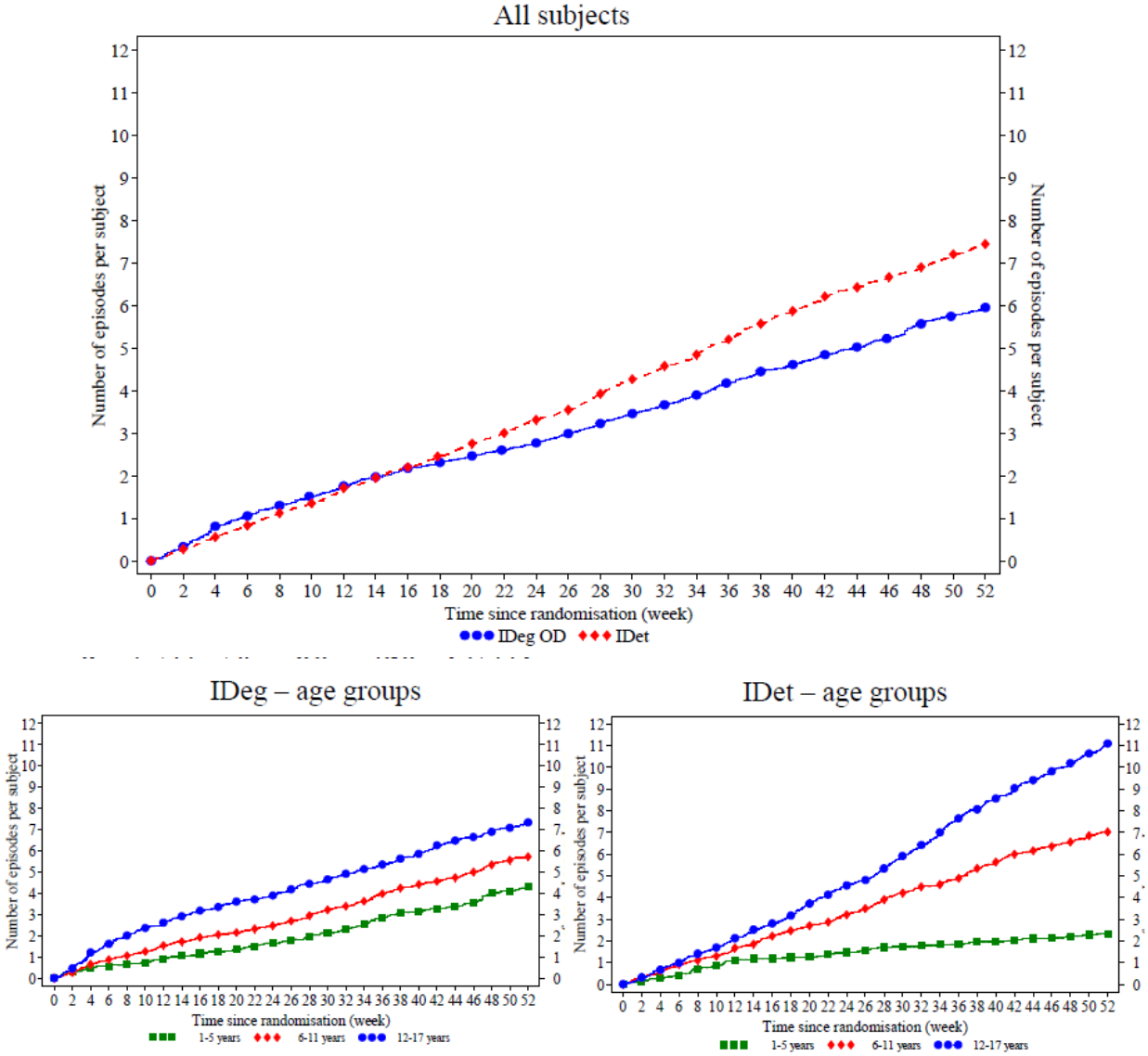
	IDeg					IDet			
	n	(%)	E	R		n	(%)	E	R
All subjects, N=174	31	(17.8)	82	51	All subjects, N=175	24	(13.7)	48	33
1-5 yrs, N=43	8	(18.6)	19	49	1-5 yrs, N=41	6	(14.6)	11	32
6-11 yrs, N=70	14	(20.0)	47	71	6-11 yrs, N=68	11	(16.2)	20	34
12-17 yrs, N=61	9	(14.8)	16	28	12-17 yrs, N=66	7	(10.6)	17	31

N: number of subjects in the safety analysis set, n: number of subjects with severe hypoglycaemia. %: Percentage of subjects with the event, E: Number of events, R: Event rate per 100 patient year(s) of exposure.
Severe hypoglycaemia: subject has altered mental status and cannot assist in his care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or i.v. glucose).

