2 Synopsis

Trial Registration ID-number NCT01087606	**IND Number –** IND 73,198 **EudraCT number –** 2009-013412-13
Title of Trial A 26-Week, Multinational, Multicentre, Open-label, Two-arm, Parallel, Randomised, Treat-to-target Extension Trial Comparing Safety and Efficacy of NN5401[1] Once-daily Plus Meal-time Insulin Aspart for the Remaining Meals vs. Basal-Bolus Treatment with Insulin Detemir Plus Meal-time Insulin Aspart in Subjects with Type 1 Diabetes This synopsis contains the results after 52 weeks treatment (26 weeks in the main trial NN5401-3594 and 26 weeks in the present extension trial NN5401-3645)	
Investigators There were 71 principal investigators. [redacted] MD was appointed as signatory investigator: – [redacted]	
Trial Sites The trial was conducted at 71 sites in 9 countries: Denmark (3 sites), Poland (6 sites), Romania (7 sites), France (2 sites), United Kingdom (6 sites), Russian Federation (10 sites), Israel (4 sites), Australia (7 sites) and United States (26 sites).	
Publications None	
Trial Period 15 March 2010 to 02 December 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

To investigate the long-term safety and tolerability of IDegAsp OD + meal-time IAsp for the remaining meals. This was done by comparing the difference between IDegAsp OD + meal-time IAsp for the remaining meals and IDet + meal-time IAsp treatment (26 weeks of treatment in the main trial NN5401-3594 plus 26 weeks of treatment in the present extension trial NN5401-3645) in terms of the listed safety assessments:

- Adverse events
- Hypoglycaemic episodes
- Clinical evaluations
- Central laboratory assessments including lipid profile and insulin antibodies
- Body weight
- Insulin dose

Secondary Objectives:

To compare the efficacy between IDegAsp OD + meal-time IAsp for the remaining meals and IDet + meal-time IAsp after 52 weeks of treatment in terms of the listed assessments:

- HbA_{1c}
- Fasting plasma glucose (FPG)
- 9-point self measured plasma glucose profile [9-point profile (SMPG)]
- Self measured plasma glucose (SMPG) for dose adjustments

[1] NN5401 was the name previously used for insulin degludec/insulin aspart (IDegAsp)

Methodology

The main trial (NN5401-3594) was a 26-week, 2:1 randomised, parallel group trial comparing two treatment regimens in subjects with type 1 diabetes: IDegAsp OD + IAsp for the remaining meals and IDet + meal-time IAsp, and the 26-week extension trial was with the same treatment regimen to ensure the most optimal coverage of both basal and bolus requirements. Subjects who consented to participate in the extension trial continued to receive treatment with either IDegAsp OD + meal-time IAsp or IDet + meal-time IAsp as previously randomly allocated in the main trial NN5401-3594.

The subjects were randomised in a 2:1 ratio to either IDegAsp OD (meal time) + IAsp at the remaining meals or IDet OD + meal-time IAsp using an IV/WRS at the beginning of the main trial and there was no further randomisation in the extension trial period.

The treatment groups consisted of subjects randomised to:

- IDegAsp OD administered with the meal that ensures the most optimal coverage of both basal and bolus requirements + injection of IAsp for the remaining insulin requiring meals. The injection of IDegAsp could be moved to another main meal during the course of the trial.
- IDet OD + injection of meal-time IAsp for the insulin requiring meals. Adding a second dose of IDet could be considered in case the subjects meet the criteria for inadequate glycaemic control.

The main trial included a screening visit and a randomisation visit. The subjects were required to attend further visits and phone contacts during the 26 weeks of treatment, followed by a follow-up visit of one week. All subjects were offered to participate in the 26-week extension trial following the completion of the 26-week main trial. The extension trial included a screening visit to assess eligibility on the same day as the follow-up visit in the main trial. The subjects were required to attend further 7 visits and 7 phone contacts during the 26 weeks of treatment, followed by a follow-up visit of one week after discontinuing the trial treatment. There were two 1-week follow-up periods after 26 weeks and 52 weeks of treatment respectively for safety follow-up. During follow-up periods, subjects were instructed to switch to treatment with NPH insulin BID plus meal-time IAsp before each main meal.

