18 December 2014
EMA/CHMP/355375/2015
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Tresiba

### International non-proprietary name: INSULIN DEGLUDEC

### Procedure No. EMEA/H/C/002498/II/0011

## 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 10 June 2014 an application for a variation.

This application concerns the following medicinal product:

| **Centrally authorised Medicinal product:**<br><br>**For presentations: See Annex A** | **Common name:** |
|---|---|
| Tresiba | INSULIN DEGLUDEC |

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 |

The Marketing authorisation holder (MAH) applied for an extension of the indication for the treatment of diabetes mellitus in adolescents and children from the age of 1 year. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The 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/0129/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0129/2014 was completed.

The PDCO issued an opinion on compliance for the PIP P/0129/2014.

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

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

| Timetable | Dates |
|---|---|
| Submission date | 10 June 2014 |
| Start of procedure: | 27 June 2014 |
| CHMP Rapporteur Assessment Report | 20 August 2014 |
| PRAC Rapporteur Assessment Report | 22 August 2014 |
| PRAC Rapporteur Updated Assessment Report | 3 September 2014 |
| PRAC Meeting, adoption of PRAC Assessment Overview and Advice | 11 September 2014 |
| Rapporteur Revised Assessment Report | 19 September 2014 |
| Request for supplementary information (RSI) | 25 September 2014 |
| CHMP Rapporteur Assessment Report | 17 November 2014 |
| PRAC Rapporteur Assessment Report | 17 November 2014 |
| PRAC Rapporteur Updated Assessment Report | 24 November 2014 |
| PRAC Meeting, adoption of PRAC Assessment Overview and Advice | 4 December 2014 |
| Opinion | 18 December 2014 |

## 2. Scientific discussion

### *2.1. Introduction*

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

IDeg (Tresiba) is a basal insulin. On 21 January 2013, the European Commission approved Tresiba 100 units (U)/mL and 200 U/mL for treatment of adult patients with diabetes mellitus (T1DM or T2DM) by once-daily (OD) subcutaneous administration.

Compared to human insulin, IDeg is a long-acting basal insulin analogue. Due to the changed structure IDeg forms soluble and stable multi-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of IDeg monomers from the multihexamers results in a slow and continuous delivery of IDeg from the subcutaneous injection site into the circulation, leading to the observed long pharmacokinetic and pharmacodynamic profiles. Furthermore, binding of the fatty acid moiety of IDeg to albumin contributes to some extent to the protraction mechanism. At the target tissues, IDeg monomers bind to and activate

insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake. IDeg has a duration of action exceeding 24 hours, which means it can be dosed once daily in all subjects.

The purpose of this application is to update current prescribing information to include specific information on the use of IDeg in children 1 to less than 18 years of age with diabetes mellitus. It is further proposed that exposure of IDeg in children and adolescents (between 1 and less than 18 years of age) with T1DM or T2DM is no longer considered as missing information. Sections 4.1, 4.2, 4.8 and 5.1 are proposed to be updated.

All of the components included in this application were planned and conducted in agreement with the European Medicines Agency (EMA) Paediatric Committee (PDCO) as key binding elements in the PIP for IDeg. As Trial 3561 was a global trial, feedback on the protocol was also obtained from US Food and Drug Administration (FDA) and incorporated into the trial, and Pharmaceuticals and Medical Devices Agency (PMDA), Japan acknowledged including Japanese children in this trial.

The clinical trials were conducted in children and adolescents with T1DM. Although the incidence of T2DM is increasing in the paediatric population, the absolute number of adolescents with T2DM is still relatively low. Given that the number of paediatric subjects with T2DM requiring insulin on a maintenance basis would only be a subset of this population, recruiting an adequate number of patients would be extremely challenging. Due to these limitations to the conduct of a clinical trial, a waiver was granted for a clinical trial in children below 10 years of age with T2DM. For adolescents, an extrapolation and modelling study was accepted as an alternative approach to explore the efficacy and safety of IDeg in the treatment of adolescents with T2DM, as reflected in the Decision of 20 May 2014 (P/0129/2014) on the PIP for IDeg.

Trial 3561 have already been assessed by the CHMP within procedure EMEA/H/C/XXXX/LEG/WS/0501. The main conclusions from this assessment are reflected in the following, including the assessment of the RSI.

## *2.2. Non-clinical aspects*

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

### 2.2.1. Ecotoxicity / environmental risk assessment

Not applicable.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

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

- Clinical pharmacology trial – Trial 1995 (Measure #2 of the IDeg paediatric investigational plan [PIP]): A randomised, single-centre, double-blind, two-period cross-over, single-dose trial investigating the pharmacokinetic properties of IDeg and IGlar in children (6-11 years),adolescents (12-17 years) and adults (18-65 years) with T1DM. This trial was submitted as part of the original Marketing authorisation application (MAA) for IDeg.
- Therapeutic confirmatory trial – Trial 3561(Measure #3 of the IDeg PIP):
  A 26-week multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of IDeg and IDet in children and adolescents 1 to less than 18 years of age with T1DM on a basal-bolus regimen with insulin aspart (IAsp) as bolus insulin, followed by a 26-week extension

investigating long-term safety.

- Pharmacokinetic/pharmacodynamic (PK/PD) modelling study (Measure #4 of the IDeg PIP):
  A modelling study in children from 1 to less than 18 years of age, compared to adults, all with T1DM. The modelling study consisted of a population pharmacokinetic analysis based on data from Trials 1995 and 3561, and an exposure-response study, which was only based on data from Trial 3561. The objectives of the two analyses were to develop a population PK model for IDeg in children younger than 6 years and to conduct an exposure-response analysis focusing on this age group.
- Extrapolation and modelling study (Measure #6 of the IDeg PIP):
  An extrapolation and modelling study to extend efficacy and safety results in adults with T2DM and in adolescents with T1DM to adolescents with T2DM. The objective was to support the clinical use of IDeg as basal insulin in adolescents with T2DM, not sufficiently controlled with non-insulin medicinal products.

- **Tabular overview of clinical studies**

**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)<br><br>**Extension period:** (152/128) | **Basal/bolus:**<br><br>*Basal:* IDeg OD[a] or IDet OD/ BID[b]<br><br>*Bolus:* IAsp in both treatment groups | • T1DM subjects<br>• Age: 1− <18 years<br>• 26 weeks + 26 weeks extension<br>• Parallel group<br>• Open-label<br>• Treat-to-target<br>• Non-inferiority<br>• Stratification in age groups (1−5 years, 6−11 years, 12−17 years) | **Primary endpoint**:<br>• Change in $HbA_{1c}$ (after 26 weeks)<br><br>**Secondary endpoints:**<br>• Change in $HbA_{1c}$ (52 weeks)<br>• Change in FPG (26 and 52 weeks)<br>• 8-point SMPG (26 and 52 weeks)<br>• 4-point SMPG for dose adjustment (26 and 52 weeks)<br>• 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 “PK/PD Modelling”

## 2.3.3. Pharmacodynamics

see section “PK/PD Modelling”

### 2.3.4. PK/PD modelling

In accordance with the agreed paediatric investigational plan (PIP) for IDeg (EMEA-000456- PIP01-08-M02), data from Trials 1995 and 3561 and trials in adults have been analysed to fulfil the measures described in the tables below.

**Table 1–2 Measure 4 of the IDeg PIP[1]**

| Study identifier | Study #4 |
|---|---|
| Type of study, study design | PK/PD modelling study in children from 1 to less than 18 years of age, compared to adults, all with type 1 diabetes mellitus (T1DM) |
| Study objective(s) | To model the PK and PD of IDeg in children younger than 6 years of age |
| Study population | PK data from the rich sampling single-dose PK study NN1250-1995 in children older than 6 years and in adults, and PK and self-measured plasma glucose (SMPG) data from the sparse sampling in NN1250-3561, which includes children younger than 6 years, will be used to construct the models |
| Statistical plan | The PK data from the two trials must be used to develop a population PK model, which must subsequently be used to simulate PK following multiple dosing in children younger than 6 years of age. Further, pre-breakfast SMPG data from NN1250-3561 must be used to develop an exposure-response model, which must be used to attempt to predict pre-breakfast SMPG in children younger than 6 years.<br><br>Validation of the model (standard goodness-of-fit plots, evaluation of parameter estimates and their uncertainty, assessment of sensitivity towards outliers, visual and/or posterior predictive check) must be performed and discussed explicitly. Sensitivity analysis on the assumptions of the model must be performed and discussed. |

[1]Agreed paediatric investigational plan (PIP) for insulin degludec (IDeg), EMEA-000456-PIP01-08-M02.

**Table 1–3 Measure 6 of the IDeg PIP[1]**

| Study identifier | Study #6 |
|---|---|
| Type of study, study design | Extrapolation and modelling study, to extend efficacy results in adults with type 2 diabetes mellitus and in adolescents with type 1 diabetes mellitus, to adolescents with type 2 diabetes mellitus. |
| Study objective(s) | To support the clinical use of LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin in adolescents with type 2 diabetes mellitus, not sufficiently controlled with non-insulin medicinal products. |
| Study population | Data from efficacy studies with LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin in adults with T2DM (preferably obese) and in adolescents with T1DM must be analysed and modelled to extrapolate efficacy to adolescents with T2DM. |
| Extrapolation and modelling approach | A combination of model-based extrapolation of pre-breakfast SMPG and more qualitative (non-model-based) extrapolation of trial results on HbA1c and important safety parameters, must be used. |

[1] Agreed paediatric investigational plan (PIP) for insulin degludec (IDeg), EMEA-000456-PIP01-08-M02.

For Measure 6, the approach of extrapolating to adolescents with T2DM based on available data in adolescents with T1DM (Trial 3561), adults with T1DM (Trial 3585/3725) and adults with T2DM (Trial 3579) is illustrated in the table below:

**Table 1–4 Extrapolation approach for adolescents with T2DM**

| | T1DM | T2DM |
|---|---|---|
| Adults | ② Clinical trial in adults (Trial 3585, 26 weeks) | ③ Clinical trial in adults (Trial 3579, 26 weeks, sub-population) |
| Adolescents | ① Clinical trial in adolescents (Trial 3561, 26 weeks) | ④ No clinical trial (Dose-response estimate) |

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

**Measure 4 of the PIP (model PK and PD of IDeg in children younger than 6 years of age):**

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 IDeg and insulin detemir (IDet) 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 1995 was a randomised, single-centre, double-blind, two-period cross-over, single-dose trial, investigating the PK properties of IDeg and insulin glargine (IGlar) in children (6-11 years), adolescents (12-17 years) and adults (18-65 years) with T1DM. Only the IDeg PK data from this trial was included in the present analysis.

Population

In Trial 3561 a total of 350 subjects with T1DM were randomised to either IDeg or IDet, using a 1:1 randomisation scheme. 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 1995 a total of 39 subjects with T1DM (13 in each of the age groups: children (6-11 years), adolescents (12-17 years) and adults (18-65 years)) were randomised to one of two treatment sequences (IDeg/IGlar or IGlar/IDeg). The subjects included were male or female subjects with T1DM, aged between 6 and 65 years, with an HbA1c up to 10%, who had been on multiple daily injections of insulin or continuous subcutaneous insulin infusion for at least 12 months with a total daily dose of 0.6-1.2 U/kg.

Dosing regimen

In Trial 3561 subjects administered IDeg once-daily (OD) at approximately the same time of the day every day. The starting dose for IDeg was determined based on the subjects' pre-trial total daily insulin dose, according to a pre-specified procedure. During the trial, titration of the IDeg dose was performed

once-weekly according to a titration guideline and based on the lowest of three pre- breakfast SMPG values. The target pre-breakfast plasma glucose range was 5.0-8.0 mmol/L.