Nocturnal hypoglycaemia

The observed rate of nocturnal confirmed episodes was numerically lower with IDeg compared to IDet (603 and 760 episodes per 100 PYE), although there was no statistically significant difference between treatment arms (estimated rate ratio IDeg/IDet: 0.99 [0.72; 1.34]95%CI). As seen for all confirmed hypoglycaemic episodes, the observed rates of nocturnal confirmed hypoglycaemia differed more between the age groups in the IDet arm than in the IDeg arm. Within the IDet group, the observed rate was lowest in the 1-5 year age group, please refer to figure 4 below.

Figure 4: Nocturnal 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). Nocturnal period: the period between 23:00 p.m. and 07:00 a.m. (both included).

In general, the number of nocturnal severe hypoglycaemic episodes was low in both treatment arms, which precluded meaningful statistical analysis comparisons between treatments, and any comparison should be taken with caution. 10 subjects treated with IDeg and 9 subjects treated with IDet reported a total of 18 vs. 10 nocturnal severe hypoglycaemic episodes leading to similar low observed rates (11 vs. 7 episodes per 100 PYE)

Hyperglycaemia and hyperglycaemia with ketosis

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.

Continuous glucose monitoring

CGM was performed before and after 26 weeks of treatment in a subset of the trial population and fulfilled the requirements specified in the PIP. This included a total of 74 subjects in the IDeg arm and 75 subjects in the IDet arm distributed with a minimum of 19 subjects in each age group of each treatment arm. Due to the small number of subjects within the age groups and the relatively large variation associated with these measurements, comparison across age groups should be done with caution.

No statistically significant differences between the IDeg and IDet treatment arms were shown for any of the endpoints related to CGM after 26 weeks of treatment. However, the rates of low interstitial glucose (IG; <3.1mmol/L or ≤3.9 mmol/L) generally reflected the pattern for hypoglycaemic episodes during the main 26-week treatment period, and the results related to high IG (>11.1 mmol/L) were generally in agreement with the assessments for hyperglycaemic episodes during the main trial period.

Differences in hypoglycaemia and hyperglycaemia between subjects continuing or discontinuing after 26 weeks of treatment

A higher proportion of subjects randomised to IDet (21%) than to IDeg (10%) did not continue into the extension phase of the trial. To evaluate whether there were any apparent differences between subjects who continued in the extension period and those who left the trial after completing the main trial period, comparisons were made between these two subsets of subjects.

The observed rates of confirmed and severe hypoglycemia differed markedly between the subjects who did not continue after completing the main trial and those who continued in the extension period with a different pattern observed for the two treatment arms, see table 7 below; however, data should be interpreted with caution due to the low number of subjects not continuing.

Table 7– Hypoglycemic episodes by classification – treatment emergent – summary - main completers not in extension vs. extended trial set – Week 26.

	IDeg OD N	(%)	E	R	IDet N	(%)	E	R
Main completers not in extension								
Number of Subjects	18				37			
Confirmed	18	(100.0)	515	5499	37	(100.0)	1514	7948
Severe	1	(5.6)	1	11	7	(18.9)	12	63
Nocturnal confirmed	13	(72.2)	87	929	27	(73.0)	131	688
Extension trial set (ETS) Week 26								
Number of Subjects	152				128			
Confirmed	148	(97.4)	4581	5788	117	(91.4)	3306	4956
Severe	21	(13.8)	38	48	9	(7.0)	21	31
Nocturnal confirmed	96	(63.2)	431	545	77	(60.2)	486	729

N: Number of subjects, %: Percentage of subjects with the event, E: Number of events
R: Event rate per 100 patient year(s) of exposure
Confirmed hypoglycaemia was defined as hypoglycaemic episodes confirmed by plasma glucose < 3.1 mmol/L or severe (according to ISPAD definition).

