2 Synopsis

Trial Registration ID-number NCT00978627	**IND Number –** IND 73,198 **EudraCT number –** 2008-005769-71
Title of Trial A 26-Week, Multinational, Multicentre, Open-label, Two-arm, Parallel, Randomised, Treat-to-target Trial Comparing Efficacy and Safety of NN5401 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	
Investigators There were 79 principal investigators. [redacted] MD was appointed as signatory investigator: – [redacted]	
Trial Sites The trial was conducted at 79 sites in 9 countries: Denmark (3 sites), Poland (6 sites), Romania (8 sites), France (3 sites), United Kingdom (8 sites), Russian Federation (11 sites), Israel (4 sites), Australia (7 sites) and United States (29 sites).	
Publications None	
Trial Period 25 August 2009 to 31 May 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

To confirm efficacy of insulin degludec/insulin aspart (IDegAsp) once daily (OD) + meal-time insulin aspart (IAsp) for the remaining meals in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA_{1c}) after 26 weeks of treatment. This was done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment between IDegAsp OD + meal-time IAsp for the remaining meals and insulin detemir (IDet) + meal-time IAsp to a non-inferiority limit of 0.4%, and if non-inferiority was confirmed to a superiority limit of 0%.

Secondary Objectives:

To confirm superiority of IDegAsp OD + meal-time IAsp for remaining meals over IDet + meal-time IAsp after 26 weeks of treatment in terms of:

- Fasting plasma glucose (FPG) measured at a central laboratory
- Frequency of responders for HbA_{1c} without hypoglycaemic episodes
- Nocturnal hypoglycaemic episodes

To compare efficacy and safety after 26 weeks of treatment in terms of:

- 9-point profile, self-measured plasma glucose (SMPG)
- Self-measured plasma glucose (SMPG) for dose adjustments
- Frequency of responders for HbA_{1c}
- Adverse events (AEs)
- Hypoglycaemic episodes
- Clinical and laboratory assessments
- Insulin antibodies
- Body weight
- Insulin dose
- Patient reported outcome (PRO)

Methodology

This trial was multinational, multi-centre, open-labelled, randomised, two-arm, parallel group, treat-to-target confirmatory efficacy/safety trial of 26 weeks' duration comparing treatment with IDegAsp OD (meal time) + IAsp (for the remaining meals) with that of IDet + meal time IAsp in subjects diagnosed with type 1 diabetes mellitus. There was a 1-week follow-up period after the 26 weeks' treatment period for safety follow-up.

The randomisation was carried out in a 2:1 manner to either IDegAsp OD (meal time) + IAsp at the remaining meals or IDet OD + meal time IAsp, respectively. Randomisation was stratified with respect to previous insulin regimen with either basal-bolus (BB) regimen or other insulin regimen.

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 trial included a screening visit to assess eligibility, followed by a randomisation visit to assign treatment group. The subjects were required to attend a total of 13 visits and 14 phone contacts during the 26 weeks of treatment, followed by a follow-up visit after discontinuing the trial treatment.

Total duration of the individual subjects participating in this trial was approximately 28 weeks.

All subjects were offered to participate in an extension trial following the one week follow-up period. The purpose of the extension trial was to collect safety data. 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

Based on the sample size calculation, the planned number of subjects to be screened and randomised was 754 and 528, respectively, while 447 subjects were expected to complete the trial. 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)
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	320 (87.4)	156 (85.7)	476 (86.9)
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)

N: Number of subjects %: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Male or female subjects aged ≥ 18 years with type 1 diabetes mellitus (diagnosed clinically) ≥ 12 months, 7.0 ≤

$HbA_{1c} \leq 10.0$ 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 trial.

Subjects were excluded from the 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 $\geqq$ 180 millimetre (mm) mercury (Hg) and/or diastolic blood pressure $\geq$ 100 mmHg) or any clinically significant disease or disorder.

A subject was to be withdrawn 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 with the meal that ensures 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. Rotation of injection sites within a given region was recommended.

IDegAsp 100 U/mL, 3 mL FlexPen®. Batch no.: For all countries XP50558 and expiry date is 07 January 2011.

Duration of Treatment

The total duration of the trial for each subject was approximately 28 weeks including screening and follow-up visits.