In Trial 1995 all subjects received a single dose of 0.4 U/kg of IDeg on a single occasion.

Blood sampling

In Trial 3561 blood samples were drawn to measure the serum concentration of IDeg after 2, 12 and 26 weeks of treatment. The investigator recorded the exact clock time of blood sampling, and the subjects recorded the dose level, date and exact clock time of all IDeg doses taken within three days of the day of blood sampling, including any doses taken prior to blood sampling on the actual day.

In Trial 1995 blood samples were drawn to measure the serum concentration of IDeg at 0 h (predose), 1h, 4h, 7h, 9h, 11h, 13h, 15h, 18h, 21h, 24h, 36h, 48h, and finally at 72h after administration.

Assay

IDeg concentration in serum was determined using a validated IDeg specific sandwich enzymelinked immunosorbent assay (ELISA) with a lower limit of quantification (LLOQ) of 20 pmol/L.

Data

For the population PK analysis, data records with missing concentration values and data records with concentration values below the LLOQ were flagged in the data files and 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.

Analysis POP-PK

The final data set comprised a total of 894 IDeg concentration records from 205 subjects, of whom 169 were from Trial 3561 and 36 were from Trial 1995.

The first order conditional estimation method with interaction (FOCE+I) in NONMEM was used for the population PK analysis.

A one-compartment model with first-order absorption through a single transit compartment and with first-order elimination was used to describe the PK.

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

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.

Summary of key assumptions

The following overall assumptions were made:

All missing data (dosing history, PK, pre-breakfast SMPG) were assumed to be missing at random and not confounded with exposure and/or response levels.

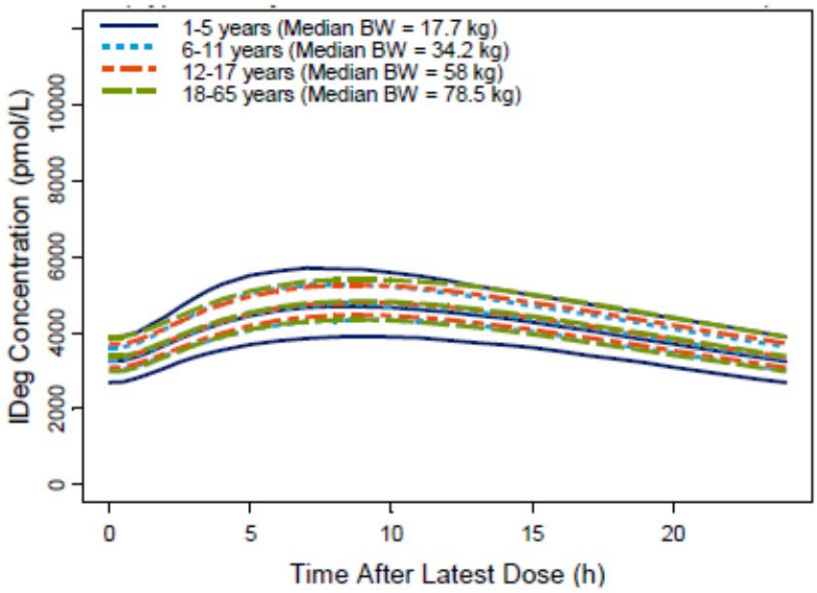
For the population PK analysis, the following additional assumptions were made:

- The PK of IDeg was assumed to be at steady-state at the time point, where detailed dosing history recording began, i.e. three days prior to the day of blood sampling. Deviations from this were considered to have negligible impact on the predicted concentration of IDeg at the time of blood sampling due to the half-life of approximately 25 hours following s.c. administration.
- A one-compartment model with first-order absorption through a single transit compartment and with first-order elimination was used to describe the PK of IDeg. This time-invariant, dose-proportional model has previously been found to adequately describe the PK of IDeg in trials with frequent blood sampling (e.g. in a separate analysis of the Trial 1995).
- Between-subject variability for clearance (CL/F) and 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

The concentration-time profile in small children (1-5 years) was similar to the concentration-time profiles in children (6-11 years), adolescents (12-17 years) and adults (18-65 years), as shown in Figure 1, as steady-state IDeg exposure was found to be independent of age.

**Figure 1 Model-derived concentration-time profiles over a 24 hour dosing interval at steady-state following once-daily dosing of 0.4 U of IDeg per kg body weight to a typical subject (based on median body weight) in four different age groups. Data are medians with 95% CI obtained from the final population PK model.**




**Measure 6 of the PIP (extrapolation to adolescents with T2DM):**

**Qualitative approach**

A number of key efficacy and safety endpoints were defined for the qualitative extrapolation to facilitate comparisons between the adult and adolescent populations from available data in adolescents with T1DM (Trial 3561), adults with T1DM (Trial 3585/3725) and adults with T2DM (Trial 3579):

- Efficacy: HbA1c, FPG, basal and bolus insulin dose
- Safety: Hypoglycaemic episodes, adverse events and antibody formation

For efficacy, the primary focus is after 26 weeks treatment. Safety is evaluated across the entire 52 weeks treatment in the trials.

Efficacy

Overall, the results in T1DM subjects indicated that adolescents have higher dose requirements (IDeg 0.46 vs. 0.35 units/kg, adolescents and adults respectively) and less improvement in glycaemic control than their adult counterparts. This applied to both IDeg and the basal insulin comparator and is possibly due to multiple factors, including increased insulin resistance during puberty, higher pre-breakfast SMPG titration targets defined for adolescents than adults and potentially greater challenges in treatment adherence amongst adolescents as compared with adults. As these general factors are not specific to T1DM, a similar relative difference between adolescents and adults is expected between adolescents and adults with T2DM.

The results for adult subjects with T2DM (BMI ≥ 30 kg/m2 previously treated with metformin only) indicated that glycaemic control and basal insulin dose levels would be similar for IDeg and the basal insulin comparator also for this sub-population. The dose requirements were higher in this population as expected (IDeg 0.61 units/kg).

Safety

No safety concerns were raised for adolescents as compared with adults with T1DM or in the sub-population of adults with T2DM in terms of adverse events or antibody profiles. In T1DM patients, the rate of confirmed hypoglycaemic episodes was comparable between IDeg+IAsp and IDet+IAsp in adolescents after 52 weeks treatment (4913 vs 5011 episodes per 100 PYE) as well as in adults after 52 weeks treatment (3778 vs 3926 episodes per 100 PYE). In T2DM patients, the rate of confirmed hypoglycaemic episodes was lower with IDeg than IGlar during 52 weeks treatment (99 vs 191 episodes per 100 PYE, respectively).

## 2.3.5. Discussion on clinical pharmacology

**T1DM**

According to the PIP, the applicant should develop a population PK model for IDeg in children younger than 6 years of age. This has been done by using a rather large data set from studies 1995 and 3561.

Based on rich data from the single dose study 1995, IDeg AUC and $C_{max}$ was 48 % and 20 % higher in children (6-11 years, median 11 (range 8-11)), compared to adult (18-65 years, median 21 (range 18-57) subjects. While the total exposure of IDeg was greater in children and adolescents compared with adult subjects with T1DM in Trial 1995, this was based on a small number of subjects after a single-dose administration. In addition to the single dose data from 36 subjects from Trial 1995, the population PK analysis also included steady-state data from 169 subjects from Trial 3561. The population PK analysis demonstrated that the steady-state IDeg exposure was independent of age and the estimated steady-state concentration-time profile for small children (1-5 years) was similar to that of children (6-11 years), adolescents (12-17 years) and adults (18-65 years). The appended validation report seems to support the conclusion regarding similarity in PK vs age.

In line with the PIP, the applicant also performed an analysis of exposure-response where the results were inconclusive and therefore the analysis is not presented. Nevertheless, measure 4 of the PIP is considered fulfilled.

The use of IDeg in children 1 to less than 18 years of age with T1DM is also supported by clinical data from study 3561.

**T2DM**

According to the “Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, CPMP/EWP/1080/00 Rev. 1”, if efficacy and safety of a novel insulin is demonstrated in adults with type 2 diabetes and in children with type 1 diabetes, additional data in paediatric patients with type 2 diabetes may not be needed (i.e. extrapolation may be possible). It is not stated how such an extrapolation should be done.

A supportive extrapolation and modelling study to extend efficacy and safety results in adults with T2DM and in adolescents with T1DM to adolescents with T2DM was performed. However, as such data was considered inconclusive; the CHMP has primarily relied on an extrapolation of efficacy and safety data from adolescents with T1DM, adults with T1DM and adults with T2DM as a basis for a potential approval of use in adolescents with T2DM at this stage. Nevertheless,measure 6 of the PIP is considered fulfilled.

The qualitative data show that insulin requirements are higher in adolescents than in adults with T1DM, which may be explained by multiple factors, as put forward by the applicant. The results for the sub-population of adult subjects with T2DM (BMI ≥ 30 kg/$m^2$ previously treated with metformin only) confirms that higher insulin doses are needed in this insulin-resistant population with no apparent differences in glycaemic control and basal insulin dose levels for IDeg and the basal insulin comparator. Since the general factors that may contribute to the higher insulin requirement in T1DM adolescents are not specific to T1DM, a similar relative difference between adolescents and adults can be expected between adolescents and adults with T2DM. Such higher dose requirements for adolescents than for adults are considered of limited impact for the use of IDeg 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 IDeg in adolescents with T2DM.

No safety concerns arise from the comparison of adverse events in adolescents and adults with T1DM. The main safety concern with insulin treatment is hypoglycaemia and hypoglycaemia was much less common in the obese T2DM population than in patients with T1DM. The risk of hypoglycaemia was somewhat higher in adolescents with T1DM than in adults. When extrapolating these data to adolescent T2DM patients, a somewhat higher risk of hypoglycaemia than in adult T2DM patients would be expected. Thus it is expected that in an even more insulin-resistant adolescent T2DM population, hypoglycaemia would be manageable.

## 2.3.6. Conclusions on clinical pharmacology

Regarding the exploration of PK in children, it is deemed that the model adequately describes data and it can be concluded that the concentration-time profile in small children (1-5 years) was similar to the concentration-time profiles in children (6-11 years), adolescents (12-17 years) and adults (18-65 years), as steady-state IDeg exposure was found to be independent of age.

For a discussion of efficacy data and safety data from study 3561 in support of the T1DM indication, see sections “Clinical Efficacy” and “Clinical Safety”.

Efficacy and safety data for adolescent T2DM patients have been extrapolated from data for adolescent and adult patients 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 IDeg may be used also in adolescent patients with T2DM. Insulin requirements are expected to be high in this population; however, as IDeg is individually titrated this is not of concern. There is no indication that the safety profile would be markedly different in this population than in adult patients with T2DM and hypoglycaemia, although not negligible, would be manageable. Section 5.1 has been amended with brief information on the extrapolation of data to adolescent T2DM patients.