The observed rate of hyperglycaemic episodes and hyperglycaemic episodes with ketosis also differed between subjects discontinuing after 26 weeks and those who continued. In the IDeg arm, the observed rates of hyperglycaemia were similar for the two subsets of subjects. The observed rate of hyperglycaemia with ketosis was higher in subjects discontinuing after the main trial period, albeit this observation was based on few subjects with relatively few episodes. In the IDet arm, the observed rates for both hyperglycaemia and hyperglycaemia with ketosis were higher in subjects, who discontinued after 26 weeks compared to those who continued in the extension period

Laboratory findings

Antibody development

All subjects were naïve to IDeg at baseline. The number of subjects naïve to IDet is unknown, but 48% of the subjects randomised to the trial (and 47.2% of those randomised to IDet treatment) were treated with IDet at screening.

Cross-reacting antibodies

The mean level of insulin antibodies cross-reacting between IDeg or IDet and human insulin decreased slightly with IDeg and increased slightly with IDet during the 52-week treatment period. The same patterns were observed for the 3 age groups, though the mean levels at baseline varied slightly with age. Cross-reacting insulin antibodies at Week 52 were plotted against HbA1c, change from baseline in HbA1cand total daily insulin dose in units/kg. There was no apparent correlation between cross-reacting antibodies and any of these variables.

Insulin-specific antibodies

The mean level of insulin antibodies specific to IDeg or IDet remained low during the trial at a slightly higher level with IDet than IDeg; mean levels with IDeg was around 0 % B/T and mean levels with IDet was around 4 % B/T. The mean level of insulin antibodies specific to IAsp remained low during the trial at a similar level within the IDeg and IDet arms.

Insulin antibodies specific to IDeg or IDet at Week 52 were plotted against HbA1c, change from baseline in HbA1cor total daily insulin dose in units/kg. There was no apparent correlation between specific antibodies and any of these variables.

Clinical laboratory evaluations

Mean biochemistry, haematology and lipids laboratory values remained stable during the trial, and there was no apparent difference between the two treatment arms in the mean level of the specific laboratory parameters assessed. The majority of subjects' values remained within the reference ranges at baseline and at the end of trial. Few clinically relevant changes from baseline in individual laboratory parameters were reported as adverse events, none of which were considered to have a possible or probably relation to basal insulin.

Vital signs, physical findings and other observations related to safety

Due to the heterogeneity in the trial population with respect to age and country of origin, standard deviation (SD) score for body weight was included as a post-hoc endpoint in order to be able to compare body weight across age groups. To estimate the growth of children, standardised weight was calculated for each year of age and for each sex. Thus, a child with a weight equal to the mean value for its age and sex has an SD score of 0, while a child with a weight 2 SDs above the mean value for its age and sex has an SD score of +2.

The weight SD scores were similar between treatment groups at baseline (0.33 vs. 0.32 with IDeg and IDet). During the treatment period, there was a small increase in weight SD score of +0.11 in the IDeg arm and a small decrease of -0.06 in the IDet arm. After 52 weeks of treatment, a statistically significant treatment difference was observed in the analysis of change from baseline in weight SD score (IDeg-IDet: 0.17 $[0.10; 0.25]_{95\% CI}$), demonstrating that subjects in the IDeg arm gained weight, whereas subjects in the IDet arm lost weight relative to the adjusted weight SD score. This is in accordance with the results from previous studies showing that adult and paediatric subjects with T1DM and adults with T2DM typically gain less weight with IDet than with other basal insulin products. The change in weight during the trial across the three age groups reflected that seen for all subjects, except in the young children aged 1-5 years in the IDet arm, where the decrease in SD-score was more pronounced compared to the other age groups. This decrease was not considered clinically relevant.

Discontinuation due to adverse events

A total of 3 subjects were withdrawn from the trial due to AEs, all from the IDet arm. One subject was withdrawn due to 'hypoglycaemic seizure', one due to 'anxiety disorder' and one due to 'wrong dose administered'. The 3 subjects were 5, 11 and 13 years. The anxiety disorder was regarded as unlikely related to basal insulin while the two other events were judged as having a probable or possible relation to trial product. The rate of withdrawal due to AEs was low and did not give rise to any safety concerns.