A separate protocol, subject information and informed consent form were prepared for the extension trial. Verbal and written information was provided to the subjects and the informed consent form was signed by the subject and the investigator.

Number of Subjects Planned and Analysed

The trial population constituted a population with type 1 diabetes mellitus who would benefit from intensified therapy, applying a treat-to-target concept. The planned number of subjects to be screened and complete the main trial was 754 and 447. The planned number of subjects to be screened and complete the present extension trial was 335 and 285. All subjects enrolled in the extension trial had previously participating in the 26-week main trial (NN5401-3594) and received maximum 52 weeks of treatment in total. The actual numbers of subjects included in the trial are shown below:

	IDegAsp OD N (%)	IDet N (%)	Total N (%)
Screened			706
Screening Failures			158
Withdrawn before Randomisation			0
Randomised	366 (100.0)	182 (100.0)	548 (100.0)
Exposed	362 (98.9)	180 (98.9)	542 (98.9)
Completed Main Trial	320 (87.4)	156 (85.7)	476 (86.9)
Withdrawn at/after Randomisation	46 (12.6)	26 (14.3)	72 (13.1)
Adverse Event	4 (1.1)	3 (1.6)	7 (1.3)
Ineffective Therapy	2 (0.5)	0 (0.0)	2 (0.4)
Non-Complicance With Protocol	8 (2.2)	6 (3.3)	14 (2.6)
Withdrawal Criteria	7 (1.9)	5 (2.7)	12 (2.2)
Other	25 (6.8)	12 (6.6)	37 (6.8)
Completed Main Trial Not screened for extension	66 (18.0)	34 (18.7)	100 (18.2)
Completed Main Trial screening failure in extension	0 (0.0)	0 (0.0)	0 (0.0)
Included in Extension	254 (69.4)	122 (67.0)	376 (68.6)
Withdrawn during extension	21 (5.7)	9 (4.9)	30 (5.5)
Adverse Event	3 (0.8)	0 (0.0)	3 (0.5)
Ineffective Therapy	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance	4 (1.1)	1 (0.5)	5 (0.9)
Withdrawal Criteria	2 (0.5)	1 (0.5)	3 (0.5)
Other	12 (3.3)	7 (3.8)	19 (3.5)
Completed Extension	233 (63.7)	113 (62.1)	346 (63.1)
Full Analysis Set	366 (100.0)	182 (100.0)	548 (100.0)
PP Analysis Set	336 (91.8)	168 (92.3)	504 (92.0)
Safety Analysis Set	362 (98.9)	180 (98.9)	542 (98.9)
Extension Trial Set	254 (69.4)	122 (67.0)	376 (68.6)

N: Number of subjects %: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Subjects ≥ 18 years of age with type 1 diabetes mellitus (diagnosed clinically) ≥ 12 months, $7.0 \leq HbA_{1c} \leq 10.0$ by central laboratory analysis, body mass index (BMI) ≤ 35.0 kg/m^2 and ongoing daily treatment with insulin (in a BB regimen, premix insulin regimen or self-mix regimen) for at least 12 months prior to Visit 1 were included in the main trial.

Subjects who completed the first 26-week treatment in main trial NN5401-3594 were eligible to attend the 26-week extension trial.

Subjects were excluded from the main trial if they had been treated with insulin regimens other than BB, premix or self-mix within 3 months prior to Visit 1, treated with a BB regimen with basal insulin injected BID, treated with any antidiabetic glucose-lowering drug other than insulin within the last 3 months prior to Visit 1, or had anticipated a change in concomitant medication known to interfere significantly with glucose metabolism, or had cardiovascular disease within the last 6 months prior to Visit 1, or uncontrolled treated/untreated severe hypertension (systolic blood pressure ≥ 180 millimetre (mm) mercury (Hg) and/or diastolic blood pressure ≥ 100 mmHg) or any clinically significant disease or disorder.