## *2.4. Clinical efficacy*

### 2.4.1. Main study

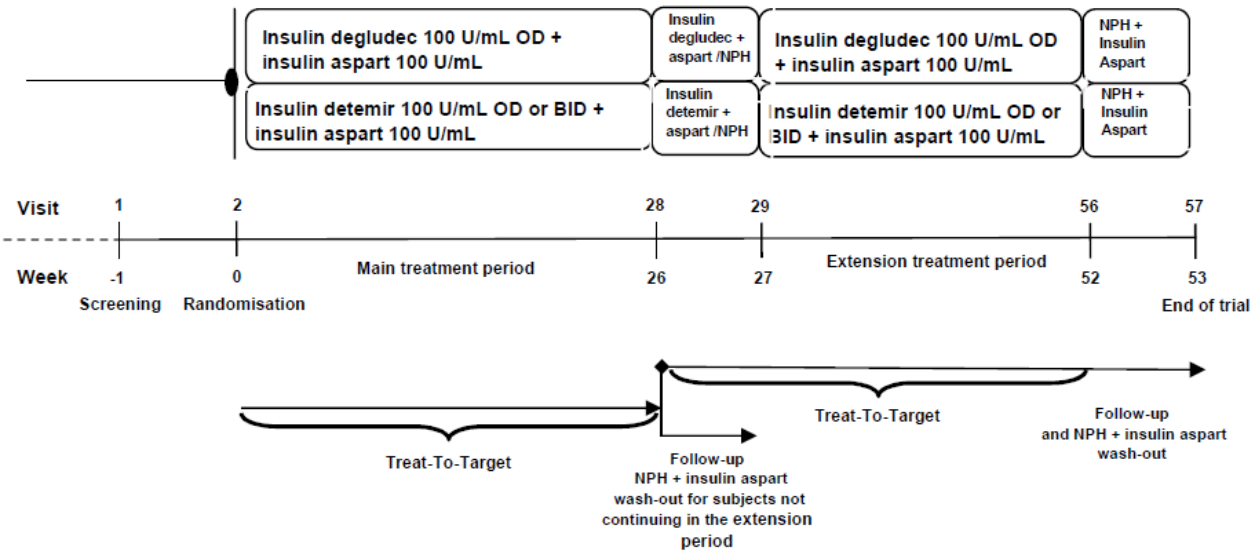
**A trial investigating the efficacy and safety of insulin degludec in children and adolescents with type 1 diabetes mellitus (Trial 3561)**

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.

**Methods**

In general, the trial design of Trial 3561 was similar to the design of the previous therapeutic confirmatory trials with IDeg. It was an open-labelled, randomised (1:1), multi-national, multi-centre, two-arm parallel group, 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 trial was divided into a main period of 26 weeks followed by a 26-week extension period investigating long term safety and immunogenicity. Subjects were invited to participate in the extension trial period by signing a new voluntary informed consent. A wash-out period with insulin NPH was performed after the last treatment visit in the main trial period for subjects not continuing in the extension to limit the interference of IDeg and IDet in the blood with the assay for antibody measurement. For the subjects who continued in the extension period, the wash-out period with insulin NPH was not required until the end of the extension period, and the assigned insulin treatment continued between the main and extension treatment periods. The trial design is presented in Figure 5.

**Figure 2 Trial 3561 – trial design**




U: units, NPH: neutral protamine Hagedorn, OD: once daily, BID: twice daily

**Study participants**

A total of 346 subjects were planned to be included in this trial, with a minimum of 300 planned to complete the main part and a minimum of 200 planned to complete the extension. As specified in the PIPs for IDeg and IDet, at least 80 of the randomised subjects had to be children aged 1-5 years (both inclusive), and at least

30% and no more than 70% should be girls. Eligible subjects were 1 to less than18 years of age, diagnosed with T1DM, treated for at least 3 months on any insulin regimen (no OADs were allowed), with a total daily insulin dose ≤ 2.00 units/kg and at screening HbA1c was to be ≤ 11%. Subjects with clinically significant concomitant diseases were not included in this trial. Subjects who met all of the inclusion criteria and none of the exclusion criteria were eligible to participate in the trial, see Table 1 for a list of the key selection criteria.

**Table 1 Key selection criteria**

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

**Treatments**

At randomisation, subjects were to switch to either IDeg or IDet from their previous basal insulin dose(s) in accordance with the titration guideline included as part of the protocol. IDeg was to be administered OD at approximately the same time of the day. IDet was to be administered OD or BID according to labelling. Subjects were permitted to switch dosing of IDet from OD to BID (and vice versa) based on the investigator's judgement. Both treatment arms included insulin aspart (IAsp) as bolus insulin.

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

**Titration of insulin degludec and insulin detemir**

Basal insulin titration was done according to the lowest pre-breakfast SMPG value measured on the three days prior to visits or phone contacts for IDeg and IDet OD. For IDet BID the morning dose adjustment was to be based on the lowest pre-dinner SMPG value measured on the three days prior to visit/phone contacts. For details, please see Table 2.

**Table 2 Adjustment of insulin degludec and insulin detemir doses**

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

**Titration of insulin aspart**

IAsp was adjusted according to a sliding scale (see Table 3) or following the principles of flexible dosing as described below. The total dose could be divided into two to four daily doses. When using the sliding scale, IAsp titration was done once weekly based on the lowest of three SMPG values measured prior to the next meal and bedtime on the three days prior to 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 3 Adjustment of insulin aspart doses**

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

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.

**Insulin devices**

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

**Comparator**

IDet was chosen as comparator since it is a safe and widely used basal insulin, and IDet was the only basal insulin analogue, which had been investigated in children down to the age of 2 years.

**Objectives**

**Primary Objective**

The primary objective of Trial 3561 was to confirm the efficacy of IDeg administered once daily plus mealtime IAsp in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA1c) after 26 weeks of treatment. This was done by comparing the difference in change in HbA1c

between IDeg + IAsp and IDet + IAsp to with a non-inferiority limit of 0.4%, and if non-inferiority was confirmed with a superiority limit of 0%.

**Secondary objectives**

The secondary objectives were:

- To compare the efficacy and safety between the two treatment arms in terms of:
    - Parameters of glycaemic control
    - Safety
- To investigate the pharmacokinetics of insulin degludec and insulin detemir in different age groups using a sparse sampling approach and population pharmacokinetic (PK) modelling.

The pharmacokinetic evaluations were made in a separate report covering the main trial period (26weeks treatment) as part of the agreed PIPs (key binding element, study #4).

**Outcomes/endpoints**

**Efficacy endpoints**

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

**Secondary endpoints**

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

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

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

**Sample size**

The primary objective of this trial was to confirm efficacy of IDeg + IAsp in terms of glycaemic control after 26 weeks of treatment. This was to be done by showing that IDeg + IAsp is non-inferior to IDet + IAsp in terms of glucose lowering effect as assessed by mean change from baseline in HbA1c after 26 weeks of treatment using a non-inferiority margin of 0.4% (absolute).

The non-inferiority margin of 0.4% (absolute) was chosen in agreement with EMA and in accordance with the US FDA guidance. Sample size was determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D=0%). Based on experience from previous phase 3 trials in children and adolescents with T1DM treated with insulin, a conservative estimate for the standard deviation (SD) of 1.25% for HbA1c was used in the sample size calculation. With these assumptions, the minimum sample size required to meet the primary objective with at least 80% was 310 subjects.

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

The number of subjects to continue in the extension period was limited to the number of subjects who completed the main period and wished to continue in the extension period. It was expected that at least 300 subjects would complete the main period of the trial. Of these, it was expected that at least 200 would complete the entire trial period.

**Randomisation/Blinding (masking)**

A randomised, open-label trial was chosen as IDeg was administered once daily (OD), whereas IDet could be dosed OD or BID in accordance with the label.

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). Stratification was employed to ensure an approximately equal distribution of subjects between the treatment arms within each age group.

**Statistical methods**

All efficacy endpoints were summarised and analysed based on the full analysis set (FAS), following the intention-to-treat principle with subjects contributing to the evaluation ‘as randomised’. The primary endpoint and the secondary endpoint ‘change from baseline in HbA1cafter 52 weeks of treatment’ were in addition analysed based on the per protocol (PP) analysis set, including subjects (‘as treated’) with no major protocol violations, which could affect the analysis of HbA1cand who fulfilled a number of pre-specified criteria.

Safety endpoints were summarised using the safety analysis set (SAS), including all subjects exposed to at least one dose of trial product, with the subjects contributing to the evaluation ‘as treated’. Analyses of safety endpoints were based on the FAS.

In addition, selected endpoints were analysed and/or summarised based on the extension trial set (ETS), which included all subjects who had consented to participate in the extension trial period and had received at least one dose of trial product in the extension period (after the 26-Week Visit).

Only endpoints derived after 26 and 52 weeks of treatment were analysed statistically. The primary endpoint, change from baseline in HbA1cafter 26 weeks of treatment, was analysed using an analysis of variance (ANOVA) method with treatment, region, sex and age group as fixed factors and baseline HbA1cas covariate. Most of the secondary efficacy endpoints were analysed using an ANOVA model similar to that used for the primary endpoint. The number of treatment emergent hypoglycaemic episodes during the trial was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode was considered treatment emergent as offset. The model includes treatment, sex, region and age group as fixed factors. A post-hoc analysis was performed for treatment emergent hypoglycaemic episodes during the maintenance period (defined as the period from Week 16 until end of trial). In addition, the number of days without confirmed hypoglycaemic episodes was analysed using a negative binomial regression model similar to that described above. The number of

treatment emergent hyperglycaemic episodes and the number of treatment emergent episodes of ketosis was analysed using a negative binomial regression model similar to that described above.

Unless otherwise specified, missing values (including intermittent missing values) were imputed using the Last Observation Carried Forward (LOCF) method. In previous treat-to-target trials with IDeg, the use of the LOCF method has generally provided results similar to those obtained from alternative methods applicable for handling of missing data, such as repeated measures models. In the present trial, a sensitivity analysis based on a repeated measures model was also performed for the primary endpoint.

**Results**

**Recruitment / Numbers analysed**

The requirements for the trial population specified in the PIPs for IDeg and IDet were both fulfilled. It was specified that at least 80 of the subjects randomised in the trial should be children aged 1-5 years, and at least 30% and no more than 70% should be girls. In Trial 3561, a total of 84 children aged 1-5 years were exposed to trial products and 45% of the subjects in the trial were girls.

**Subject disposition**

A total of 350 subjects were randomised to the trial and 349 subjects were exposed to trial products. An overview of the subject disposition during the main trial and the extension period is presented in Table 4. All subjects who completed the main treatment period (335 subjects) were offered to continue in the extension period by signing a new informed consent. In total, 280 subjects (80% of randomised subjects) continued in the extension period, of which 273 subjects (78%) completed the full 52-week treatment period.

**Table 4 Subject disposition for Trial 3561 main trial period and extension period**

| | IDeg OD N (%) | IDet N (%) | Total N (%) |
|---|---|---|---|
| Screened | | | 363 |
| Screening failures | | | 13 |
| Withdrawn before randomisation | | | 0 |
| Randomised | 174 (100.0) | 176 (100.0) | 350 (100.0) |
| Exposed | 174 (100.0) | 175 ( 99.4) | 349 ( 99.7) |
| Completed main trial | 170 ( 97.7) | 165 ( 93.8) | 335 ( 95.7) |
| Withdrawn at/after randomisation and before extension | 4 ( 2.3) | 11 ( 6.3) | 15 ( 4.3) |
| Adverse event | 0 ( 0.0) | 2 ( 1.1) | 2 ( 0.6) |
| Withdrawal criteria | 4 ( 2.3) | 7 ( 4.0) | 11 ( 3.1) |
| Other | 0 ( 0.0) | 2 ( 1.1) | 2 ( 0.6) |
| Completed main trial. Did not consent to participate in extension | 18 ( 10.3) | 37 ( 21.0) | 55 ( 15.7) |
| Included in extension | 152 ( 87.4) | 128 ( 72.7) | 280 ( 80.0) |
| Withdrawn during extension | 1 ( 0.6) | 6 ( 3.4) | 7 ( 2.0) |
| Adverse event | 0 ( 0.0) | 1 ( 0.6) | 1 ( 0.3) |
| Withdrawal criteria | 1 ( 0.6) | 5 ( 2.8) | 6 ( 1.7) |
| Other | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Completed extension | 151 ( 86.8) | 122 ( 69.3) | 273 ( 78.0) |
| Full analysis set | 174 (100.0) | 176 (100.0) | 350 (100.0) |
| PP analysis set | 171 ( 98.3) | 167 ( 94.9) | 338 ( 96.6) |
| Safety analysis set | 174 (100.0) | 175 ( 99.4) | 349 ( 99.7) |
| Extension trial set | 152 ( 87.4) | 128 ( 72.7) | 280 ( 80.0) |

N: Number of subjects
%: Proportion of randomised subjects

The percentage of subjects withdrawn from the trial was low in both treatment arms, particularly in the IDeg treatment arm. The most common reason for withdrawal was due to subjects meeting a withdrawal criterion (including subjects who withdrew consent: 4 and 6 subjects treated with IDeg and IDet, respectively). Only 3 subjects were withdrawn due to an adverse event, all of them were treated with IDet.

