25 June 2015
EMA/467959/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

NovoRapid

insulin aspart

Procedure no: EMEA/H/C/000258/P46/045

Note

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

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Introduction

On 7 April 2015, the MAH submitted completed paediatric study for NovoRapid, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that "A trial investigating the efficacy and safety of insulin degludec/insulin aspart once daily plus insulin aspart for the remaining meals versus insulin detemir once or twice daily plus meal time insulin aspart in children and adolescents with type 1 diabetes mellitus" (NN5401-3816) is a standalone study.

1.2. Information on the pharmaceutical formulation used in the study

Insulin aspart

This is a rapid-acting insulin analogue indicated for the treatment of DM in adults as well as children and adolescents aged 2 to 17 years. It can be used in children in preference to soluble human insulin when a rapid onset of action might be beneficial, e.g. in the timing of the injections in relation to meals. Novo Nordisk has conducted a paediatric trial (NN1250-3561) including subjects down to 1 year of age using IAsp as mealtime insulin. No unexpected safety issues were identified in the trial population.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

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

1.3.2. Clinical study

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

Description

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

The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice.

Methods

Objectives

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

The secondary objective was to compare the efficacy and safety between the two treatment groups.

Study design

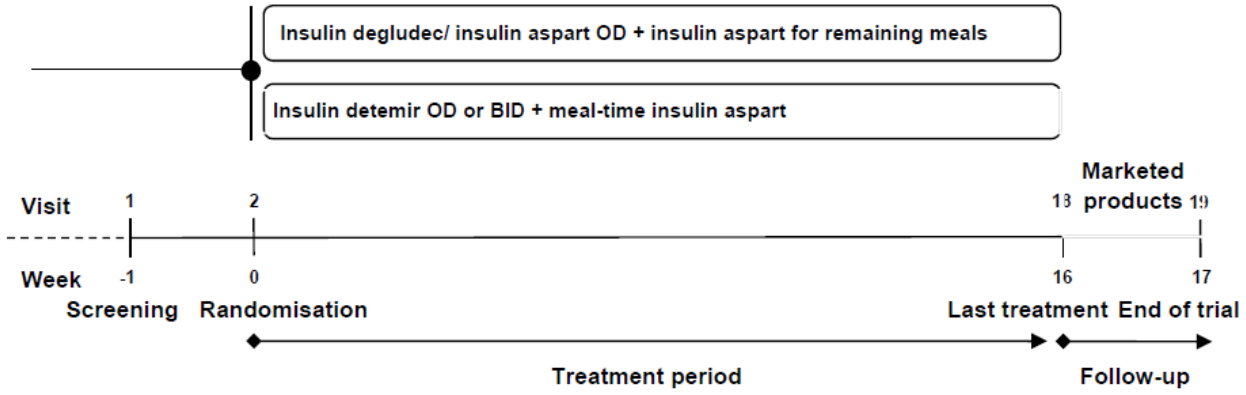
Trial 3816 was a 16-week multi-national, multi-centre, open-label, two-arm, parallel group, randomised, treat-to-target, efficacy and safety trial in children and adolescents with T1DM between 1 and 18 years of age. Subjects received one of the following treatment regimens:

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

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

The total trial duration for the individual subjects was approximately 18 weeks (Figure 1). The trial included a screening visit (visit 1), followed by a 16-week randomised treatment period and a follow-up visit (visit 19) 7-12 days after the last treatment visit (visit 18).

Figure 1 Trial design



Rapporteur's comment

The general study design was adequate. A randomised, open-label trial was chosen since the two treatment regimens require different number of daily injections. This is acceptable. The trial design was agreed upon with EMA (PDCO) as a binding element of the PIP for IDegAsp. Previous studies in adult T1DM patients comparing IDegAsp with IDet showed that HbA1c levels had stabilised after 12 to 16 weeks of treatment. The study duration is therefore considered adequate in the paediatric population.

Sample size

As this was a non-inferiority trial, sample size was determined such that the anticipated power was at least 80% in the evaluation of the PP analysis set. In previous phase 3 trials, in insulin treated children and adolescents with T1DM, less than 9% of the randomised subjects were excluded from the PP analysis set. In this trial, an estimate of 10% was used and sample size was ceiled in the FAS to have integer sample size for each group that adheres exactly to the group allocation weights (1:1). Hence 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.

Study population

A total of 346 subjects were planned for enrolment. Subjects were aged 1 to < 18 years at randomisation and diagnosed with type 1 diabetes. In accordance with the approved PIP, at least 60 randomised subjects had to be younger than 6 years at inclusion. Additionally at least 30% and not more than 70% were to be girls.

Inclusion criteria

Important inclusion criteria included:

- Informed consent
- Subjects diagnosed with type 1 diabetes mellitus
- Age: 1 to <18 years
- Ongoing daily treatment with insulin (any regimen including continuous s.c. insulin infusion) for at least 3 months prior to visit 1
- Total daily dose of insulin: ≤2 units/kg
- HbA1c ≤11.0%
- Ability and willingness to adhere to the protocol

Exclusion criteria

Important exclusion criteria included:

- Known hypoglycaemic unawareness or recurrent severe hypoglycaemic events as judged by the investigator
- More than 1 episode of diabetic ketoacidosis requiring hospitalisation within the 3 months prior to screening
- Any chronic disorder or significant concomitant disease which, in the investigator's opinion, might have jeopardised the subject's safety or compliance with the protocol

Rapporteur's comment

The inclusion and exclusion criteria were adequate. Due to the rise in the incidence of T1DM noted in many countries, with a disproportionately greater increase in children under 5 years, inclusion of the very young age groups in this trial was required by EMA (PDCO).

Treatments

At visit 2 subjects discontinued their current diabetes treatment and were to be randomised into one of two treatment groups:

- IDegAsp group: IDegAsp OD with a main meal + bolus IAsp for the remaining meals

- IDet group: IDet OD or twice daily (BID) + bolus IAsp at all meals.

At randomisation, each subject's total daily insulin dose was to be reduced by 20%. During the trial treatment period, all subjects were titrated on an individual basis according to an insulin titration guideline protocol and aim to adjust the basal-bolus ratio to be between 50:50 and 30:70.

IDegAsp was to be administered subcutaneously in the thigh, upper arm (deltoid area) or abdomen OD in connection with a main meal. The dosing time could be moved to a different main meal at any time during the trial.