Reference Therapy, Dose and Mode of Administration, Batch Number

IDet OD + injection of 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 if the subject fulfilled the predefined criteria for inadequate glycaemic control. NPH insulin was given twice daily (BID) from Visit 28 until Visit 29 + 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. Rotation of injection sites within a given region was recommended.

IDet (Levemir®) 100 U/mL, 3 mL FlexPen®. Batch no.: European Union, Australia, Israel, Russia is XP51112, expiry date is 19 February 2011. For United States: XP50990 and expiry date is 28 February 2011.

IAsp (NovoRapid®, NovoLog®) 100 U/mL, 3 mL FlexPen®. Batch no.: European Union, Australia, Israel, Russia: XP50716, expiry date is 15 July 2011. For United States: XP51084 and expiry date is 12 September 2011.

Insulin Neutral Protamine Hagedorn (Insulatard®, Prothaphane®, Novolin® N) 100 U/mL, 3 mL FlexPen®. Batch no.: For all countries XP51117 and expiry date is 19 April 2011.

Criteria for Evaluation – Efficacy

The following efficacy variables were assessed:

- HbA_{1c}
- FPG
- SMPG
  - 4-point profiles (SMPG)
  - 9-point profile (SMPG) with additional 4-point profiles (SMPG)
- PRO questionnaires

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".

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.

Primary Efficacy Analysis

Change from baseline in HbA_{1c} after 26 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 antidiabetic therapy at screening was a factor with two levels according to stratification: 1: basal-bolus regimen 2: other insulin regimen. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval (CI) for the treatment difference (investigational product-comparator) for the mean change in HbA_{1c} was below or equal to 0.4%. Superiority was considered confirmed if the upper bound of the two-sided 95% CI was < 0%.

Confirmatory Secondary Analyses

Provided that non-inferiority was confirmed for the primary endpoint, a number of confirmatory secondary endpoints were tested to confirm superiority of the investigational product over the comparator. The hierarchical testing procedure allowed control of the overall type 1 error. Consequently, superiority can only be confirmed for endpoints where all previous hypotheses have been confirmed. The order of the endpoints defines the testing sequence :

1. Change from baseline in FPG after 26 weeks of treatment (analysed at central laboratory)

- Change from baseline in FPG after 26 weeks of treatment was analysed using an ANOVA method similar to that used for the primary analysis.

2. Responder without hypoglycaemic episodes (HbA_{1c} <7.0% at end of trial and no 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)
   - Responder without hypoglycaemic episodes is a dichotomous endpoint (responder/non-responder) that is defined based on whether a subject has met the American Diabetes Association (ADA) HbA_{1c} target at end of trial (HbA_{1c} <7% at end of trial) without 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.
3. Number of treatment emergent nocturnal confirmed hypoglycaemic episodes
   - The number of treatment emergent confirmed nocturnal (00:01-05:59 a.m.) hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in 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.

Supportive Secondary Efficacy Analyses

- The HbA_{1c} responder endpoints were analysed separately based on a logistic regression model using same factors and covariates as 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 26 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 26 weeks of treatment was analysed using an ANOVA method similar to that used for the primary 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 will assume 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.
- The change in patient reported outcome score from baseline was analysed separately using an ANOVA method similar to that used for the primary analysis.

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 most recent version (version 13.0) of the Medical Dictionary for Regulatory Activities (MedDRA) 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 BG 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 26 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 with only marginal differences 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. At total of 91% of subjects in the IDegAsp group and 89% 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.

	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
HbA1c (%)			
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

From the results of this 26-week trial of treatment with IDegAsp + IAsp at remaining meals or IDet + IAsp, the following can be concluded:

Primary Endpoint (HbA_{1c})

- **HbA_{1c}**: IDegAsp effectively improved glycaemic control, and non-inferiority to IDet in terms of lowering HbA_{1c} was confirmed; estimated mean treatment difference (IDegAsp–IDet) -0.05% point [-0.18; 0.08] $_{95\%CI}$. The

estimated mean change in HbA_{1c} was -0.75% points with IDegAsp and -0.70% points with IDet. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.6 (0.9)% with IDegAsp and 7.6 (0.8)% with IDet.