Summary of safety data for extrapolation to children/adolescents aged 10-17 years with T2DM

The extrapolation and modelling study included a qualitative component evaluating key safety parameters from the efficacy and safety trials in children/adolescents and adults in context of the estimated dose-response relationships (please refer to section 2.3.4. PK/PD Modelling). For safety data, a qualitative extrapolation was applied to the hypoglycaemic episodes and AEs.

No safety concerns were raised for children/adolescents as compared with adults with T1DM in terms of hypoglycaemic episodes, AEs or antibody profiles or in the sub-population of adults with T2DM in terms of hypoglycaemic episodes or AEs.

Overall, the results support the extension of safety in adults with T2DM and children/adolescents with T1DM to children/adolescents aged 10-17 years with T2DM.

The extrapolation and modelling study report thus supports the potential to obtain a similar effective glycaemic control with IDet in children/adolescents aged 10-17 years with T2DM as observed in adults without compromising safety.

2.5.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

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. 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. The MAH monitors injection site reactions from the paediatric population through the routine pharmacovigilance, which is considered adequate.

Although not significantly different, 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. Due to the higher rate of observed severe hypoglycaemia a warning has been implemented in section 4.4 of the Tresiba SmPC (In children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimise the risk of hypoglycaemia). In the Levemir SmPC no warning in section 4.4 was initially proposed, and the MAH was asked to discuss if a warning in section 4.4 like the one for Tresiba also should be included for Levemir. The MAH agreed to include the same warning in section 4.4 in the SmPC for Levemir as included in the SmPC for Tresiba.

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 higher in the IDet arm compared to the IDeg arm. This information is reflected in the Levemir SmPC section 5.1.

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.

2.5.2. Conclusions on clinical safety

Both insulin products provided an efficacious treatment with acceptable safety profiles.

2.5.3. PSUR cycle

Even though no new safety information has arisen during the procedure, the information in this patient group is very limited. The CHMP therefore recommends that the PSUR cycle should be changed to 1 year instead of 3 years.

The annex II related to the PSUR, refers to the EURD list which needs to the updated.

2.6. Risk management plan

No RMP was submitted as part of this procedure.

Analysis of additional data from Trial 3561 did not lead to any significant change to the established benefit risk profile of insulin detemir, and the MAH confirmed that the currently approved risk management plan remains unchanged and is still applicable.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. 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), which were reviewed and accepted by the CHMP.

Section 4.1

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

Section 4.2

Posology

…

When Levemir is used in combination with oral antidiabetic medicinal products or when added to GLP-1 receptor agonists it is recommended to use Levemir once daily, initially at a dose of ~~10 units or~~ 0.1-0.2 units/kg or of 10 units **in adult patients**. The dose of Levemir should be titrated based on the individual patient's needs.

…

For individual dose adjustments, the following two titration guidelines are recommended for adults:

…

Paediatric population

~~The efficacy and safety of Levemir were demonstrated in adolescents and children aged 2 years and above in studies up to 12 months (see section 5.1).~~ Levemir can be used in adolescents and children from the age of 1 year (see section 5.1). When changing basal insulin to Levemir, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to minimise the risk of hypoglycaemia (see section 4.4).

In children and adolescents, glucose monitoring should be intensified and the Levemir dose adjusted on an individual basis

~~Levemir has not been studied in children below the age of 2 years~~. The safety and efficacy of Levemir in children below the age of 1 year have not been established.

No data are available

Section 4.4

…

Hypoglycaemia

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

In children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimise the risk of hypoglycaemia.

…

Section 4.8

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in the paediatric population do not indicate any differences to the broader experience in the general diabetes population

Section 5.1

…

Paediatric population

The efficacy and safety of Levemir has been studied for up to 12 months, in three ~~wo~~ randomised controlled clinical trials in adolescents and children (n=1045~~694~~ in total); ~~one of~~ the trials ~~studies~~ included in total 167~~82~~ children aged ~~2~~1-5 years~~. Both~~ The trials demonstrated that glycaemic control (HbA1c) with Levemir is comparable to NPH insulin and insulin degludec when given as basal-bolus therapy, using a non-inferiority margin of 0.4%. In the trial comparing Levemir vs insulin degludec, the rate of hyperglycaemic episodes with ketosis was significantly higher for Levemir, 1.09 and 0.68 episodes per patient-year of exposure, respectively~~. In addition l~~Less weight gain (SD score, weight corrected for gender and age) was observed with Levemir than with NPH insulin.