IDet was to be administered subcutaneously according to local labelling. Subjects randomised into the IDet treatment group continued with their pre-trial dosing scheme (OD or BID) and were allowed to switch from OD to BID dosing. IDet is not currently approved for children below the age of 2 years and therefore in this trial IDet was used under careful medical supervision for this age group. No unexpected safety issues were identified in the trial population.

IAsp was to be administered subcutaneously according to local labelling as mealtime insulin, 2−4 times daily in subjects randomised to IDet and 1−3 times daily for subjects randomised to IDegAsp. IAsp is not currently approved for children below the age of 2 years and therefore in this trial IAsp was used under careful medical supervision for this age group.

Rapporteur's comment

The choice of comparator and bolus insulin is acceptable. Both IDet and IAsp are currently not approved for use below the age of 2 years, however limited data is available from other clinical trials and no safety concerns have arisen from these data.

Outcomes/endpoints

Primary endpoint

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

Secondary endpoints

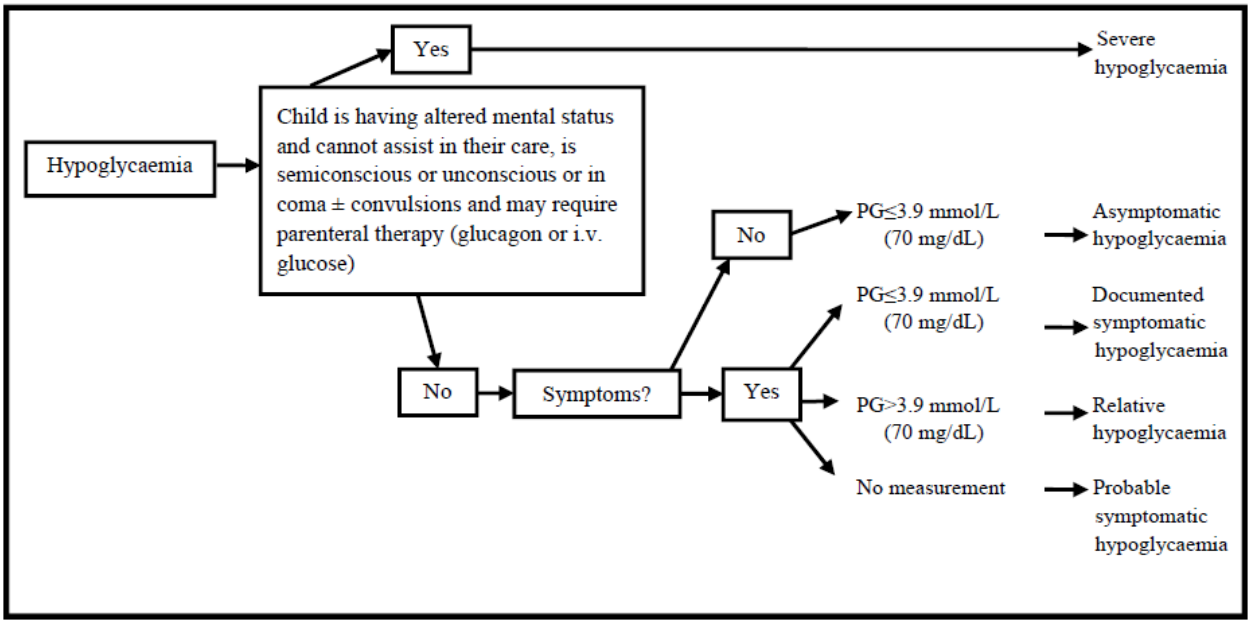
- Change from baseline in FPG after 16 weeks of treatment
- SMPG measurements (4-point profiles) obtained throughout the trial for dose adjustments
    - Mean PG before meals and before bedtime after 16 weeks of treatment
    - Within subject variability as measured by the CV% after 16 weeks of treatment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

Safety endpoints

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

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

Figure 2 Classification of hypoglycaemia according to ADA / ISPAD



Rapporteur's comment

The endpoints chosen were adequate and relevant.

Statistical Methods

Allocation of subjects to treatment groups

The subjects were randomly allocated to one of two treatment groups, either IDegAsp in combination with IAsp or IDet in combination with IAsp. Randomisation was stratified according to three age groups: 1-5 years; 6-11 years; and 12-17 years. Stratification was employed to ensure an approximately equal distribution of subjects between the treatment groups within each age group.

Analysis sets

The full analysis set (FAS) included all randomised subjects. In exceptional cases subjects from the FAS could be eliminated. In such cases the elimination was to be justified and documented. The statistical evaluation of the FAS followed the intention-to-treat principle and subjects contributed to the evaluation "as randomised".

The per protocol (PP) analysis set consisted of all subjects in the FAS who fulfilled the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have non-missing HbA1c at screening or randomization
- Have at least one non-missing HbA1c after 12 weeks of exposure
- Have at least 12 weeks of exposure.

The safety analysis set (SAS) included all subjects receiving at least one dose of the trial product or its comparator. Subjects in the safety set contributed to the evaluation "as treated".

Two subjects in the FAS (1 in each group) did not receive trial product and were therefore excluded from the SAS. Seventeen (17) subjects in the FAS (8 in the IDegAsp group and 9 in the IDet group)

were excluded from the PP analysis because they did not have a valid assessment of HbA1c after 12 weeks. Twelve (12) subjects in the FAS (5 in the IDegAsp group and 7 in the IDet group) did not contribute information to the HbA1c analysis after 16 weeks of treatment.

Statistical analysis

Primary endpoint

All observed HbA1c measurements available post-randomisation at scheduled measurement times were analysed using a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. The model included treatment, sex, region, age group and visit as factors and baseline HbA1c as covariate. Interactions between visit and all factors and covariates were also included in the model. Region was a factor with 3 levels: EU including Russia and Israel; North America; Other. Age group was a factor with the following three levels: 1-5 years; 6-11 years; 12-17 years.

The model was fitted to all the data simultaneously (all treatment groups) and the relevant treatment differences were estimated.

Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval (CI) was below or equal to 0.4% or equivalent if the p-value for the one-sided test of the null-hypothesis (H_0) against the alternative hypothesis (H_A),

H_0: $D > 0.4\%$ against H_A: $D \leq 0.4\%$,

was less than or equal to 2.5%, where D was the mean treatment difference after 16 weeks of treatment (IDegAsp minus IDet).

If non-inferiority was confirmed, the superiority of the IDegAsp over IDet was to be investigated. Superiority was considered confirmed if the upper bound of the two-sided 95% CI, which was calculated using the FAS, was below 0%. The PP analysis was considered supportive.

Sensitivity analysis

The primary efficacy analysis was repeated on the PP analysis set and the set of all completed subjects.