Subjects were not eligible for trial participation from the extension trial if they had anticipated a change in concomitant medication known to interfere significantly with glucose metabolism, or anticipated significant lifestyle changes during the trial, or pregnancy, breast-feeding, or known or suspected allergy to any of the trial products or

related products, or any clinically significant disease or disorder.

A subject was to be withdrawn from the main trial or the extension trial if the following applied:

- Hypoglycaemia during the treatment period posing a safety problem as judged by the investigator.
- Initiation or significant change of any systemic treatment which in the investigator's opinion could have interfered with glucose metabolism (inhaled corticosteroids were allowed).
- Lack of effect: After Week 12, if the subject had not had reduction in HbA_{1c} and had a pre-breakfast SMPG reading > 13.3 mmol/L (> 240 mg/dL) on 3 consecutive days despite appropriate dose adjustments.

Test Product, Dose and Mode of Administration, Batch Number

IDegAsp OD was injected with the meal that ensured the most optimal coverage of both basal and bolus requirements + injection of IAsp for the remaining insulin-requiring meals. Insulin products used in this trial were to be injected in the abdomen, upper arm (deltoid region) or thighs.

IDegAsp 100 U/mL, 3 mL FlexPen®. Batch no.: For all countries: XP50558; European Union: XP51553; United States, European Union, Israel, Russia: XP52373

Duration of Treatment

The total duration of the trial for each subject was approximately 54 weeks including screening and follow-up visits.

Reference Therapy, Dose and Mode of Administration, Batch Number

IDet OD + meal-time IAsp for the insulin-requiring meals. IDet was to be dosed at the evening meal or at bedtime according to local practice. A second dose of IDet could be added at breakfast from Visit 10 in main trial if the subject fulfilled the predefined criteria for inadequate glycaemic control. NPH insulin was given twice daily (BID) during the follow-up period from Visit 28 until Visit 29 and from Visit 44 until Visit 45 + injection of IAsp for the insulin-requiring meals.

All insulin products used in this trial were to be injected in the abdomen, upper arm (deltoid region) or thighs. .

IDet (Levemir®) 100 U/mL, 3 mL FlexPen®. Batch no.: European Union, Australia, Israel, Russia is XP51112. European Union: YP50152. United States: XP50990 and XP52645.

IAsp (NovoRapid®, NovoLog®) 100 U/mL, 3 mL FlexPen®. Batch no.: European Union, Australia, Israel, Russia: XP50716. United States: XP51084. European Union: XP52291.

Insulin Neutral Protamine Hagedorn (Insulatard®, Prothaphane®, Novolin® N) 100 U/mL, 3 mL FlexPen®. Batch no.: For all countries XP51117.

Criteria for Evaluation – Efficacy

The following efficacy variables were assessed:

- HbA_{1c}
- FPG
- SMPG
  - 4-point profiles (SMPG)
  - 9-point profile (SMPG) with addition to 4-point profiles (SMPG)

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes[#]
- Insulin dose
- Physical examination
- Vital signs
- Eye examination
- Electrocardiogram (ECG)
- Laboratory safety variables

[#]Hypoglycaemic episodes were categorised according to the ADA classification. In addition "minor episodes" with a PG < 3.1 mmol/L were recorded. The pool of severe and minor episodes is referred to as "confirmed hypoglycaemia".

Statistical Methods

Analysis Sets

The following analysis sets were defined:

- Full analysis set (FAS): included all randomised subjects. The statistical evaluation of the FAS was to follow the intention-to-treat (ITT) principle and subjects were to contribute to the evaluation "as randomised".
- Per protocol (PP) analysis set: included subjects without any major protocol violations that may have affected the primary endpoint. Moreover, subjects must have been exposed to the investigational product or its comparator for more than 12 weeks and must have had a valid assessment necessary for deriving the primary endpoint. Subjects in the PP set were to contribute to the evaluation "as treated".
- Safety analysis set: included all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set were to contribute to the evaluation "as treated".
- Extension Trial Set: included subjects receiving at least one dose of the investigational product or its comparator in the extension trial.