A total of 55 subjects completed the main trial period without consenting to continue in the extension period, including 12 South African subjects (5 and 7 subjects treated with IDeg and IDet, respectively) who could not continue, as the amendment of the protocol to include the extension trial period was not approved by the local authorities. More subjects treated with IDet than with IDeg did not consent to continue, see Table 4. One possible reason for this difference may be that subjects were treated with an already marketed product and that participation in the trial imposed a substantial burden on some families with respect to frequency of clinical site visits and volume of data to be reported per protocol. Due to this difference between the treatment groups, selected descriptive data were repeated for demographic and baseline characteristics, dosing and key efficacy (HbA1c and fasting plasma glucose [FPG])and safety endpoints(serious adverse events [SAEs], hypoglycaemia, hyperglycaemia with ketosis and antibodies) to investigate whether there were any apparent differences between subjects, who continued in the extension trial period and those who left the trial after completing the main trial period. The distribution of subjects within the 3 age groups was similar for the IDeg and IDet treatment arms. There were no major differences in the withdrawal pattern between the 3 age groups or between the treatments. Within each treatment group, the percentage of

subjects completing the main trial but not continuing in the extension period was comparable for the 3 age groups.

**Baseline data**

The trial population was generally well balanced with only marginal differences between the two treatment arms in the demographic characteristics (Table 5). The majority of subjects were 'White' (75%) with the second most common race being 'Asian-non-Indian'(16%). 3% of subjects were of hispanic or latino origin, and 97% were of 'Not hispanic or latino' origin. Other baseline characteristics were also similar with the exception of slightly higher mean HbA1cand FPG in the IDeg arm (8.2% and 9.0 mmol/L) than in the IDet arm (8.0% and 8.4mmol/L)(Table 6). The proportion of subjects with diabetes complications at baseline was very low. Only 4 subjects reported diabetes complications at screening (IDeg: 1 subject with diabetic ketoacidosis; IDet: 3 subjects with diabetic neuropathy). The frequency of concomitant illnesses at screening was low with both treatments and, with the exception of seasonal allergy; no concomitant illnesses were reported in more than 5% of subjects.

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

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

**Table 5 Demographics and baseline characteristics - summary - full analysis set (abbreviated)**

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

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

**Table 6 Baseline and diabetes characteristics - descriptive statistics - full analysis set**

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

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

## Outcomes and estimation

### HbA1

#### *Primary analysis-HbA1cafter 26 weeks of treatment*

The primary endpoint in Trial 3561 was change from baseline in HbA1cafter 26 weeks of treatment. The result from the 26-week main trial period showed that both IDeg+IAsp and IDet+IAsp effectively improved glycaemic control and non-inferiority between the two treatment arms in terms of lowering HbA1cwas confirmed as the upper limit of the 95% CI for the estimated treatment difference was ≤0.4%(estimated

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

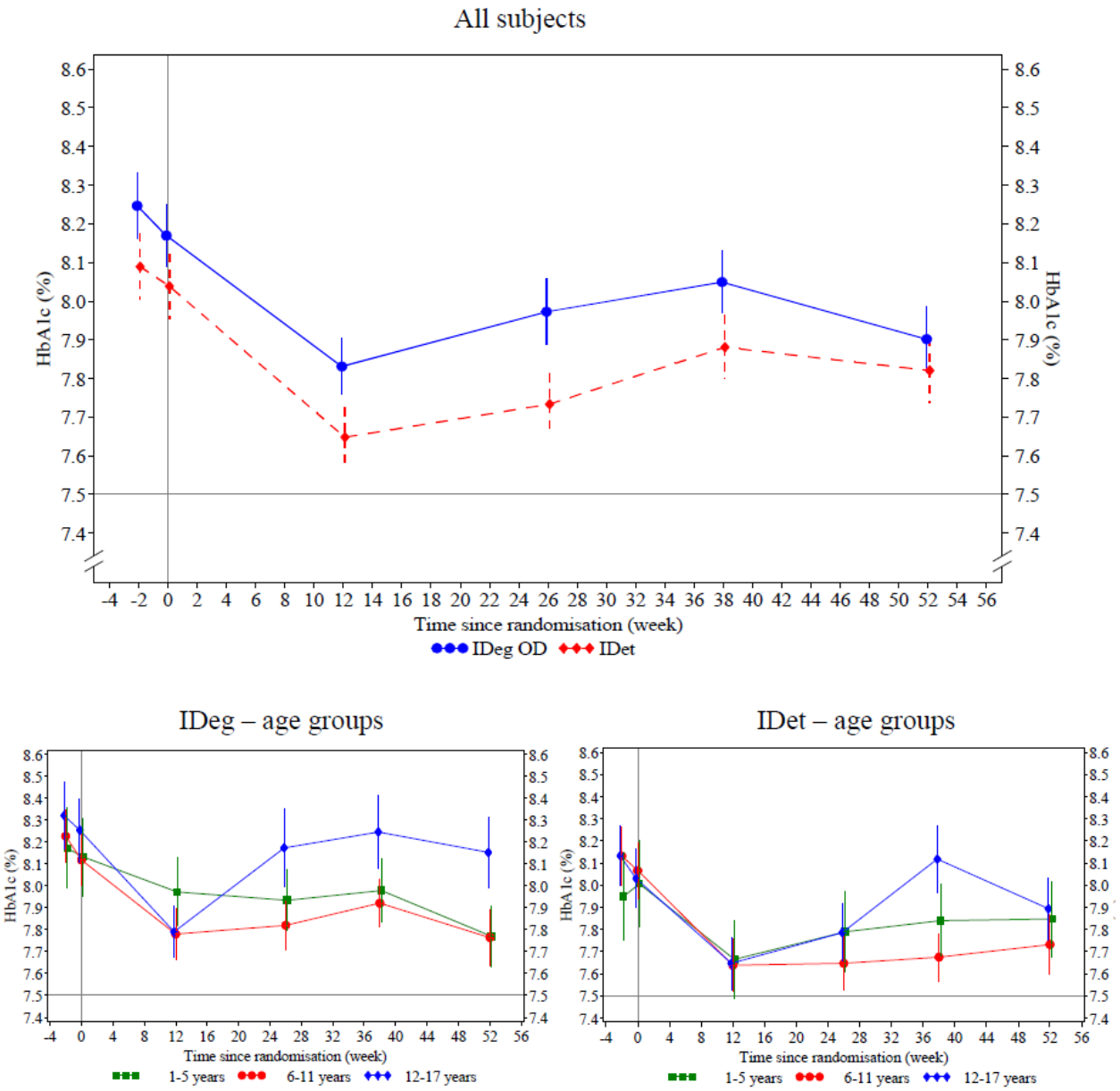
There was an overall reduction in HbA1c from baseline to 26 weeks with both treatments with the observed HbA1c being reduced from 8.2% to 8.0% in the IDeg arm and from 8.0% to 7.7% in the IDet arm. The overall change over time in HbA1c within the 3 age groups was comparable to that seen for all subjects. Thus, in all age groups the observed mean HbA1cwas lower after 26 weeks of treatment than at baseline for both treatments.

***HbA1c after 52 weeks of treatment***

The reduction in HbA1c was maintained after 52 weeks of treatment in both treatment groups indicating that the glycaemic effect was sustained, and at the end of trial, the estimated mean HbA1c was similar for IDeg and IDet with an estimated treatment difference of -0.01 %-points $[-0.20;0.19]_{95\%CI}$). As seen for the 26-week data, the sensitivity analysis using repeated measurements as well as the analyses based on the PP analysis set and the extension trial set, including all subjects who continued in the extension period, supported this result. The observed change from baseline was -0.27 %-point with IDeg and -0.22 %-point with IDet, and the observed mean HbA1cafter 52 weeks was 7.9% in the IDeg arm and 7.8% in the IDet arm.

The mean profiles for HbA1cover time was similar with the two treatments, see Figure 6. For both treatments, the initial reduction in HbA1cwas followed by a slight increase from Week 12 to 38 before it decreased again towards the end of the trial. The slight increase during the middle period of the trial was primarily driven by the adolescent age groups. Effective glycaemic control in adolescents is particularly challenging due to multiple factors including physiological changes of puberty (increased insulin resistance), and psychosocial factors. This age group is often associated with deterioration in glycaemic control. However, it was notable that in Trial 3561, the observed HbA1c was lower after 52 weeks of treatment than at baseline across all age groups in both the IDeg and the IDet treatment arms.

**Figure 3 Mean HbA1c (%) over 52 weeks – for all subjects (upper panel) and by treatment and age group (lower panel) – full analysis set**