Secondary Endpoints:

Confirmatory Endpoints

- **FPG:** FPG decreased during the trial to similar mean (SD) levels; 8.7 (4.0) mmol/L with IDegAsp and 8.6 (3.8) mmol/L with IDet. The estimated mean change in FPG was -1.65 mmol/L with IDegAsp and -1.88 mmol/L with IDet and the estimated mean treatment difference (IDegAsp–IDet) was 0.23 mmol/L $[-0.46; 0.91]_{95\%CI}$. Superiority could not be confirmed and consequently, the hierarchical testing procedure was stopped. Therefore, superiority could not be confirmed for the remaining confirmatory secondary efficacy and safety endpoints.
- **Responders without severe hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without severe hypoglycaemic episodes was 24.3% with IDegAsp and 20.7% with IDet. The estimated odds of achieving this target were numerically higher (24%) with IDegAsp compared to IDet; odds ratio (IDegAsp/IDet) 1.24 $[0.77; 2.02]_{95\% CI}$).
- **Nocturnal confirmed hypoglycaemia**: see conclusion in Safety Results and Conclusions section below.

Supportive Efficacy Endpoints

- **Responders for HbA_{1c}:** A total of 24.6% of subjects treated with IDegAsp achieved HbA_{1c} <7% compared to the observed proportion of 20.3% for subjects treated with IDet. The odds of achieving this target were numerically higher (35%) with IDegAsp compared to IDet (estimated odds ratio (IDegAsp/IDet) 1.35 $[0.85; 2.14]_{95\% CI}$).
- **Responders for HbA_{1c} without confirmed hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemia was 4.5% with IDegAsp and 3.0% with IDet. The odds of achieving this target were numerically higher (53%) with IDegAsp compared to IDet (estimated odds ratio (IDegAsp/IDet) 1.53 $[0.54; 4.38]_{95\% CI}$).
- **9-point SMPG profiles:** Fluctuation (mmol/L) in the 9-point profile was lower with IDegAsp than with IDet, with an estimated treatment ratio (IDegAsp/IDet) of 0.84 $[0.75; 0.94]_{95\% CI}$. The change in nocturnal PG was greater with IDegAsp than with IDet from bedtime to breakfast and from 04:00 a m. to breakfast; the estimated mean treatment difference (IDegAsp-IDet) was -1.01 mmol/L $[-1.82; -0.19]_{95\% CI}$, and -0.87 mmol/L $[-1.56; -0.17]_{95\% CI}$, respectively.
- **SMPG for dosing:** The estimated treatment ratio for within-subject variation (%CV) (IDegAsp/IDet) was 0.91 $[0.83; 1.00]_{95\% CI}$, meaning that no statistically significant treatment difference was detected.
- **PRO:** The results related to PRO appeared similar between the two treatment groups, with only marginal changes over time. Work productivity score was higher with IDegAsp than with IDet, based on the DPM questionnaire: estimated treatment difference was 2.9 points $[0.5 ; 5.2]_{95\%CI}$.

Safety Results and Conclusions

From the results of this 26-week trial of treatment with IDegAsp + IAsp at remaining meals or IDet + IAsp, the following can be concluded:

Secondary Endpoints

Confirmatory Safety Endpoint

- **Hypoglycaemic episodes:**
  - The observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was 371 episodes for IDegAsp and 572 episodes for IDet. The rate of nocturnal confirmed hypoglycaemia was 37% lower with IDegAsp than with IDet; estimated rate ratio (IDegAsp/IDet) was 0.63, $[0.49; 0.81]_{95\% CI}$ The hierarchical testing was stopped prior to testing this endpoint for superiority.

Supportive Safety Endpoints

- **Hypoglycaemic episodes:** The observed rate of confirmed hypoglycaemic episodes, per 100 PYE was 3917 for IDegAsp and 4434 for IDet. The observed rates of severe and nocturnal severe hypoglycaemia per 100 PYE were 33 and 6 for IDegAsp and 42 and 17 for IDet, respectively. The estimated rate ratios (IDegAsp/IDet) for confirmed hypoglycaemia and severe hypoglycaemia were 0.91 $[0.76; 1.09]_{95\% CI}$ and 1.19 $[0.58; 2.41]_{95\% CI}$, respectively.
- **Body weight:** IDegAsp was associated with more weight gain than IDet after 26 weeks of treatment as the lower limit of the 95% CI for the estimated treatment difference was > 0, 1.04 kg $[0.38; 1.69]_{95\% CI}$. The mean (SD) body

weight at baseline and at the end of the trial was 76.5 kg (14.4) and 78.9 kg (15.6) in the IDegAsp group and 76.1 kg (13.9) and 77.5 kg (14.4) in the IDet group, respectively.