The following sensitivity analyses were performed using the FAS only.

Change from baseline in HbA1c after 16 weeks of treatment was analysed using an analysis of variance method with treatment, sex, region and age group as fixed factors and baseline HbA1c as covariate and where the missing values were imputed using the Last Observation Carried Forward method.

All observed HbA1c measurements available post-randomisation at scheduled measurement times were also analysed with an MMRM with an unstructured covariance matrix where the only factors were treatment and visit and baseline HbA1c was included as a covariate. The two interactions between visit and treatment and visit and baseline HbA1c were also included in the model.

Secondary endpoints

All observed FPG measurements available post-randomisation at scheduled measurement times were analysed using an MMRM with an unstructured covariance matrix. The model included treatment, sex, region, age group and visit as factors and baseline FPG as covariate. Interactions between visit and all factors and covariates were also included in the model.

All observed mean of before meals and all observed before bedtime PG values available post-randomisation at scheduled measurement times were analysed separately with a MMRM with an unstructured covariance matrix. The model included treatment, sex, region, age group and visit as

factors and baseline response value as covariate. Interactions between visit and all factors and covariates were also included in the model.

The logarithmically transformed SMPG values available before breakfast after 16 weeks were analysed as repeated measures in a linear mixed model with treatment, sex, region and age group as fixed factors and subject as random factor. The model assumed independent within- and betweensubject errors with variances depending on treatment. Within-subject variability as measured by CV% for a treatment could be calculated from the corresponding residual variance σ^2 as

$$CV\% = 100\sqrt{(\exp(\sigma^2) - 1)}.$$

The confidence interval for the CV ratio between treatments was calculated using the delta method.

All observed mean and fluctuation in the 8-point profile and prandial PG increments available post-randomisation at scheduled measurements times were analysed with an MMRM with an unstructured covariance matrix. The model included treatment, sex, region, age group and visit as factors and baseline values of the response as covariate. Interactions between visit and all factors and covariates were also included in the model. Fluctuation in the 8-point profile was logarithmically transferred before analysis.

All observed 8-point profile (SMPG) measurements available post-randomisation at scheduled measurements times were analysed with an MMRM with an unstructured covariance matrix. The model included treatment, sex, region, age group, time-point within the 8-point profile and visit as factors and corresponding baseline SMPG as covariate. Interactions between visit and all factors and covariates were also included in the model and, in addition, interaction between treatment and visit and time-point was included. This was a post-hoc analysis.

The number of treatment emergent hypoglycaemic episodes was analysed separately using a negative binomial regression model with a log-link function and the logarithm of the time period for which a hypoglycaemic episode was considered treatment emergent as offset. The model included treatment, sex, region and age group as fixed factors. Separate analyses were performed for severe episodes and confirmed episodes considering all episodes and nocturnal episodes.

The number of treatment emergent hyperglycaemic episodes and the number of treatment emergent hyperglycaemic episodes with ketosis were analysed separately using a negative binomial regression model with a log-link function and the logarithm of the time period for which an episode was considered treatment emergent as offset. The model included treatment, sex, region and age group as fixed factors.

Other safety parameters were summarised descriptively.

Rapporteur's comment

The statistical methods were adequate. The chosen non-inferiority margin is generous as currently a margin of 0.3 % is recommended. However, the final assessment depends on the actual outcome of the data.

Results

Recruitment / Number analysed

A total of 362 children and adolescents were randomised, of whom 360 received at least one dose of trial product and 342 completed the trial. Of those randomised, 82 were aged 1-5 years, 122 were aged 6-11 years and 158 were aged 12-17 years (Table 2).

Table 1 Subject disposition – summary

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

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

Table 2 Subject disposition

	IDegAsp OD N (%)	IDet N (%)	Total N (%)
All subjects			
Screened			387
Randomised	182 (100.0)	180 (100.0)	362 (100.0)
Exposed	181 (99.5)	179 (99.4)	360 (99.4)
Withdrawn at/after Randomisation	8 (4.4)	12 (6.7)	20 (5.5)
Completed	174 (95.6)	168 (93.3)	342 (94.5)
1-5 years			
Randomised	41 (100.0)	41 (100.0)	82 (100.0)
Exposed	40 (97.6)	41 (100.0)	81 (98.8)
Withdrawn at/after Randomisation	3 (7.3)	5 (12.2)	8 (9.8)
Completed	38 (92.7)	36 (87.8)	74 (90.2)
6-11 years			
Randomised	61 (100.0)	61 (100.0)	122 (100.0)
Exposed	61 (100.0)	61 (100.0)	122 (100.0)
Withdrawn at/after Randomisation	1 (1.6)	2 (3.3)	3 (2.5)
Completed	60 (98.4)	59 (96.7)	119 (97.5)
12-17 years			
Randomised	80 (100.0)	78 (100.0)	158 (100.0)
Exposed	80 (100.0)	77 (98.7)	157 (99.4)
Withdrawn at/after Randomisation	4 (5.0)	5 (6.4)	9 (5.7)
Completed	76 (95.0)	73 (93.6)	149 (94.3)

N: Number of subjects
%: Proportion of randomised subjects

Rapporteur's comment

Overall 94.5 % of patients completed the study. Withdrawals were evenly distributed between treatments and age groups.

Baseline data

Demographics and baseline characteristics

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

The demographics and baseline diabetes characteristics at week 0 were comparable between the treatment groups apart from slight differences in mean FPG and mean duration of diabetes (Table 3). For the overall study population, the mean (standard deviation [SD]) FPG at baseline was slightly higher in the IDegAsp group than in the IDet group: 8.6 (4.4) mmol/L versus 8.1 (4.2) mmol/L, respectively. The mean (SD) duration of diabetes was slightly higher in the IDegAsp group than in the IDet group: 4.4 (3.7) years versus 3.8 (3.2) years, respectively.

Table 3 Baseline and diabetes characteristics - descriptive statistics - full analysis set

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

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

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

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

Rapporteur's comment

The baseline characteristics were generally well balanced between groups. Notably, only one child below the age of 2 years was included (IDet). Duration of diabetes was slightly longer in the IDegAsp

treated group, however, numerically more diabetes complications were reported in the IDet treated group.

Efficacy results

Primary endpoint

IDegAsp OD + IAsp effectively maintained glycaemic control and was non-inferior to IDet + IAsp in terms of change from baseline in HbA1c, with an estimated mean treatment difference (IDegAsp OD − IDet) of −0.04%-points [−0.23; 0.15]95% CI (Table 4). Superiority was not confirmed.