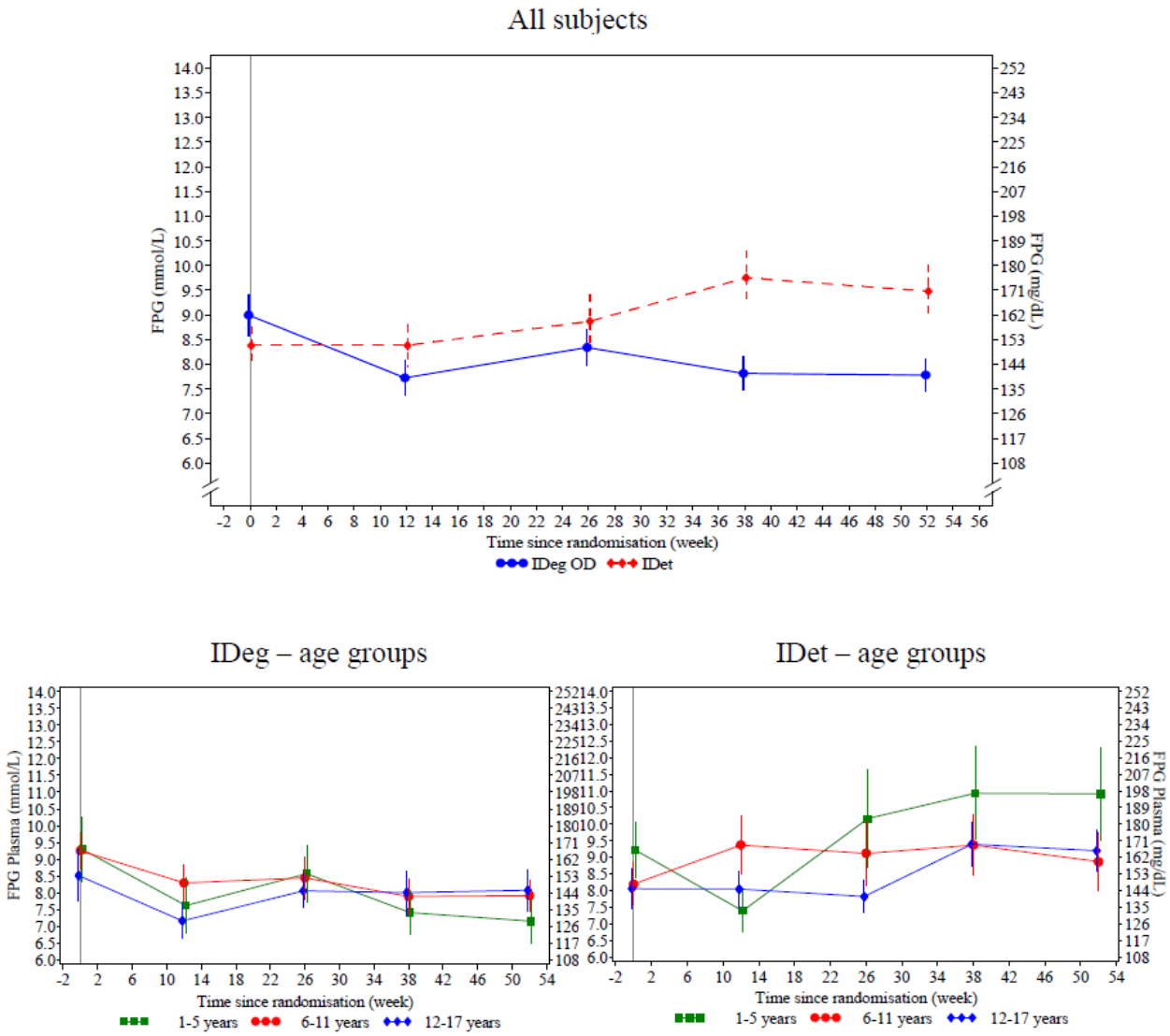

FAS; LOCF imputed data. Error bars ± standard error (mean)

**Secondary endpoints**

*Fasting plasma glucose*

During the trial, mean FPG decreased in the IDeg treatment groups and increased in the IDet treatment group, see Figure 7. With IDeg, the observed mean FPG decreased from 9.0 mmol/L at baseline to 7.8 mmol/L after 52 weeks of treatment, whereas it increased in the IDet treatment group from 8.4 mmol/L at baseline to 9.5 mmol/L, and the change from baseline in FPG was statistically significantly different for the two treatments (IDeg-IDet: -1.62mmol/L[-2.84; -0.41]$_{95\%CI}$).The overall change over time in the 3 age groups was comparable to that seen for all subjects in both treatment groups.

**Figure 4 Mean FPG (mmol/L) over 52 weeks - for all subjects (upper panel) and by treatment and age group (lower panel) - full analysis set**




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

*8-point self-measured plasma glucose profiles*

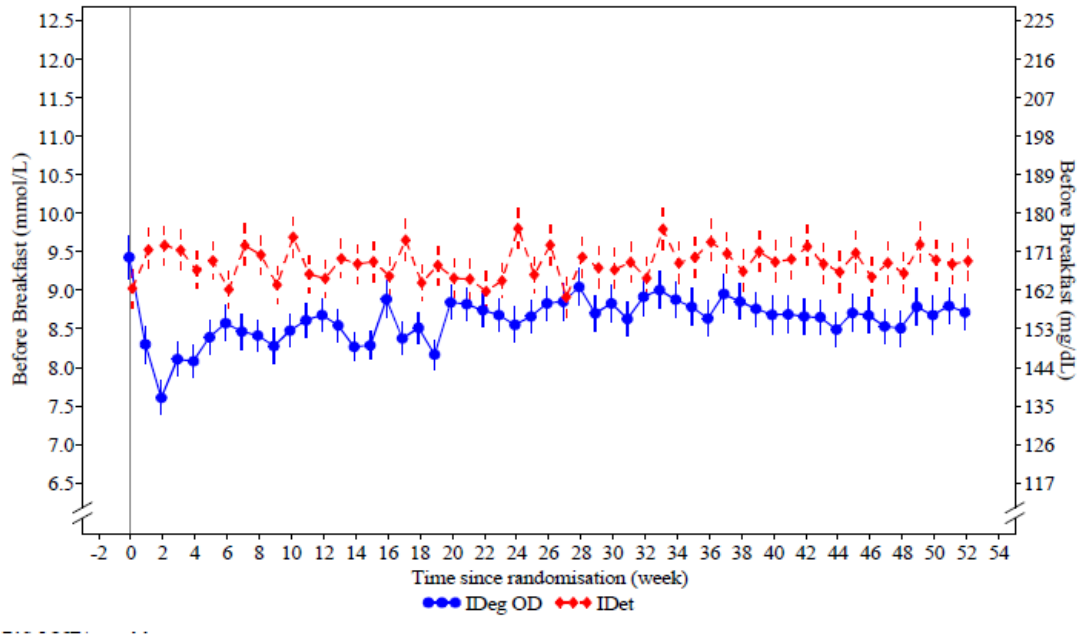
The mean of the 8-point SMPG profile was statistically significantly lower with IDeg compared to IDet after 52 weeks of treatment with an estimated treatment difference(IDeg –IDet) of −0.79mmol/L $[-1.32;-0.26]_{95\%CI}$.The lower mean reflected the statistically significantly lower SMPG values(IDeg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

*4-point self-measured plasma glucose for dose adjustment*

The 4-point SMPG profiles, which were measured weekly on 3 consecutive days, were used for the titration of the insulin doses. The observed mean pre-breakfast value was higher in the IDeg arm than in the IDet arm at baseline but was lower after one week of treatment and throughout the remaining 52-week treatment period (see Figure 8). The mean pre-breakfast SMPG was statistically significantly lower in the IDeg arm compared to the IDet arm (IDeg – IDet: −0.76mmol/L $[-1.46; -0.05]_{95\%CI}$) after 52 weeks of treatment.

Hence, the result based on self-measured PG values were in accordance with the lower FPG concentrations obtained in the IDeg treatment arm based on central laboratory analyses.

**Figure 5 Mean pre-breakfast self-measured plasma glucose for dose adjustment by treatment week – full analysis set**




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

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

*Plasma concentrations of basal insulin*

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

**Insulin doses over time**

Titration algorithms for basal and bolus insulin were provided in the protocol. The same titration algorithm was used for IDeg and IDet, and the algorithm specified the PG target range and the recommended dose adjustments at different PG levels. All subjects were to be individually titrated with the aim of achieving a pre-specified fasting PG target of 5.0-8.0 mmol/L as recommended by the International Society for Paediatric and Adolescent Diabetes (ISPAD) Guidelines. Investigators were in weekly contact with subjects throughout the trial in order to optimise and maintain glycaemic control by individually adjusting insulin doses taking diet, activity level and hypoglycaemic episodes into account. All insulin dose adjustments were done at the discretion of the Investigator. The mean IDeg dose remained relatively constant throughout the trial with the mean daily IDeg dose being 0.37 units/kg at baseline and 0.38 units/kg at the end of the trial. In contrast, the mean daily IDet dose increased from 0.40 to 0.55 units/kg. The lower mean dose of IDeg compared to IDet may be related to the long duration of IDeg which allows OD dosing in all subjects, whereas IDet could be dosed either OD or BID. The mean daily bolus insulin dose increased slightly during the trial in both treatment groups. From Week 1 to 52, it increased from 0.50 to 0.55 units/kg in the IDeg

arm and from 0.52 to 0.58 units/kg in the IDet arm. After 52 weeks of treatment, the ratio of the observed mean basal insulin doses (units/kg) was lower by 30% in the IDeg arm as compared to the IDet arm, whereas the bolus insulin dose ratio was close to 1, indicating that subjects received almost similar doses of IAsp in both the IDeg and IDet treatment arms. Therefore, the total daily dose ratio, which was 18% lower with IDeg than IDet, primarily reflected the lower amount of basal insulin used in the IDeg arm. The higher daily basal insulin dose in the IDet arm is probably related to the fact that more than 60% of the subjects treated with IDet were dosed BID at trial end, as it is well-known that BID dosing generally leads to higher basal doses. Furthermore, the basal/bolus insulin ratio demonstrated use of a relative lower proportion of basal than bolus insulin in the IDeg than in the IDet arm. Hence, after 52 weeks the basal/bolus ratio was 41%/59% in the IDeg arm compared to a more even ratio of 48%/52% in the IDet arm.

The results observed in Trial 3561 support the general recommendations for transfer of subjects from one insulin product to another. As with all insulin medicinal products, glucose monitoring should be intensified and the insulin dose adjusted on an individual basis.

**Differences in key efficacy parameters between subjects continuing or discontinuing after 26 weeks of treatment**

A higher proportion of subjects randomised to IDet than to IDeg did not continue into the extension phase of the trial. To evaluate the potential impact of this difference, comparison was made between subjects discontinuing the trial after the main 26-week period and subjects entering the extension phase. Descriptive data for HbA1cand FPG indicated that a poorer response to the treatment was observed in the subset of subjects, who discontinued, as compared to those subjects who continued in the extension trial period. However, for both HbA1cand FPG, the results of the statistical analyses of change from baseline to the end of trial (52 weeks) were similar for the full analysis set and the extension trial set indicating that the observed differences after 26 weeks did not lead to major differences in the 52-week results for HbA1cand FPG.

**Persistence of efficacy**

There was no evidence to suggest differences between the two treatment arms in the overall persistence of efficacy in the present trial. Basal-bolus therapy with IDeg+IAsp or with IDet+IAsp effectively improved long-term glycaemic, control with a similar reduction in HbA1c in both treatment arms after 52 weeks of treatment. After 26 weeks of treatment, IDeg was confirmed to be non-inferior to IDet, and the mean observed HbA1cwas reduced with both treatments. At the end of the trial, the observed mean HbA1cwas 7.9% and 7.8% with IDeg and IDet, respectively, and the observed mean change from baseline was −0.27%-point with IDeg and −0.22%-point with IDet. Hence, the reduction observed in HbA1cafter 26 weeks of treatment was maintained after 52 weeks of treatment with both treatments. There was no indication of a differential development of tolerance to insulin with IDeg and IDet. The observed mean levels of insulin antibodies cross reacting to human insulin decreased slightly with IDeg and increased slightly with IDet. The levels of IDeg, IDet and IAsp-specific antibodies remained low throughout the trial. Furthermore, no correlations were observed when cross-reacting antibodies or antibodies specific to IDeg and IDet at Week 52were plotted against HbA1c, change from baseline in HbA1c or total daily insulin dose. The mean daily basal insulin dose measured in units per kg was lower with IDeg than IDet throughout the trial and remained relatively constant with IDeg, whereas there was an increase over time with IDet. In contrast the bolus doses in units per kg were similar for the two treatments and increased slightly over time with both treatments. Hence the reduction in HbA1c observed with IDeg (OD), was achieved with lower daily insulin doses compared to IDet (OD or BID). Finally, the proportion of subjects withdrawn from the trial was low in both treatment arms (Table 4) indicating that the two trial products were well tolerated.

**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 7 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.<br><br>[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.<br><br>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.<br><br>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 plasma glucose before breakfast after 26 weeks of treatment | Comparison groups | IDeg – IDet |
| | | Treatment contrast | -0.87 |
| | | 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 8 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 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<br><br>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.<br><br>[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.<br><br>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.<br><br>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 | Comparison groups | IDeg – IDet |
| | | Treatment contrast | -0.92 |

| | | | |
|---|---|---|---|
| | main evening meal from 8 point SMPG profile at end of treatment | 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 (paediatric data)

**Design and conduct of clinical studies**

The results of trial 3561 has already been submitted and assessed with procedure EMEA/H/C/XXXX/LEG/WS/0501, in accordance with Article 46 of the Regulation (EC) No 1901/2006.