The trial including children above 2 years was extended for an additional 12 months (total of 24 months treatment data) to assess antibody formation after long-term treatment with Levemir. After an increase in insulin antibodies during the first year, the insulin antibodies decreased during the second year to a level slightly higher than pre-trial level. Results indicate that antibody development had no negative effect on glycaemic control and Levemir dose.

Efficacy and safety data for adolescent patients with type 2 diabetes mellitus have been extrapolated from data for children, adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results support the use of Levemir in adolescent patients with type 2 diabetes mellitus.

Section 5.2

Paediatric population

The pharmacokinetic properties of Levemir were investigated in young children (1–5 years), children (6–12 years) and adolescents (13–17 years) and compared to adults with type 1 diabetes. There were ~~as~~ no

clinically relevant differences in pharmacokinetic properties between young children, children, adolescents and adults.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of IDet in the treatment of children with T1DM is supported by clinical data from trial 3561, an open-labelled, randomised, treat-to-target, safety and efficacy trial comparing IDet and IDeg in combination with IAsp in subjects with T1DM between aged 1 to 18 years. 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 study included a total of 350 subjects out of which 280 continued in the 26-week extension period. In terms of change in HbA1c after 26 weeks, non-inferiority between the two treatments was demonstrated as the upper limit of the 95% CI for the estimated treatment difference was ≤0.4% (0.15 %-points [-0.03; 0.32]$_{95\%CI}$). This was confirmed in the PP analysis set and based on sensitivity analyses for the primary endpoint. The results within the three age groups were comparable to the results seen for all subjects. Thus the study demonstrates that IDet was as efficacious as IDeg in terms of reducing HbA_{1c} with both treatments approaching the target HbA1c of <7.5%. After 52 weeks of treatment with IDet and IDeg the glycaemic control improved in both groups with similar HbA1c levels in the two groups and lower FPG in the IDeg arm. This glycaemic control was achieved with fewer daily IDeg units compared to IDet. Subjects treated with IDeg required less total as well as basal insulin compared with subjects treated with IDet.

Uncertainty in the knowledge about the beneficial effects

The number of patients in the youngest age group (1-5 years of age) is still limited. A slight increase in HbA_{1c} was observed in the age group 6-11 years after 12 weeks, whereas fluctuations were also observed in the other age groups during the trial, especially among adolescents. This is not unexpected considering that these age groups are difficult to treat. Importantly, HbA_{1c} was lower after 52 weeks of treatment compared to baseline across all age groups with both treatments. No clinical data has been presented for adolescent patients with T2DM; instead efficacy in this subgroup has been extrapolated from available data in adolescents and adults with T1DM and a representative subpopulation with T2DM. The data in T1DM indicate that higher insulin doses may be required in adolescent patients, partly due to higher insulin resistance during puberty, and this is expected also in T2DM patients. However, data in adult T2DM patients show an adequate effect on glycaemic control also in obese patients. Higher dose requirements for adolescents than for adults are considered of limited impact for the use of IDet in adolescents, as insulin doses are always individually titrated. Thus from an efficacy point of view there are no concerns with regards to the use of IDet in adolescents with T2DM.

The population PK analysis based on two paediatric studies did not focus on the age group of patients aged 1-<2 years. Rather it compared small children (1-5 years), children (6-11 years), adolescents (12-17 years) and adults (18 years -). The conclusion of the PK analysis was that the weight-based dosed concentration-time profile in small children (1-5 years) is comparable to the concentration-time profiles in the other age groups. Study 3561 enrolled only four patients aged less than 2 years, two on insulin detemir and two receiving insulin degludec.

Thus, there is uncertainty about the validity of the PoP-PK model as relevant for children between 1 and <2 years of age since the model only includes data for one such child. The vast majority of the data for small children are from children aged 2.5 - 5 years. Consequently, if there is a different covariate effect in 1 - <2 year olds, one would not know, and the model derived factors would not be of help. This argument is also applicable to the linearity of the relationship between body weight and clearance. So even if no age related difference is apparent, there is no solid evidence of an absence of a difference.