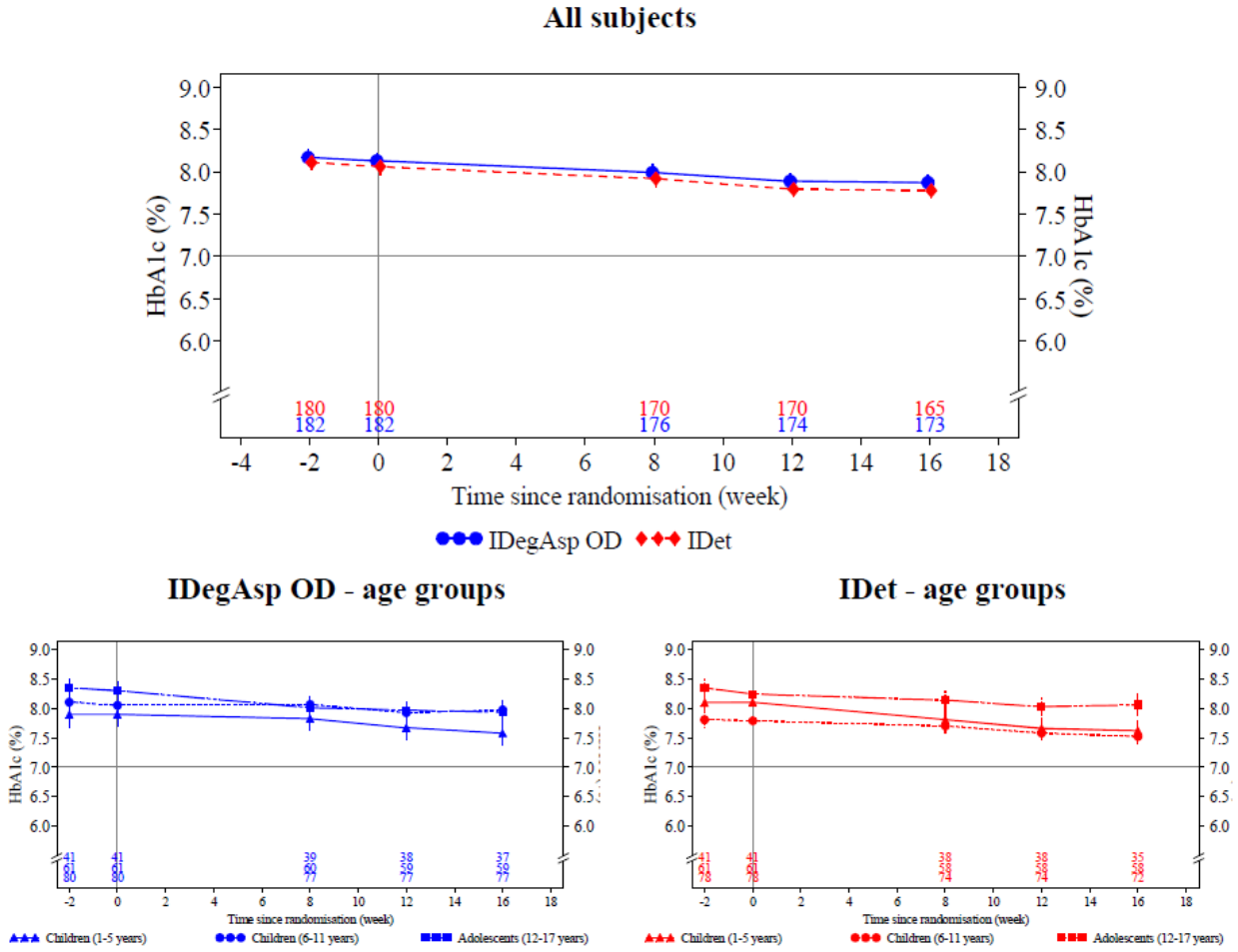
Table 4 HbA1c after 16 weeks of treatment - primary statistical analysis – full analysis set

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

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

After 16 weeks of treatment, the observed mean (SD) HbA1c was 7.9% (1.2) with IDegAsp OD + IAsp and 7.8% (1.3) with IDet + IAsp (Figure 3). Within both the IDegAsp and the IDet treatment group, the trend for HbA1c was similar in all age groups, with a minor reduction from baseline to week 16.

Figure 3 HbA1c (%) by treatment week - mean plots (upper panel: all subjects; lower panel: age groups)



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

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

Rapporteur's comment

Both treatments resulted in a reduction of HbA1c compared to baseline and non-inferiority was demonstrated. The upper limit of the CI was 0.15 which is well within both the pre-defined non-inferiority margin of 0.4 % and the currently recommended non-inferiority margin of 0.3 %.

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

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

Secondary endpoints

Fasting plasma glucose

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

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

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

8-point self-measured plasma glucose profiles

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

4-point SMPG for dose adjustment

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

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

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

Rapporteur's comment

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

Safety results

Extent of exposure

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

Insulin dose

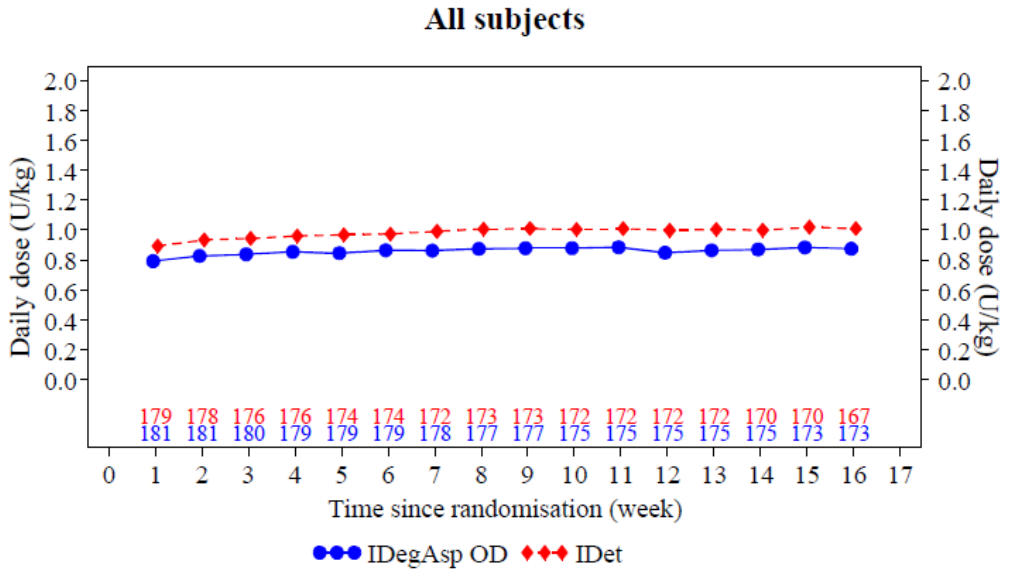
At randomisation the total daily insulin dose was to be reduced by 20%. Subjects were transferred from pre-trial basal insulin to IDegAsp or IDet aiming for a basal:bolus ratio of between 50:50 and 30:70 with no specific recommendations for basal dose reduction. Daily basal insulin dose relates to the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