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 are 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 applicant’s explanation for this difference, that subjects in this group were treated with an already marketed product, is endorsed. The applicant has performed comparison between

subjects discontinuing the trial after the main 26-week period and subjects entering the extension phase. Descriptive data for indicates 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 adolescent age groups after 12 weeks there is no obvious explanation. Fluctuations were also observed in the other age groups during the trial, especially among adolescents. As noted by the applicant this is 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*

**Intorduction**

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

**Patient exposure**

In total, 174 subjects were exposed to IDeg and 175 subjects were exposed to IDet (Table 4). The total exposure was higher in the IDeg arm (161.5 years) than in the IDet arm (147.4 years) and in both treatment arms, the mean exposure for an individual subject was close to 1 year. The mean exposure was comparable between the two treatment groups during the main trial period (first 26 weeks), but higher in the IDeg arm than in the IDet arm during the last 26 weeks, reflecting the higher proportion of subjects continuing on IDeg

compared to IDet in the extension phase of the trial. Males had a higher total exposure than females (175.3 vs. 133.5 years, respectively) reflecting the higher proportion of males to females exposed to trial products in both treatment arms. The total exposure was distributed similarly across the 3 age groups in the two treatment arms.

**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 9. 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; see Table 4.

**Table 9 Adverse events - treatment-emergent - summary - safety analysis set**

| | IDeg OD | | | | IDet | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | 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 3 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’. Furthermore, injection site reactions were reported more frequently with IDeg than with IDet.

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 are 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 observed rates of ‘blood ketone body increased’ judged by the investigator to be possibly or probably related to basal insulin or to bolus insulin were also lower (by approximately 50%) in the IDeg arm than in the IDet arm.

Injection site reactions

Injection site reactions occurred in a relatively small proportion of subjects. These events were more frequently reported in the IDeg arm than in the IDet arm (20 vs. 9 events per 100 PYE) across a range of preferred terms, but none of the injection site reactions were serious. With the exception of 5 moderate events, they were all mild in severity. About 50% of the injection site reactions were considered possibly or probably related to IDeg or IDet. About 40% of the injection site reactions were considered possibly or probably related to bolus insulin. Given that nearly 50% of subjects in both treatment arms were already treated with IDet at trial entry, one might expect more injection site reactions to be reported in the IDeg arm as subjects not tolerating IDet would be less likely to participate in the trial.

**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 (Table 10). 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 10 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 (Table 10). The rates of SAEs were similar in the SAS and the ETS. Few of the hypoglycaemic events in both treatment arms were associated with seizure (1 episode with IDeg and 4 episodes with IDet) or unconsciousness (1 episode in each treatment arm). It should be noted that a total of 5 AEs related to hypoglycaemic seizure or hypoglycaemic unconsciousness (2 episodes with IDeg and 3 episodes with IDet) were regarded as non-serious by the investigators but as serious by the applicant. As the clinical database reflects the investigator reported data, these events were included as non-serious AEs in the clinical database (tables and listings), but are included as SAEs in the narratives from the safety database.

**Table 11 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

The observed rate of TEAEs leading to dose reduction was similar with IDeg and IDet (41 vs. 35 events per 100 PYE) as were the rates of SAEs (4 vs. 3 events per 100 PYE). Dose reduction due to TEAEs was most frequently related to 'infections and infestations', 'metabolism and nutrition disorders' and 'gastrointestinal

disorders'. For hypoglycaemia-related AEs the observed rates were 18 and 6 events per 100 PYE for IDeg and IDet, respectively.

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 applicant's definition of 'confirmed hypoglycaemia'. In normal physiology, hypoglycaemia symptoms occur at a PG level of approximately < 3.1 mmol/L (56 mg/dL), and the applicant has therefore used this cut-off value to define 'confirmed hypoglycaemia'. Hypoglycaemic episodes with time of onset in the period 23:00-07:00 (both included) were considered nocturnal. In the following sections, hypoglycaemia will be described based on severe hypoglycaemia as well as confirmed hypoglycaemia.

Severe hypoglycaemia – definition

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

Confirmed hypoglycaemia – definition

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

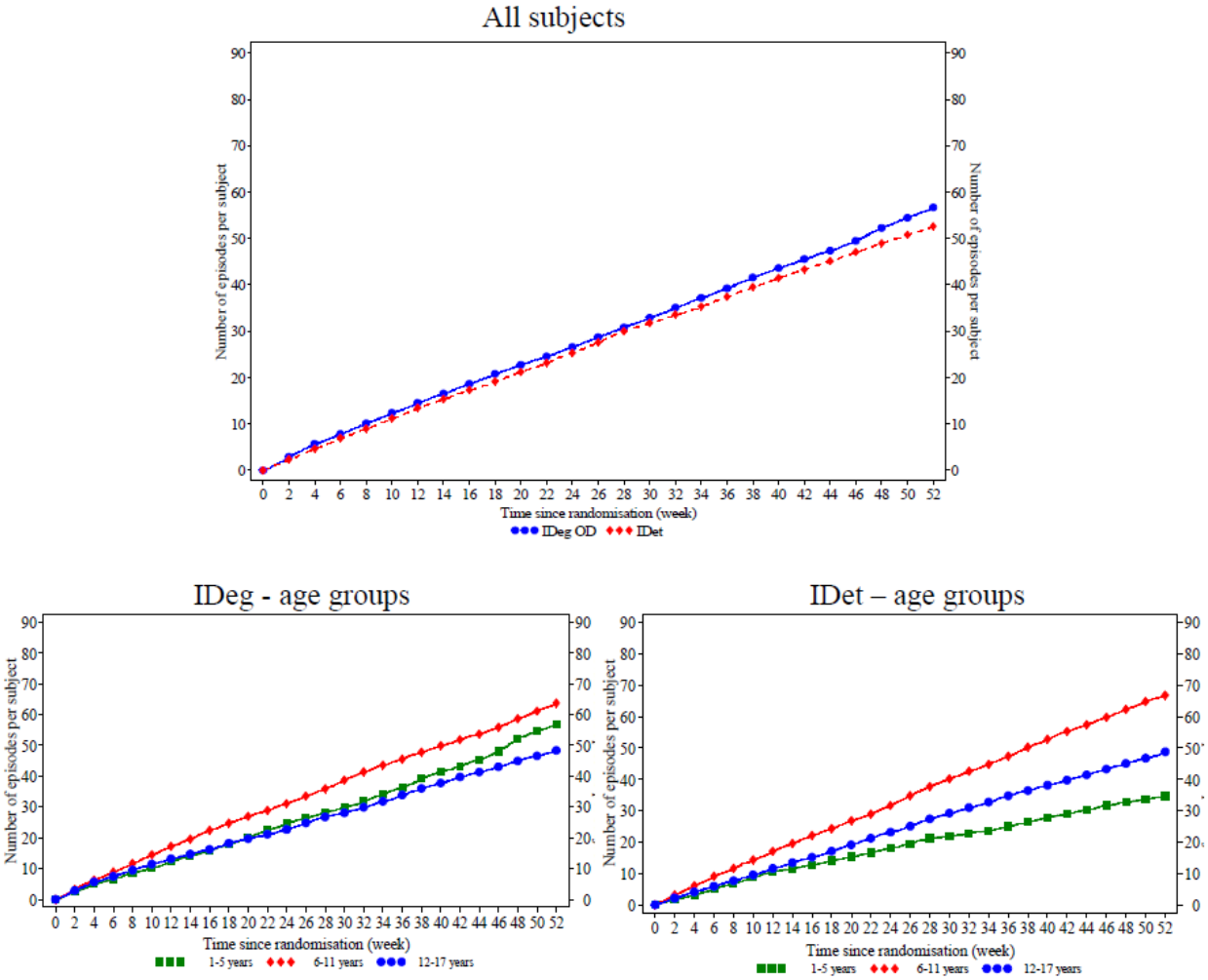
*Confirmed hypoglycaemia*

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

[0.89; 1.38]95%CI). A post-hoc analysis of confirmed hypoglycaemia during the maintenance period from 16 weeks of treatment to end of trial led to a similar result (rate ratio IDeg/IDet: 1.05[0.83; 1.32]95%CI), and a post-hoc sensitivity analysis showed that the number of days without confirmed hypoglycaemia was similar with IDeg and IDet treatment (rate ratio IDeg/IDet: 0.99[0.96;1.02]95%CI).

Confirmed hypoglycaemia over time is shown in Figure 9. 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. The observed rates of confirmed hypoglycaemia differed between the age groups in the IDet arm, which was related to a lower observed rate in children aged 1-5 years. With both treatments, the highest rate was observed in children aged 6-11years.

**Figure 6 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*

Severe hypoglycaemic episodes were reported by 18% of subjects in the IDeg arm and 14% in the IDet arm. 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 (rate ratio (IDeg/IDet):1.30 [0.64; 2.64]95%CI. The result of a post-hoc analysis comparing the rate of severe hypoglycaemia episodes during the maintenance period was in line with the analysis of the total

trial period (IDeg/IDet rate ratio of 1.36 [0.60;3.08]95%CI).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 in the youngest age group. Therefore, all reported episodes of severe hypoglycaemia were reviewed by an independent, external paediatric endocrinologist in a blinded manner, who determined whether the episodes fulfilled criteria for severe hypoglycaemia or not. Based on the external classification, the observed rates of severe hypoglycaemia were lower in both treatment groups (38 and 26 events per 100 PYE in the IDeg and IDet arms, respectively) compared to the observed rates for all reported episodes of severe hypoglycaemia. The majority of the severe episodes were related to 'altered mental status' and the number of episodes associated with being 'semiconscious or unconscious' or 'coma +/-convulsions' were similar or lower in the IDeg arm compared to IDet arm, see Table 12.

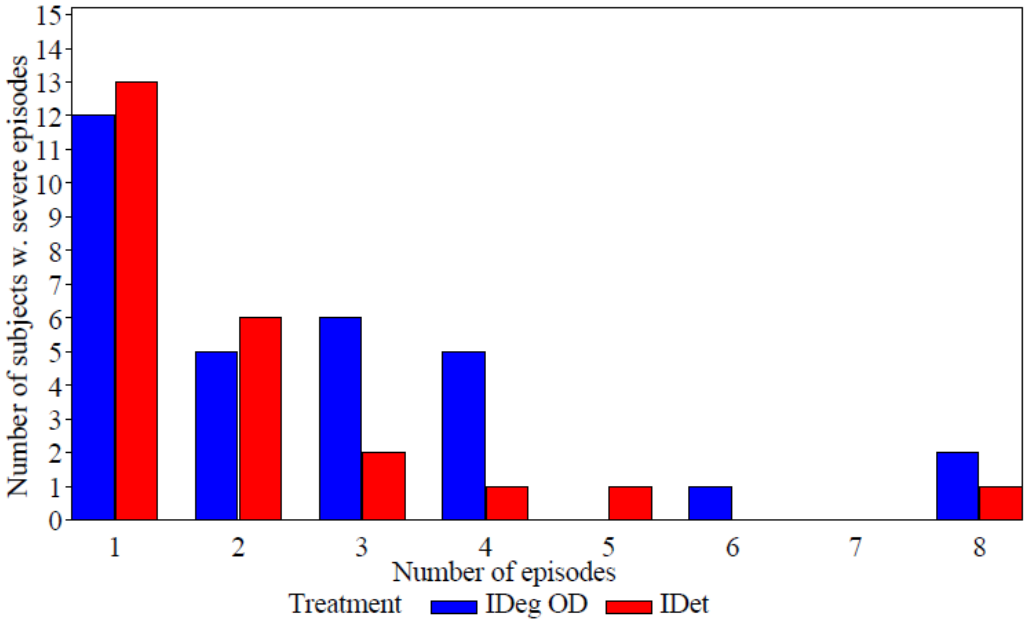
**Table 12 External classified severe hypoglycaemic episodes – treatment-emergent - summary - safety analysis set**

| | IDeg OD | | | | IDet | | | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | E | R | 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)

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 10), 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.