Risks

Unfavourable effects

In terms of safety, no differences overall were observed between IDet and IDeg in terms of TEAEs and the rate of AEs. Injection site reactions were more frequently reported in the IDeg group compared to the IDet arm. 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. The applicant monitors injection site reactions from the paediatric population through the routine pharmacovigilance, which is considered adequate.

Although not significantly different, there was a higher rate of observed severe hypoglycemia in the IDeg arm compared to the IDet arm. The proposal of the applicant to modify the dosing recommendation for children and adolescents in relation to transfer or switch from other insulin products to IDeg is endorsed. 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; this is reflected in SmPC section 5.1. 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.

Uncertainty in the knowledge about the unfavourable effects

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, which again were driven by 5 subjects reporting 22 of the 28 episodes reported during the extension. Children in this age group go to school and many participate in various physical activities, while they still may not be able to take full responsibility of adjusting their bolus doses accordingly. Thus, it may be particularly challenging to ensure that the insulin dose matches food intake and physical activity, as adult assistance may not be available. This is adequately reflected in the SmPC. Hypoglycaemia is an identified risk in the RMP, and the applicant has committed to expand routine pharmacovigilance activities to include the presentation of post-marketing cases of hypoglycaemia reported in the paediatric population stratified by age group in future PSURs. This is acceptable. There is no available safety data in adolescents with T2DM; however, analysis of the safety data in adolescents and adults with T1DM does not indicate any difference in the safety profile between these two populations. With regards to hypoglycaemia, data from a representative

subpopulation of adult T2DM patients (BMI≥30 kg/m^2, insulin naïve, previously on metformin only) show that the risk of hypoglycaemia is considerably lower in this population (99 episodes per 100 PYE) compared to adolescent and adult patients with T1DM (4913 vs 3778 episodes per 100 PYE, respectively). When extrapolating these data to adolescent T2DM patients, a somewhat higher risk of hypoglycaemia than in adult T2DM patients would be expected.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Sufficient data have been provided showing that the efficacy of IDet in achieving an adequate metabolic control is comparable to that of IDeg in children aged 1 to 18 years.

The stable insulin levels achieved with long-acting insulin such as IDet may however cause more hypoglycaemias in insulin sensitive individuals with low insulin doses and fluctuations in insulin need due to variations in food intake and physical activity. Actually, severe hypoglycaemias were more common in the IDeg treated group, especially in children aged 6-11 years. On the other hand, nocturnal hypoglycaemias were numerically less with IDeg than with IDet, in line with the observations made in adult patients with T1DM.In the absence of clinical data in adolescents with T2DM, the efficacy and safety of IDet has been extrapolated from data in adolescents and adults with T1DM and adult patients with T2DM. Although the absence of data means that some uncertainty remains, these data are considered sufficient to conclude that IDet may be used also in adolescent patients with T2DM. Insulin requirements are expected to be high in this population; however, as IDet is individually titrated this was not of concern. There was no indication that the safety profile would be markedly different in this population than in adult patients with T2DM. Hypoglycaemia, being less common than in T1DM, was considered to be manageable.

Regarding the uncertainty about the age group 1 - <2 years, the following should be considered: There is clearly a medical need for basal insulin treatment even in children as young as 1 - <2 years of age. Further, from the perspective of biological plausibility, it is difficult to argue that covariates other than body weight would be critical in this age group when they appear not to be in children aged 2.5-5 years. It should be noted that the dose in any case will be titrated based on careful monitoring which is particularly important in this age group due to the irregular patterns of food intake compared to older children (as highlighted by the MAH). In terms of the risk of hypoglycaemia, the proposed warning in section 4.4 aims at drawing the attention of prescribers to this issue and stresses the importance of being vigilant in adjusting the dose in children. Based on these considerations and despite the limitations of the Pop-PK analysis, it is considered acceptable to extend the indication of Levemir to also include children aged 1 - <2 years.

Discussion on the Benefit-Risk Balance

The benefit-risk balance for IDet in children and adolescents aged 1 to 18 years is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of Indication for Levemir to include new population, i.e. children between 1 and less than 2 years of age; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the PK, efficacy and safety information. The Package Leaflet is updated accordingly.

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0172/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.