In terms of dosing patterns, the mean total daily insulin dose was lower in the IDegAsp group compared to the IDet group throughout the trial. At week 16, the mean (SD) total daily insulin doses were 0.88 (0.29) vs. 1.01 (0.40) units/kg in the IDegAsp and IDet groups, respectively (Figure 4).

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

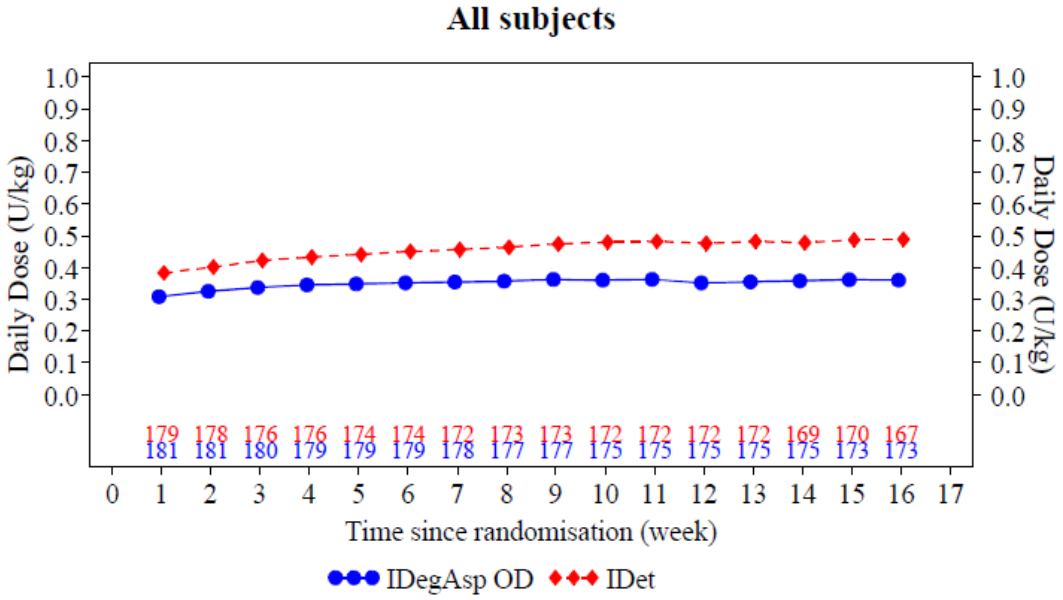
In the IDet treatment group, mean total daily insulin dose per body weight was lowest in children 1-5 years and highest in adolescents 12-17 years throughout the trial.

Figure 4 Total daily insulin dose (actual) in units/kg by treatment week – mean plot – safety analysis set



Similarly, the mean (SD) daily basal dose was lower in the IDegAsp group: 0.36 (0.15) units/kg IDeg from IDegAsp vs. 0.49 (0.27) units/kg IDet at week 16 (Figure 5). After 16 weeks, 97 (54.2%) subjects in the IDet group were using IDet BID.

Figure 5 Daily basal insulin dose (actual) in units/kg by treatment week – mean plot – safety analysis set



The mean daily IAsp dose (including IAsp administered as IDegAsp) was similar in the two treatment groups throughout the trial; at week 16, mean (SD) daily IAsp dose was 0.52 (0.19) units/kg in the IDegAsp group and 0.52 (0.23) units/kg in the IDet group.

In both the IDegAsp and the IDet treatment group, the mean daily bolus insulin dose per body weight was fairly constant in all three age groups during the trial and was similar between age groups.

Rapporteur's comment

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

Adverse events

The overall rate of AEs was similar in the two treatment groups (915 vs. 853 events per 100 patient years of exposure [PYE] in the IDegAsp and IDet groups, respectively). The majority of events were mild or moderate in severity and were considered as unlikely to be related to the trial products. The rates of AEs considered possibly or probably related to trial product (IDegAsp or IDet), as judged by the investigator, were 47 vs. 37 events per 100 PYE, respectively, and approximately 75% of all subjects in either treatment group had an outcome of recovered at end of trial.

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

The most frequent AEs occurring in ≥5% and ≥1% of the subjects are summarised in Table 5. Apart from hypoglycaemic episodes reported on the hypoglycaemic episode form, the most frequently reported AEs (≥5%) in both treatment groups were 'headache', 'nasopharyngitis', 'abdominal pain upper', 'pyrexia' and 'vomiting'

Table 5 Adverse events by system organ class and preferred term – most frequent [>=5%] – treatment emergent – summary – safety analysis set

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

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

Rapporteur's comment

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

Serious adverse events

The rates of SAEs were low: 14 SAEs reported by 11 (6.1%) subjects in the IDegAsp group and 7 SAEs reported by 7 (3.9%) subjects in the IDet group. For IDegAsp, the most frequently reported SAE were hypoglycaemia related AEs; 5 events of 'hypoglycaemia' in 5 subjects and 1 event in 1 subject of 'hypoglycaemic seizure' vs 1 event of 'hypoglycaemia' in the IDet treatment group. All other SAEs were single occurrences in both treatment groups. No deaths were reported.

Adverse events leading to withdrawal

One subject in the IDegAsp group was withdrawn from the trial during the 16-week treatment period due to an AE of hypoglycaemic seizure.

Adverse events leading to dose reduction

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

Dose reduction due to AEs was most frequently related to events of infection or because of gastrointestinal disorders and events of 'hypoglycaemia'. In both treatment groups most of the events related to dose reduction were reported in the SOC Infections and infestations (6 events in 5 subjects with IDegAsp and 6 events in 6 subjects with IDet, respectively). Insulin adjustments are normally required in connection with infections. The infections themselves may result in a need for higher insulin doses but the associated symptoms, such as vomiting, decreased appetite and diarrhoea, may cause a need for reducing the dose. Five (5) hypoglycaemia related AEs led to dose reductions in the IDegAsp treatment group compared to 0 events in the IDet treatment group.