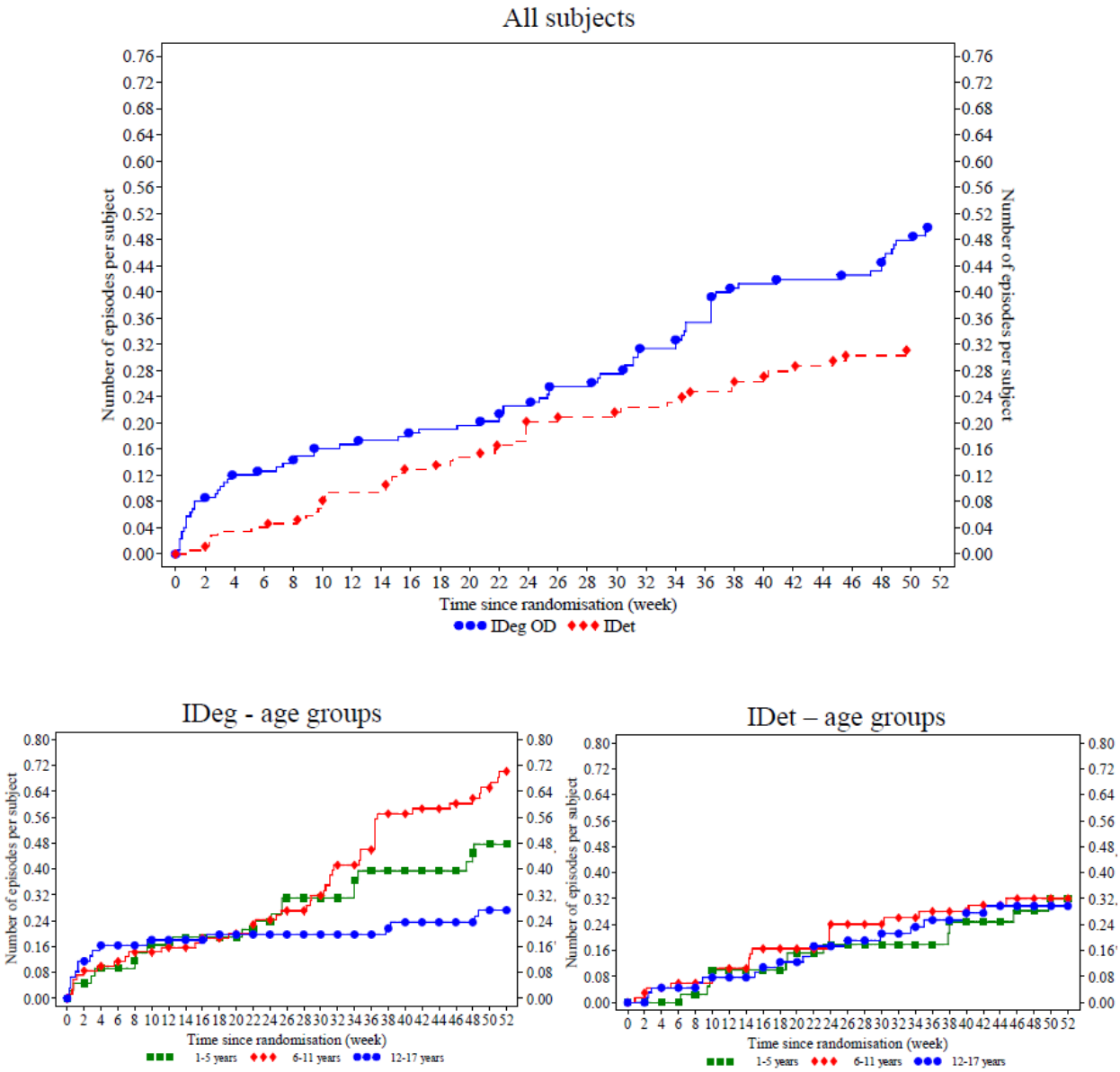
**Figure 7 Distribution of severe hypoglycaemic episodes - subject counts against number of episodes - safety analysis set**




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

The observed rate of severe hypoglycaemic episodes tended to be higher with IDeg than IDet, especially during the first 4 weeks of treatment as well as during the last weeks of treatment as indicated by the steeper slope in Figure 11. It should be kept in mind that based on the external classification; the observed rates of severe hypoglycaemia were lower in both treatment groups than based on all reported severe hypoglycaemic episodes. The majority of the severe hypoglycaemic episodes (close to 80%) occurred during the daytime in both treatment arms.

**Figure 8 Severe hypoglycaemic episodes - treatment emergent - mean cumulative function – for all subjects (upper panel) and by treatment and age group (lower panel) – safety analysis set**



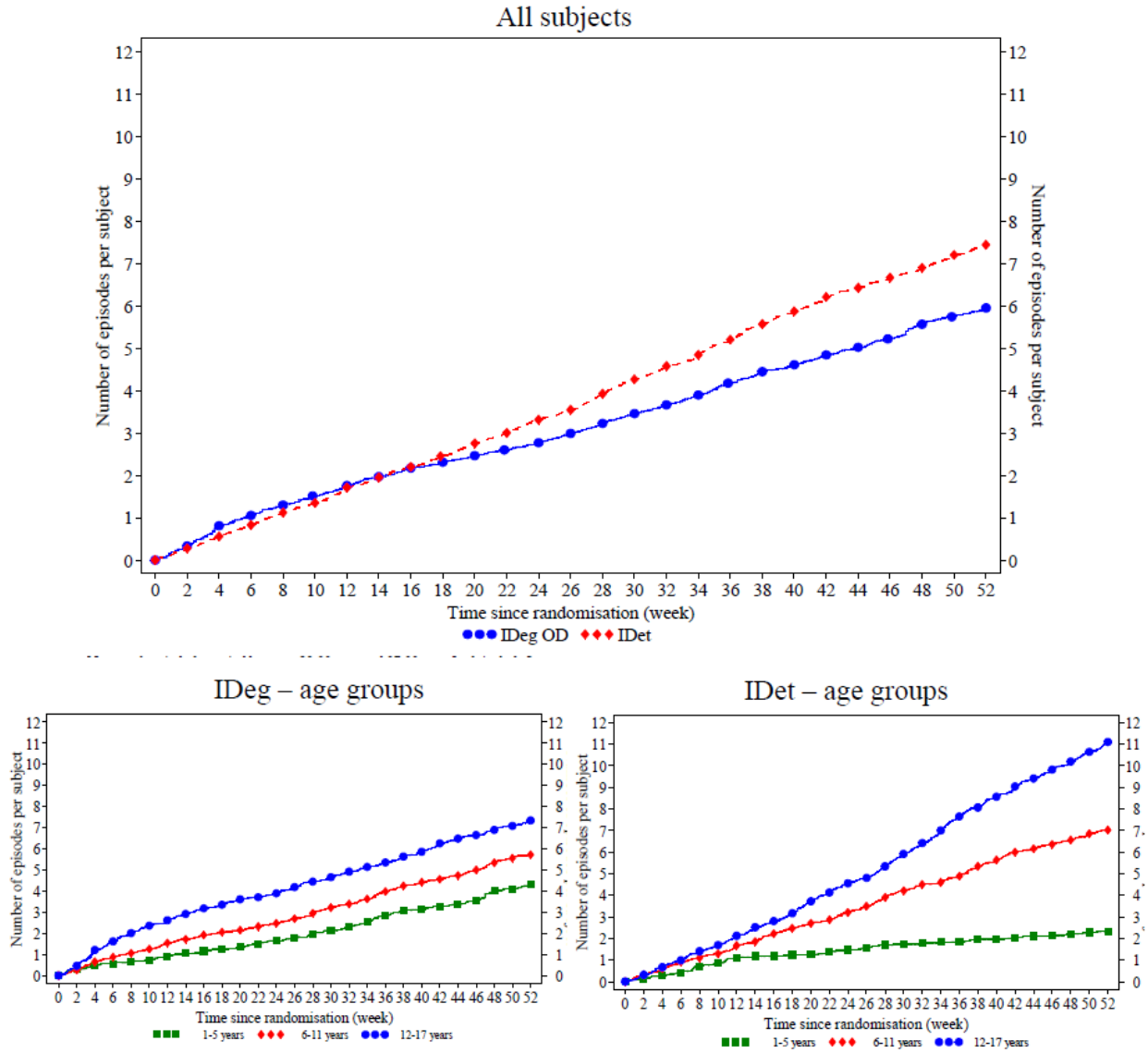

Severe hypoglycaemia according to ISPAD definition: The child has altered mental status and cannot assist in his own care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy.

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

*Nocturnal hypoglycaemia*

The proportions of subjects with nocturnal hypoglycaemia were similar with IDeg and IDet, while the observed rate of nocturnal confirmed episodes was numerically lower with IDeg compared to IDet, (603 and 760 episodes per 100 PYE, respectively). There was no statistically significant difference between treatment arms (IDeg/IDet: 0.99 $[0.72; 1.34]_{95\%CI}$).As seen from Figure 12, the observed rate of nocturnal confirmed hypoglycaemic episodes appeared to be lower with IDeg than IDet during the maintenance period of the trial from 16 weeks of treatment to end of trial. However, there was no statistically significant difference between the treatments in the post-hoc analysis of nocturnal confirmed hypoglycaemic episodes during the maintenance period (rate ratio IDeg/IDet: 0.88 $[0.63; 1.23]_{95\%CI}$). As seen for all confirmed hypoglycaemic episodes, the observed rates of nocturnal confirmed hypoglycaemia differed between the age groups in the IDet arm, which was related to a low observed rate in children aged 1-5 years and to a high observed rate in adolescents.

**Figure 9 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. For both confirmed hypoglycaemia and severe hypoglycaemia, analyses based on the extension trial (ETS) set consisting of the subjects who continued in the extension period were overall in accordance with those based on the FAS with no statistically significant differences between the treatments. The proportion of subjects experiencing confirmed or severe hypoglycaemia as well as the number of these events appeared to differ between the subjects discontinuing after completing the main trial and those who continued in the extension period, although data should be interpreted with caution due to the low number of subjects discontinuing. In the IDeg arm, the observed rates of confirmed hypoglycaemia were similar for the two subsets of subjects, but subjects who discontinued after the main trial period had lower observed rates of severe hypoglycaemia and higher observed rates of nocturnal confirmed hypoglycaemia compared to those who continued. In contrast,

the subjects in the IDet arm who discontinued after completing the main trial period had markedly higher observed rates of both confirmed and severe hypoglycaemia as compared to the subjects who continued, and similar observed rates of nocturnal confirmed hypoglycaemia. These differences should be kept in mind when evaluating rates and rate ratios between the two treatment arms during the full 52-week treatment period.

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***

There were no clinical relevant changes in vital signs in either treatment group during the trial, and the majority of subjects had normal physical examination recordings at baseline and at Week 52 in both treatment arms.