Analyses of all efficacy endpoints were based on the FAS as were analyses of hypoglycaemia, body weight and lipids. All other endpoints related to safety were based on the safety analysis set. The robustness of the results for the primary endpoint was explored by additional analysis on the PP analysis set. Analyses were repeated for serious treatment emergent AE's, number of severe and minor treatment emergent hypoglycaemic episodes, antibodies, central laboratory parameters (ALAT/SGPT, ASAT/SGOT) and HbA_{1c} using the Extension Trial Set (ETS) to assess the stability of key results.

Secondary Efficacy Analysis

- Change from baseline in HbA_{1c} after 52 weeks of treatment was analysed using an analysis of variance (ANOVA) method with treatment, antidiabetic therapy at screening, sex and region as fixed factors and age and baseline HbA_{1c} as covariates.
- The HbA_{1c} responder (HbA_{1c} <7% at end of trial) was a dichotomous endpoint. The HbA_{1c} responder endpoint was analysed based on a logistic regression model using same factors and covariates as for the HbA_{1c} analysis.
  - Responder without hypoglycaemic episodes (HbA_{1c} <7.0% at end of trial and no confirmed/severe hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks) was a dichotomous endpoint that was defined based on whether a subject had met the American Diabetes Association (ADA) HbA_{1c} target at end of trial without confirmed/severe hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after last randomised treatment. Responder analysis was based on a logistic regression model using the

same factors and covariates as for the primary analysis.

- Change from baseline in FPG after 52 weeks of treatment (analysed at central laboratory)
  - Change from baseline in FPG after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the primary analysis.
- 9-point profile (SMPG): A mixed effect model was fitted to the 9-point profile (SMPG) data. The model included treatment, time, interaction between treatment and time, antidiabetic therapy at screening, sex and region as fixed factors, age as covariate and subject as random effect. From this model, mean profile by treatment and relevant treatment differences were estimated and explored. Mean and logarithmically transformed fluctuations (mmol/L) in the 9-point profile (SMPG), prandial PG increment and nocturnal PG endpoints after 52 weeks of treatment were analysed separately using an ANOVA method similar to that used for the primary analysis.
- SMPG values used for dose adjustment: The mean of before meal/before breakfast PG values after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the HbA_{1c} analysis. The time from randomisation until the date a subject meet the titration target(s) for the first time was analysed in a Cox proportional hazards model including treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as covariate. The logarithmically transformed SMPG values available before breakfast were analysed as repeated measures in a linear mixed model with treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as covariate and subject as random factor. The model assumed independent within- and between-subject errors with variances depending on treatment. Within-subject variability as measured by CV% for a treatment can be calculated from the corresponding residual variance.

Primary Safety Analyses

- A treatment emergent adverse event (TEAE) was defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 13.0) coding. Evaluation of TEAEs was based on descriptive statistics. AEs and hypoglycaemic episodes are also presented as the rate of the events per 100 patient years of exposure (PYE).
- A hypoglycaemic episode was defined as treatment emergent using the same definition as for TEAE above. A hypoglycaemic episode with time of onset between 00:01 and 05:59 a.m. (both included) was considered nocturnal. Hypoglycaemic episodes were classified according to the ADA classification into the following five categories based on PG measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia . Furthermore, confirmed hypoglycaemic episodes were defined as episodes of severe hypoglycaemia and minor hypoglycaemic episodes with a confirmed PG value of less than 3.1 mmol/L (56mg/dL). The number of treatment emergent confirmed and severe hypoglycaemic episodes 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 is considered treatment emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. Confirmed and severe nocturnal hypoglycaemic episodes were analysed separately.
- Antibodies specific for: IDeg, IAsp and IDet as well as antibodies cross-reacting to human insulin were measured and their correlation to total insulin dose and HbA_{1c} were investigated using descriptive statistics.
- Change from baseline in body weight after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the primary analysis.
- Remaining laboratory parameters, physical examination, ECG, funduscopy / fundusphotography and vital signs were evaluated based on descriptive statistics.