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

Adverse events leading to temporary withdrawal of trial product

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

All three events were considered unlikely related to trial product. Both subjects in the IDegAsp treatment group recovered from the events. The 1 subject in the IDet treatment group was recovering at end of the trial ('Fall', tibial plateau fracture due to trampoline fall).

Rapporteur's comment

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

Adverse events of special interest

Medication errors concerning trial products

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

Allergic reactions

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

Injection site reactions

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

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

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

Rapporteur's comment

Medication errors due to mix-up between trial products and pre-trial products were reported in both treatment groups. Slightly more allergic reactions were reported in the IDegAsp treated group, however, none of the events were considered related to study product and did not result in any changes in the dose of the product. Few injection site reactions were reported, which were evenly distributed between treatments.

Hypoglycaemia

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

Hypoglycaemia reported as adverse event

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

Rapporteur's comment

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

Confirmed hypoglycaemic episodes

Almost all subjects experienced confirmed hypoglycaemic episodes during the 16-week treatment period with IDegAsp (N=168 [92.8%]) or IDet (N=164 [91.6%]) and the observed rate of confirmed hypoglycaemic episodes per 100 PYE was 4623 with IDegAsp and 4955 with IDet (Table 6).There was no statistically significant difference between treatment arms in the rate of confirmed hypoglycaemia (estimated mean treatment ratio of IDegAsp OD/IDet was 0.95 [0.76; 1.17]95%CI).

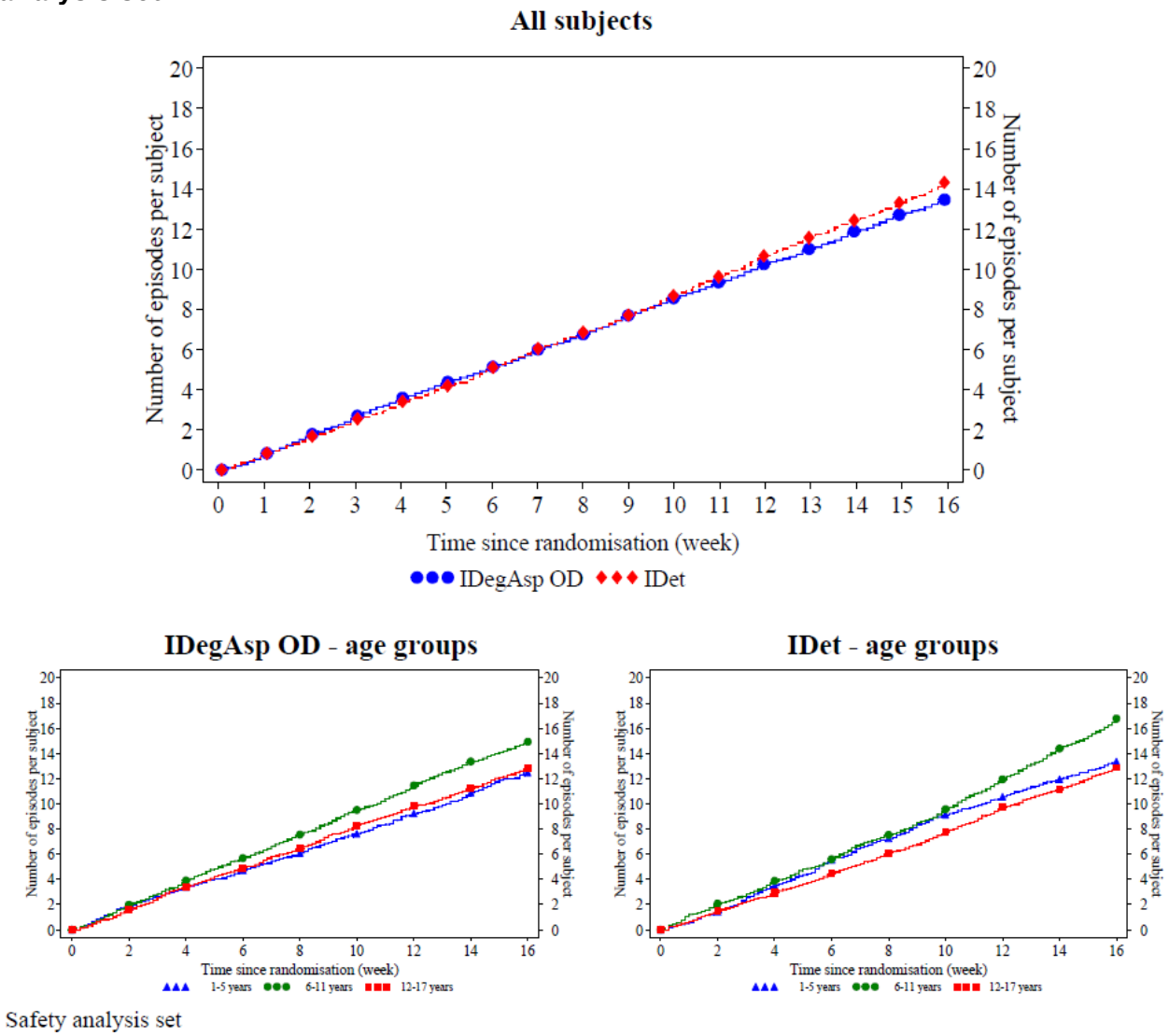
Overall, there was a tendency to a higher rate for children 6-11 years (Figure 6). This may be due to challenges in controlling glycaemia during school hours. The majority of the confirmed hypoglycaemic episodes occurred during daytime (diurnal) for both treatment groups overall and across all age groups. Approximately 50% of the subjects in both treatment groups reported 10 or fewer confirmed hypoglycaemic episodes.

Table 6 Hypoglycaemic episodes by classification – treatment emergent – summary - safety analysis set

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

N: Number of Subjects
%: Percentage of Subjects with the Event
E: Number of Events
R: Event Rate per 100 Patient Year(s) of Exposure
ISPAD: International society for pediatric and adolescent diabetes, Sympt.: Symptomatic
Confirmed hypoglycaemia: subject has altered mental status and cannot assist in his care,is semiconscious or unconscious,or in coma ± convulsions and may require parenteral therapy (glucagon or i.v. glucose) and/or have a recorded PG < 3.1 mmol/L (56mg/dL)

Figure 6 Confirmed hypoglycaemic episodes – treatment emergent - mean cumulative function (upper panel: all subjects; lower panel: age groups) – safety analysis set



Safety analysis set

Rapporteur's comment

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

Severe hypoglycaemic episodes

The majority of subjects had no severe hypoglycaemic episodes neither in the IDegAsp treatment group [170 (93.9%)] nor in the IDet treatment group [176 (98.3%)]. In the IDegAsp treatment group, 11 subjects (6.1%) reported 14 severe hypoglycaemic episodes (Table 6), leading to a rate of 26 episodes per 100 PYE (Table 7). In the IDet treatment group, 3 subjects (1.7%) reported 4 severe hypoglycaemic episodes leading to a rate of 7 episodes per 100 PYE (Table 6 and Table 7). There was no statistically significant difference between treatment groups.