*Body weight*

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. Subjects in the IDeg arm had a slightly higher weight SD score at baseline compared to the IDet arm (0.33 vs. 0.32), and 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 maintained their baseline weight. The change in weight during the trial was similar across the 3 age groups treated with IDeg. In the IDet arm, the SD-score decreased in the young children aged 1-5 years, and remained almost unchanged in the older children and adolescents.

**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, respectively. None of the AE withdrawals occurred during the first month of treatment. The anxiety disorder was regarded as unlikely related to basal insulin while the two other events were judged as having a probably or possibly relation to trial drug.

**Post marketing experience**

From the date of approval and until 31 March 2014, a total of 29 spontaneous reports of paediatric use have been received. Eighteen (18) of these reports included an adverse event and in 6 of the reports, the patient experienced an SAE (2 serious reports of hypoglycaemia, 1 serious report of hypoglycaemic unconsciousness, 1 serious report of hypoglycaemic coma, 1 serious report of hypoglycaemic seizure and 1 serious report of blood glucose increased). As the reported numbers are relatively low, it is not possible to draw any conclusions about the spontaneously reported reports in children; the reported events in children will continuously be monitored through routine pharmacovigilance.

## 2.5.1. Discussion on clinical safety (paediatric data)

In terms of safety, no differences overall were observed between IDeg and IDet in terms of TEAEs and the rate of AEs. However, injection site reactions were more frequently reported in the IDeg treatment arm than in the IDet arm (28 events and 17.3 events per 100 PYE with IDeg versus 7 events and 4.7 events per 100 PYE). Altogether 8 subjects reported 12 events which were considered to be possibly or probably related to basal insulin in the IDeg group and 5 subjects reported 6 events in the IDet group. As noted the most obvious reason for this difference is related to the open-label design, i.e. subjects in the IDet group had to have tolerated pre-trial treatment with IDet and subjects in the IDeg group might be more attentive to adverse reactions. Importantly the frequency of the of injection site reactions that were assessed possibly or probably related to IDeg was comparable to the frequency in adults. The 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 overall number of episodes of severe hypoglycaemia was higher in the IDeg group than the IDet group and this difference was primarily driven by children aged 6-11 years. The

applicant argues that the number of subjects within each age group reporting severe hypoglycaemia was low and too small to conclude upon. This argument may be plausible but does not eliminate the concern of this finding. 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. Further to this, the warnings regarding hypoglycaemia in section 4.4 of the SmPC have been strengthened. 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 the PSUR. This is considered acceptable.

The proportions of subjects with nocturnal hypoglycaemia were similar with IDeg and IDet and there was no significant difference in the observed rate of nocturnal confirmed episodes between treatment groups although the rate per 100 PY was lower for IDeg than for IDet (603 and 760 episodes per 100 PYE, respectively). The findings are largely in line with those observed in adult patients with T1DM.

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

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

### 2.5.2. Conclusions on clinical safety

Besides more frequent injection sites reactions and more severe hypoglycaemic events in the 6-11 years age group with IDeg compared to IDet both insulin products provided a beneficial efficacious treatment with acceptable safety profiles. The increased risk of hypoglycaemia in the 6-11 years age group is adequately reflected in the SmPC 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.

### 2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

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

## *2.6. Risk management plan*

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

The PRAC considered that the risk management plan Edition 5 version 2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

## *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.

**SmPC**

**Section 4.1**

Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

**Section 4.2**

*Paediatric population*

~~The safety and efficacy of Tresiba in children and adolescents below 18 years of age have not been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.~~Tresiba can be used in adolescents and children from the age of 1 year (see section 5.1). When changing basal insulin to Tresiba, 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) ~~glucose monitoring should be intensified and the basal and bolus insulin dose adjusted on an individual basis~~.

**Section 4.4**

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**

Paediatric population

Tresiba has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties (see section 5.2). Safety and efficacy have not been investigated in children and adolescents been demonstrated in a long term trial in children aged 1 to less than 18 years (see section 5.1). The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population (see section 5.1).

**Section 5.1**

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of trials with Tresiba in:

- Neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus and children from birth to less than 10 years of age with type 2 diabetes mellitus on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset (see section 4.2 for information on paediatric use).

- ~~Children and adolescents from 10 to less than 18 years of age with type 2 diabetes mellitus on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset (see section 4.2 for information on paediatric use).~~

The efficacy and safety of Tresiba has been studied in a 1:1 randomised controlled clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=350), followed by a 26-week extension period (n=280). Patients in the Tresiba arm included 43 children aged 1–5 years, 70 children aged

6–11 years and 61 adolescents aged 12–17 years. Tresiba dosed once daily showed similar reduction in $HbA_{1c}$ at week 52 and greater reduction in FPG from baseline versus the comparator insulin detemir dosed once or twice daily. This was achieved with 30% lower daily doses of Tresiba compared to insulin detemir. The rates (events per patient-year of exposure) of severe hypoglycaemia (ISPAD definition; 0.51 vs 0.33), confirmed hypoglycaemia (57.71 vs 54.05) and nocturnal confirmed hypoglycaemia (6.03 vs 7.60) were comparable with Tresiba versus insulin detemir. In both treatment arms, children aged 6-11 years had a numerically higher rate of confirmed hypoglycaemia than in the other age groups. A numerically higher rate of severe hypoglycaemia in children aged 6-11 years in the Tresiba arm was observed. The rate of hyperglycaemic episodes with ketosis was significantly lower for Tresiba versus insulin detemir, 0.68 and 1.09, respectively. No safety issues were identified with Tresiba with respect to adverse events and standard safety parameters. Antibody development was sparse and had no clinical impact. Efficacy and safety data for adolescent patients with type 2 diabetes mellitus have been extrapolated from data for adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results support the use of Tresiba in adolescent patients with type 2 diabetes mellitus.

**Section 5.2**

Paediatric population

Pharmacokinetic properties of insulin degludec ~~were investigated~~ in children (~~6~~1– 11 years) and adolescents (12–18 years) ~~and~~ were ~~in~~ at steady state comparable to those observed in adults with type 1 diabetes mellitus. Total exposure after a single dose ~~is~~ was, however, higher in children and adolescents than in adults with type 1 diabetes mellitus.

In addition, section 2 of the PIL has been updated in line with section 4.2 of the SmPC regarding advice “if you forget to take Tresiba”.

### 2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed as the impact of the proposed modifications in the Package Information Leaflet readability is considered negligible. This was agreed by the CHMP.

## 3. Benefit-Risk Balance

**Beneficial effects**

The efficacy of IDeg in the treatment of children with T1DM is supported by clinical data from trial 3561. This 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 study included a total of 350 subjects out of which 280 continued in the in the 26-week extension period. Patients in the IDeg arm included 43 children aged 1–5 years, 70 children aged 6–11 years and 61 adolescents aged 12–17 years.

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%.

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. 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; however, the requirements with regards to recruitment set out in the PIP have been fulfilled.

A slight increase in HbA1c was observed in the age group 6-11 years after 12 weeks. There is no obvious explanation to this finding. 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 (BMI≥30 $kg/m^2$, insulin naïve, previously on metformin only). 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 IDeg 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 IDeg in adolescents with T2DM.

**Risks**

**Unfavourable effects**

In terms of safety, no differences overall were observed between IDeg and IDet in terms of TEAEs and the rate of AEs.

However, injection site reactions were more frequently reported in the IDeg treatment arm than in the IDet arm (28 events and 17.3 events per 100 PYE with IDeg versus 7 events and 4.7 events per 100 PYE). The most obvious reason for this difference is related to the open-label design, i.e. subjects in the IDet group had to have tolerated pre-trial treatment with IDet and subjects in the IDeg group might be more attentive to adverse reactions. Importantly the frequency of the of injection site reactions that were assessed possibly or probably related to IDeg was comparable to the frequency in adults. Injection site reactions are included in section 4.8 in the SmPC and 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.

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. It is acknowledged that 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. Hypoglycemia 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**

To achieve good metabolic control in children with diabetes is of importance both to avoid acute symptoms of hyper- or hypoglycaemia in the everyday life and to minimise the risk of long-term complications to the disease. In order to allow individualisation of therapy, insulins with different PD profiles are needed.

With the current submission, sufficient data have been provided showing that the efficacy of IDeg in achieving an adequate metabolic control is comparable to that of IDet in children aged 1 to 18 years. This glycaemic control was achieved with fewer daily IDeg units compared to IDet which may be beneficial since undue exposure to high insulin doses may cause negative effects in the long run. Furthermore, IDeg allows for OD dosing also at low dose levels, which could be of benefit as it simplifies the treatment.

However, the stable insulin levels achieved with long-acting insulin such as IDeg may 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. Indeed, severe hypoglycaemias were more common in the IDeg treated group, especially in children aged 6-11 years. This may, however, be overcome by continuous careful dose titration and adjustment of the bolus doses.

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. This may be explained by the flatter PD profile obtained with IDeg.

In the absence of clinical data in adolescents with T2DM, the efficacy and safety of IDeg 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

IDeg may be used also in adolescent patients with T2DM. Insulin requirements are expected to be high in this population; however, as IDeg is individually titrated this is not of concern. There is 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, is considered to be manageable.

**Benefit-risk balance**

**Discussion on the benefit-risk balance**

The benefit-risk balance for IDeg 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(s) accepted | | Type |
|---|---|---|
| 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 |

Extension of Indication to include treatment of diabetes mellitus in adolescents and children from the age of 1 year for Tresiba. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the SmPC and Package Leaflet.

***Conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch targeting all physicians and nurses who are expected to be involved in the treatment and management of diabetic patients and all pharmacists who are expected to dispense Tresiba.

The educational pack is aimed at increasing awareness about the introduction of a new strength of insulin in the European market and describing key differences in the design of the packages and the prefilled pen devices to minimise the risk of medication errors and mix up between the two different strengths of Tresiba.

The educational pack should contain:

– Direct Healthcare Professional Communication letter as described below;

– Summary of Product Characteristics and Package Leaflet;

– Poster for display in pharmacies/diabetic units;

– Patient Brochures.

The MAH shall ensure that healthcare professionals are informed that all patients who have been prescribed Tresiba should be provided with a patient brochure and be trained on the correct use of the prefilled pen before prescribing or dispensing Tresiba.

The Poster for pharmacies/diabetic units shall contain the following key elements:

– That Tresiba is available in 2 strengths;

– Key differences in the design of the packages and the prefilled pen devices;

– When prescribing to make sure that the correct strength is mentioned in the prescription slip;

– Always check the insulin label before dispensing to make sure the correct strength is delivered to the patient;

– Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;

– Do not use outside of the prefilled pen device (e.g. syringes);

– Reporting of medication errors or any side effects.

The patient brochure shall contain the following key elements:

– That Tresiba is available in 2 strengths;

– Key differences in the design of the packages and the prefilled pen devices;

– Always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba;

– Patients who are blind or have poor vision must be instructed always to get help/assistance from another person who has good vision and is trained in using the insulin device;

– Always use the dose recommended by your healthcare provider;

– Always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose;

– Check how many units were selected before injecting the insulin;

– The dose counter shows the number of units regardless of strength and no dose conversion should be done;

– Reporting of medication errors or any side effects.

The MAH shall agree the final text of the Direct Healthcare Professional Communication letter and the content of the patient brochure together with a communication plan, with the National Competent Authority in each Member State prior to distribution of the educational pack in the Member State.

- **Obligation to conduct post-authorisation measures**

Not applicable.

***Paediatric data***

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0129/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

***Scope***

Extension of Indication to include treatment of diabetes mellitus in adolescents and children from the age of 1 year for Tresiba. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance.

***Summary***

Please refer to the scientific discussion Tresiba EMEA/H/C/002498/II/11 for further information.