Demography of Trial Population

The demographics and baseline characteristics in the two treatment groups were similar between the treatment groups. The majority of the subjects that reported their race were White and of non-Hispanic/Latino origin. The baseline demographic and diabetes characteristics are shown in the table below. The pre-trial insulin treatment regimens were evenly distributed in the two treatment groups. A total of 91.3 % of subjects in the IDegAsp group and 88.5 % of subjects in the IDet group were treated with a basal-bolus insulin regimen at screening. Most of the remaining subjects were treated with premix or premix + bolus insulin at screening at screening in the main trial.

	IDegAsp OD	IDet	Total
Number of Subjects	366	182	548
Age (years)			
N	366	182	548
Mean (SD)	40.7 (12.8)	42.6 (13.8)	41.3 (13.2)
Median	39.9	42.4	40.6
Min ; Max	18.3 ; 78.5	18.1 ; 80.2	18.1 ; 80.2
Body Weight (kg)			
N	366	182	548
Mean (SD)	76.7 (14.6)	76.0 (14.0)	76.5 (14.4)
Median	75.0	76.0	75.3
Min ; Max	44.0 ; 123.4	42.9 ; 137.4	42.9 ; 137.4
BMI (kg/m^2)			
N	366	182	548
Mean (SD)	26.2 (4.0)	26.7 (3.9)	26.4 (4.0)
Median	25.9	26.3	26.0
Min ; Max	16.2 ; 35.6	18.7 ; 36.2	16.2 ; 36.2
Duration of Diabetes (year)			
N	366	181	547
Mean (SD)	17.2 (11.3)	17.9 (12.3)	17.4 (11.6)
Median	14.9	15.0	14.9
Min ; Max	1.1 ; 59.7	1.0 ; 56.6	1.0 ; 59.7
HbA_{1c} (%)			
N	366	182	548
Mean (SD)	8.3 (0.8)	8.3 (0.7)	8.3 (0.8)
Median	8.2	8.2	8.2
Min ; Max	6.8 ; 10.3	6.5 ; 10.4	6.5 ; 10.4
FPG (mmol/L)			
N	365	181	546
Mean (SD)	10.3 (4.7)	11.0 (4.8)	10.5 (4.8)
Median	9.6	10.3	9.9
Min ; Max	1.8 ; 30.2	2.9 ; 28.4	1.8 ; 30.2

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation

Efficacy Results and Conclusions

After 52 weeks of treatment with IDegAsp + IAsp at remaining meals or IDet + IAsp, the following was concluded:

Secondary Endpoint

- **HbA_{1c}**: IDegAsp effectively improved long−term glycaemic control, as measured by HbA_{1c}.The estimated mean reduction in HbA_{1c} during the trial was numerically larger (0.67 %-points) with IDegAsp compared to IDet (0.57 %-points), and the estimated mean difference was -0.10 %-points [-0.24; 0.03] $_{95\%CI}$. After 52 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.7 (0.9) % with IDegAsp and 7.7 (0.9) % with IDet.
- **Responders for HbA_{1c}:** A total of 22.4% of subjects treated with IDegAsp achieved HbA_{1c} <7% compared to the observed proportion of 17.0% for subjects treated with IDet. The estimated odds of achieving this target were numerically higher (56%) with IDegAsp compared to IDet [estimated odds ratio (IDegAsp/IDet) 1.56 (0.94; 2.59)$_{95\% CI}$].
- **Responders for HbA_{1c} without hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemia was 5.3% with IDegAsp and 3.6% with IDet. The estimated odds of achieving this target were numerically higher (50%) with IDegAsp compared to IDet (estimated odds ratio [IDegAsp/IDet] 1.50 [0.57; 3.97]$_{95\% CI}$). The observed proportion of subjects achieving HbA_{1c} <7% without severe hypoglycaemic episodes was 22.0% with IDegAsp and 16.6% with IDet. The estimated odds of achieving this target were numerically higher (54%) with IDegAsp compared to IDet (odds ratio [IDegAsp/IDet] 1.54 [0.90; 2.63]$_{95\% CI}$).
- **FPG:** FPG decreased during the trial to similar observed mean levels; 8.5 mmol/L with IDegAsp and 8.6 mmol/L with IDet. The estimated mean reduction from baseline in FPG during this trial was numerically higher with

IDegAsp (2.08 mmol/L) compare to IDet (2.01 mmol/L), with an estimated mean difference (IDegAsp-IDet) of -0.07 mmol/L [-0.79; 0.66]$_{95\%CI}$.