When evaluating severe hypoglycaemic episodes it is important to note that these were mostly single occurrences in individual subjects. Three (3) subjects in the IDegAsp treatment group reported 2 severe hypoglycaemic episodes each (1 of these subjects reported the events within 19 minutes and it

was evaluated to be the same episode by the external classifier; see below) and 1 subject in the IDet treatment group reported 2 severe episodes. Two (2) of the episodes in the IDegAsp group and 1 in the IDet group appeared to be related to exercise.

The observed rate of severe hypoglycaemic episodes was higher with IDegAsp than with IDet throughout the trial. The majority of the severe hypoglycaemic episodes occurred during daytime (diurnal) in both treatment groups.

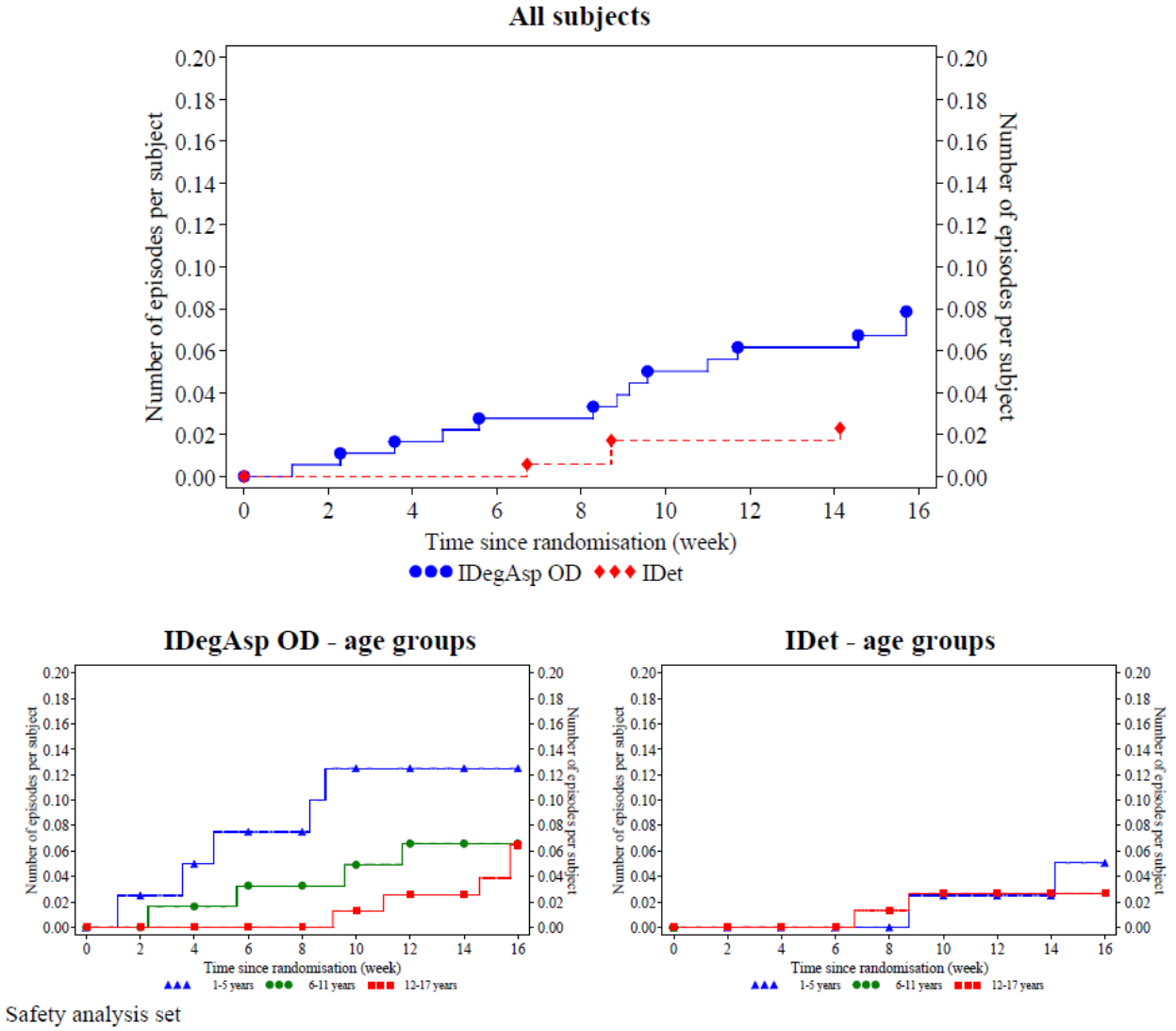
The episodes of severe hypoglycaemia according to ADA and ISPAD were reviewed by an external expert in a blinded manner in order to have a centralised assessment of severe hypoglycaemia classification, in accordance with ISPAD. The classification was based on case narratives and paraclinical findings.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

Table 7 External classified severe hypoglycaemic episodes – treatment emergent - summary - safety analysis set

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

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

Figure 7 Severe hypoglycaemic episodes - treatment emergent - mean cumulative function (upper panel: all subjects; lower panel: age groups) – safety analysis set



Severe hypoglycaemic episodes across age groups

In the IDegAsp treated group, the number of severe hypoglycaemic episodes was similar between age groups; 5 episodes in 4 subjects were reported in children 1-5 years and in adolescents 12-17 years while 4 episodes in 3 subjects were reported in children 6-11 years (Figure 7). The rate for children 1-5 years was higher compared to other age groups, although it should be noted that the rates are based on few episodes.

In the IDet treated group, two (2) episodes in 2 subjects were reported in children 1-5 years and 2 episodes in 1 subject were reported in adolescents 12-17 years. No episodes were reported in children 6-11 years (Figure 7).