- **Adverse events:** A similar percentage of subjects reported adverse events in the IDegAsp (66%) and IDet (63%) groups. The rates of all adverse events was numerically similar for the IDegAsp and IDet groups (500 vs. 520 events per 100 PYE) as were the rates of severe adverse events (37 vs. 45 events per 100 PYE). The rate of adverse events possibly or probably related to IDegAsp or IDet was numerically lower with IDegAsp than with IDet (50 vs. 81 events per 100 PYE). The most frequent adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infection, hypoglycaemia and headache. The percentage of subjects with injection site disorders was low in both treatment groups: IDegAsp: 1.4% (7 events); IDet: 4.4% (36 events).
- **Deaths, serious adverse events and other significant adverse events:** No deaths were reported in this trial. A total of 31 (8.6%) and 13 (7.2%) subjects reported serious adverse events in the IDegAsp and IDet group, respectively. The rate of serious adverse events per 100 PYE was low in both treatment groups (IDegAsp: 27, IDet: 20) with hypoglycaemia as the most frequent serious adverse events in both groups. A similar percentage of subjects withdrew from the trial due to AEs in the IDegAsp (1.4%) and the IDet (1.7%) group.
- **Insulin antibodies:** The mean level of insulin antibodies cross-reacting between insulin degludec (respective comparator) and human insulin was low at baseline and remained low with IDegAsp and increased only slightly with IDet after 26 weeks of treatment. Scatter plots did not indicate any correlation between antibody levels and HbA_{1c} or total insulin dose.
- **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 dose**: The mean daily total (basal and bolus) insulin dose after 26 weeks was numerically lower in the IDegAsp group compared with the IDet group: 69 U (0.86 U/kg) for IDegAsp and 79 U (1.00 U/kg) for IDet. The mean derived total daily basal insulin dose after 26 weeks was numerically lower in the IDegAsp group compared with the IDet group: 29 U (0.37 U/kg) for IDegAsp and 36 U (0.46 U/kg) for IDet. The mean derived total daily bolus insulin dose was lower in the IDegAsp group than in the IDet group: 39 U (0.49 U/kg) for IDegAsp and 43 U (0.54 U/kg) for IDet. The ratio of IDegAsp/IDet mean daily insulin dose (U) after 26 weeks was 0.87 for total insulin, 0.81 for derived total basal insulin and 0.92 for derived total bolus insulin, meaning that mean doses were lower in the IDegAsp group compared with the IDet group.

Conclusions

This confirmatory, randomised, controlled, 26-week study investigated the efficacy and safety of treatment with IDegAsp taken once daily at any meal, together with IAsp taken 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:

- IDegAsp effectively improves long-term glycaemic control as measured by HbA_{1c} (non-inferiority to IDet confirmed).
- FPG decreases to a similar level in both treatment groups. Plasma glucose is more stable during the day with IDegAsp compared to IDet as measured by less fluctuation in self-measured plasma glucose.
- For subjects achieving the treatment target ($HbA_{1c} < 7\%$) without severe hypoglycaemia, superiority of IDegAsp compared to IDet can not be confirmed.
- Subjects treated with IDegAsp experience a lower rate of nocturnal confirmed hypoglycaemic episodes compared to subjects treated with IDet.
- The average total daily insulin dose is numerically lower in subjects treated with IDegAsp compared to those treated with IDet.
- In this trial, no safety issues are identified with IDegAsp; there is no apparent difference between IDegAsp and IDet with respect to AEs and standard safety parameters. Body weight increases slightly more in the IDegAsp treatment group compared to the IDet group. Antibody development is sparse and only a few injection site reactions are reported with IDegAsp.

In conclusion, these findings confirm the efficacy and safety of once-daily treatment with IDegAsp taken at any meal in combination with IAsp for the remaining meals in subjects with type 1 diabetes mellitus.

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 22-Jun-2010.