- **9-point SMPG profiles:** Estimated mean SMPG values before lunch, before main evening meal and before breakfast the following day were lower with IDegAsp compared to IDet, the estimated mean treatment difference (IDegAsp-IDet) was -0.70 mmol/L [-1.35; -0.06]$_{95\%\ CI}$, -0.75 mmol/L [-1.41; -0.10]$_{95\%\ CI}$ and -0.59 mmol/L [-1.16; -0.02]$_{95\%\ CI}$, respectively. There was no difference in the fluctuation in PG based on the 9-point SMPG profile, estimated treatment ratio (IDegAsp/IDet) of 1.00 [0.89; 1.13]$_{95\%\ CI}$. The estimated mean change in nocturnal PG (bedtime to breakfast) was numerically higher with IDegAsp after 52 weeks of treatment; estimated mean difference –0.48 mmol/L [-1.23; 0.27]$_{95\%CI}$.
- **SMPG for dosing**: Mean SMPG before breakfast, lunch, main evening meal and bedtime was reduced with both IDegAsp and IDet during the trial. The estimated mean SMPG value before lunch was lower with IDegAsp (estimated mean difference –0.7 mmol/L [–1.1; –0.2]$_{95\%CI}$.). After 52 weeks of treatment, 15.0% and 17.7% of subjects in IDegAsp and IDet treatment groups achieved the prebreakfast SMPG target < 5 mmol/L. There was no statistically significant difference the within-subject variation (CV%) in pre-breakfast SMPG with IDegAsp compared to IDet (estimated treatment ratio [IDegAsp/IDet] 0.97 [0.88; 1.06]$_{95\%\ CI}$). There was no statistical significant difference regarding the time to meet the prebreakfast PG titration target between treatment groups.

Safety Results and Conclusions

After 52 weeks of treatment with IDegAsp + IAsp at remaining meals or IDet + IAsp, the following was concluded:

Primary Endpoints

- **Adverse events:** There was no clinically relevant difference between the treatment groups in the reporting of AEs. A similar percentage of subjects reported adverse events in the IDegAsp and IDet groups (73.8% and 70.6%, respectively). The rate of all adverse events was similar for the IDegAsp and IDet groups (408 and 442 events per 100 PYE, respectively). The rate of severe adverse events was numerically lower with IDegAsp than with IDet (33 and 48 events per 100 PYE, respectively). The rate of adverse events possibly or probably related to investigational product was numerically lower with IDegAsp than IDet (37 and 69 events per 100 PYE, respectively). The most frequently reported adverse events in both treatment groups were nasopharyngitis, hypoglycaemia, upper respiratory tract infection and headache. Injection site reactions were reported more frequently in the IDet group (6.7%) than in the IDegAsp group (1.9%). The majority of subjects in both treatment groups recovered from the AEs at the end of trial.
- **Deaths, serious adverse events and other significant adverse events:** No death was reported in this trial. A total of 46 (12.7%) and 20 (11.1%) subjects reported 100 serious adverse events in IDegAsp (72 events) and IDet group (28 events), respectively. The rate of serious adverse events per 100 PYE was low in both treatment groups (IDegAsp: 24, IDet: 19) with hypoglycaemia (4.4%) as the most frequent serious adverse events in both groups. A similar percentage of subjects withdrew from the trial due to AEs:4 (1.1%) in the IDegAsp group and 3 (1.6%) in the IDet group in main trial and 3 (0.8%) in the IDegAsp group and 0 (0%) in the IDet group in the extension trial treatment.
- **Hypoglycaemic episodes:** The observed rate of confirmed and nocturnal confirmed hypoglycaemic episodes, per 100 PYE was 3183 and 309 for IDegAsp and 3673 and 541 for IDet. The estimated rate ratios (IDegAsp/IDet) for confirmed hypoglycaemic episodes was 0.95 [0.79; 1.14]$_{95\%\ CI}$, whereas the estimated rate of nocturnal confirmed hypoglycaemia was 38% lower with IDegAsp than with IDet; estimated rate ratio (IDegAsp/IDet) was 0.62, [0.48; 0.79]$_{95\%\ CI}$. The observed rates of severe and nocturnal severe hypoglycaemia per 100 PYE were 27 and 5 for IDegAsp and 45 and 19 for IDet, respectively. The estimated rate ratios (IDegAsp/IDet) for severe hypoglycaemia were 0.98 [0.54; 1.79]$_{95\%\ CI}$.
- **Insulin dose**: The mean total daily (basal and bolus) insulin dose after 52 weeks was numerically lower in the IDegAsp group compared with the IDet group: 72 U (0.89 U/kg) for IDegAsp and 82 U (1.04 U/kg) for IDet. The mean derived total daily basal insulin dose after 52 weeks was numerically lower in the IDegAsp group compared with the IDet group: 30 U (0.38 U/kg) for IDegAsp and 39 U (0.49 U/kg) for IDet. The mean derived total daily bolus insulin dose was numerically lower in the IDegAsp group than in the IDet group: 41 U (0.52 U/kg) for IDegAsp and 43 U (0.55 U/kg) for IDet. The ratio of IDegAsp/IDet mean daily insulin dose (U) after 52 weeks