Rapporteur's comment

Severe hypoglycaemias were rare but more often reported in the IDegAsp treated group. Importantly most of the events occurred in daytime. The rate of severe hypoglycaemias was comparable across age groups in the IDegAsp treated group, whereas no events were reported in the age group 6-11 years treated with IDet. However, due to the low number of events no firm conclusions can be drawn.

Nocturnal confirmed hypoglycaemic episodes

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

Nocturnal confirmed hypoglycaemic episodes across age groups

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

Nocturnal severe hypoglycaemic episodes

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

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

Rapporteur's comment

The rate of nocturnal confirmed hypoglycaemias did not differ between treatment groups. In both groups, nocturnal hypoglycaemias were more common in adolescents than in younger patients. Only very few severe nocturnal hypoglycaemias were reported which were evenly distributed between groups.

Hyperglycaemic episodes and ketosis

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

The percentages of subjects experiencing hyperglycaemic episodes were similar between IDegAsp (N= 72 [39.8%]) and IDet (N= 73 [40.8%]) treatment groups. The observed rate of hyperglycaemic episodes per 100 PYE was 1094 with IDegAsp and 833 with IDet (Table 8).

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

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

4 subjects with IDegAsp versus 12 episodes in 8 subjects with IDet), implying that the difference in episodes of ketosis in favour of IDegAsp might have been underestimated.

Regarding subjects experiencing nocturnal hyperglycaemic episodes, the percentages of subjects were similar between IDegAsp (N= 26 [14.4%]) compared to the IDet (N= 30 [16.8%]) treatment group. The respective rates per 100 PYE were 184 with IDegAsp and 98 with IDet (Table 8).

Regarding nocturnal hyperglycaemic episodes with ketosis (blood ketones > 1.5 mmol/L), 1 episode in 1 subject was reported with IDegAsp vs 2 episodes in 2 subjects with IDet (Table 8). No statistical analysis was performed for nocturnal hyperglycaemic episodes nor for nocturnal hyperglycaemic episodes with ketosis.

Table 8 Hyperglycaemic episodes and episodes of ketosis – treatment emergent – summary - safety analysis set

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

N: Number of subjects
%: Percentage of subjects with the event
E: Number of events
R: Event rate per 100 patient year(s) of exposure
Hyperglycaemic episodes: all episodes registered in hyperglycaemic episode form with plasma glucose > 14.0 mmol/L where subject looks/feels ill
Ketosis:(blood ketones > 1.5 mmol/L)
Nocturnal period: the period between 23:00 p.m. and 07:00 a.m. (both included)

Rapporteur's comment

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

Hyperglycaemic episodes across age groups

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

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

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

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

Rapporteur's comment

In the IDegAsp treated group, the highest rate of hyperglycaemias was observed in the age group 6-11 years, whereas in the IDet treated group the highest rate was observed in the age group 1-5 years. No differences between age groups were observed for nocturnal hypoglycaemias for either treatment.

Vital signs and laboratory values

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

Rapporteur's comment

There were no clinically relevant differences observed with regards to vital signs or laboratory values during the study. Mean body weight increased in the IDegAsp treated group, whereas no change was observed in the IDet treated group. This difference was statistically significant.

1.3.3. Discussion on clinical aspects

With this submission the completed paediatric study NN5401-3816 (hereafter referred to as study 3816) for has been provided, in accordance with Article 46 of Regulation (EC) No1901/2006.

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

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

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

The choice of comparator and bolus insulin is acceptable. Both IDet and IAsp are currently not approved for use below the age of 2 years, however limited data in children below the age of 2 years is available from other clinical trials and no safety concerns have arisen from these data.

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

The study included 362 subjects randomised 1:1 to the two treatment groups. Overall 94.5 % of patients completed the study. Withdrawals were evenly distributed between treatments and age groups. The baseline characteristics were generally well balanced between groups. Notably, only one child below the age of 2 years was included in the IDet treated group. Duration of diabetes was slightly longer in the IDegAsp treated group, however, numerically more diabetes complications were reported in the IDet treated group.

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

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

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

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

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

Medication errors due to mix-up between trial products and pre-trial products were reported in both treatment groups. Slightly more allergic reactions were reported in the IDegAsp treated group, however, none of the events were considered related to study product and did not result in any changes in the dose of the product. Few injection site reactions were reported, which were evenly distributed between treatments.

Thus the reporting of adverse events does not evoke any new safety concerns.

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

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

Severe hypoglycaemias were rare but more often reported in the IDegAsp treated group. Importantly most of the events occurred in daytime. The rate of severe hypoglycaemias was comparable across age groups in the IDegAsp treated group, whereas no events were reported in the age group 6-11 years treated with IDet. However, due to the low number of events no firm conclusions can be drawn.

The rate of nocturnal confirmed hypoglycaemias did not differ between treatment groups. In both groups, nocturnal hypoglycaemias were more common in adolescents than in younger patients. Only very few severe nocturnal hypoglycaemias were reported which were evenly distributed between groups.

The proportion of subjects reporting hyperglycaemias did not differ between treatment groups, but more hyperglycaemic events were reported in the IDegAsp treated group. This difference was, however, not statistically significant. The reporting of hyperglycaemia with ketones was low, with fewer reports in the IDegAsp treated group. However, as noted by the MAH, more subjects had actually measured ketones in accordance with the protocol in the IDegAsp treated group, thus the rate of ketosis in this group may be overestimated. In the IDegAsp treated group, the highest rate of hyperglycaemias was observed in the age group 6-11 years, whereas in the IDet treated group the highest rate was observed in the age group 1-5 years. No differences between age groups were observed for nocturnal hypoglycaemias for either treatment.

There were no clinically relevant differences observed with regards to vital signs or laboratory values during the study. Mean body weight increased in the IDegAsp treated group, whereas no change was observed in the IDet treated group. This difference was statistically significant.

2. Rapporteur's overall conclusion and recommendation

Study 3816 was a study in subjects with T1DM, aged 1-18 years, with the aim of evaluating the efficacy and safety of Ryzodeg (IDegAsp) compared to that of Levemir (IDet). NovoRapid (IAsp) was used as mealtime bolus insulin in both treatment arms, thus no comparative data on the efficacy of NovoRapid is provided with this study. Only one subject below the age of 2 years was included in the study. No new safety concerns related to the use of NovoRapid in the paediatric population arise from the data submitted.

No further regulatory consequences for the MA of NovoRapid has been identified by the MAH based on the data from this paediatric trial. This conclusion is endorsed.

The benefit risk balance for NovoRapid in the paediatric population remains positive.

Overall conclusion

Recommendation

☒ Fulfilled:

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.