was 0.87 for total insulin, 0.78 for derived total basal insulin and 0.97 for derived total bolus insulin, meaning that mean doses were numerically lower in the IDegAsp group compared with the IDet group.

- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values**: No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed for vital signs, ECG, fundoscopy/fundusphotography, physical examination and laboratory values.
- **Insulin antibodies:** The mean level of insulin antibodies cross-reacting between IDegAsp, IDet and human insulin was low at baseline and remained low with IDegAsp and increased only slightly with IDet after 52 weeks of treatment. The mean level of IDeg, IDet and IAsp specific antibodies was very low at baseline and remained low throughout the treatment periods.
- **Body weight:** IDegAsp was associated with more weight gain than IDet after 52 weeks of treatment, and the estimated treatment difference (IDegAsp–IDet) was 1.64 kg $[0.89; 2.38]_{95\% \text{ CI}}$. The mean (SD) body weight at baseline and at the end of the trial was 76.5 (14.4) kg and 79.4 (15.6) kg in the IDegAsp group and 76.1 (13.9) kg and 77.4 (14.3) kg in the IDet group, respectively.

Conclusions

This confirmatory, randomised, controlled, 52-week trial investigated the long-term safety and efficacy of treatment with IDegAsp administered once daily at any meal, together with IAsp administered at the remaining meals, compared to treatment with IDet in combination with IAsp at all meals in subjects with type 1 diabetes mellitus. The data support the following conclusions:

- In this trial, no safety issues are identified with IDegAsp + IAsp after 52 weeks of treatment.
- There is no apparent difference between IDegAsp + IAsp and IDet + IAsp with respect to AEs and standard safety parameters with the exception of body weight, which increases more with the IDegAsp regimen compared to the IDet regimen.
- The rates of severe and confirmed hypoglycaemic episodes are numerically lower with IDegAsp + IAsp than with IDet + IAsp.
- Subjects treated with IDegAsp + IAsp experience a lower rate of nocturnal confirmed hypoglycaemic episodes compared to subjects treated with IDet + IAsp.
- Antibody development is sparse for both treatment regimens and only a few injection site reactions are reported with IDegAsp +IAsp.
- The average total daily insulin dose is numerically lower in subjects treated with IDegAsp + IAsp compared to subjects treated with IDet + IAsp.
- Treatment with IDegAsp + IAsp effectively improves long-term glycaemic control (as measured by HbA_{1c}). Improvements in HbA_{1c} and FPG are similar with both regimens after 52 weeks of treatment.

The trial was conducted in accordance with the Declaration of Helsinki(2008) and ICH Good Clinical Practice (1996.).

The results presented reflect data available in the clinical database as of 04-Jan-2011.