2 Synopsis

Trial Registration ID-number NCT01045447	**IND Number –** IND 73,198 **EudraCT number –** 2008-005767-34
Title of Trial A trial comparing efficacy and safety of NN5401[1] with insulin glargine, both in combination with oral antidiabetic drugs in subjects with type 2 diabetes (BOOST™: INTENSIFY BASAL)	
Investigators There were 61 principal investigators. [redacted], MD, [redacted], was appointed the signatory investigator: [redacted]	
Trial Sites The trial was conducted at 61 sites in 9 countries: Croatia (2 sites), France (4), India (8), Poland (4), South Africa (3), Republic of Korea (6), Sweden (5), Turkey (5) and United States (U.S.) (24). These sites enrolled subjects.	
Publications The results from this trial have not been published at the time of finalisation of this report.	
Trial Period 11 January 2010 to 25 October 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

To confirm the efficacy of insulin degludec/insulin aspart (IDegAsp) once daily (OD) + metformin ± pioglitazone ± dipeptidyl peptidase-4 (DPP-4) inhibitors in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA_{1c}) after 26 weeks of treatment. This is done by comparing the difference in change from baseline in HbA_{1c} between IDegAsp OD + metformin ± pioglitazone ± DPP-4 inhibitors and insulin glargine (IGlar) OD + metformin ± pioglitazone ± DPP-4 inhibitors to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.

Secondary Objectives:

To confirm superiority of IDegAsp OD + metformin ± pioglitazone ± DPP-4 inhibitors over IGlar + metformin ± pioglitazone ± DPP-4 inhibitors after 26 weeks of treatment in terms of:

- Prandial plasma glucose (PG) increment
- Frequency of responders for HbA_{1c} (< 7%) without hypoglycaemic episodes
- Fluctuation in nocturnal interstitial glucose (IG)[a]
- Nocturnal hypoglycaemic episodes
- Body weight

[a] Interstitial Glucose is glucose extracted from interstitial fluid.

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

- Fasting plasma glucose (FPG) from central laboratory
- 9-point self-measured plasma glucose (SMPG) profile
- SMPG for dose adjustments
- Frequency of responders for HbA_{1c}
- Glucose profile as measured with continuous glucose monitoring (CGM) in a sub-population
- Insulin dose
- Adverse events (AEs)

[1] NN5401 is synonymous with insulin degludec/insulin aspart (IDegAsp) and was previously referred to as soluble insulin analogue combination.

- Hypoglycaemic episodes
- Clinical and laboratory assessments
- Patient reported outcome (PRO)

Methodology

This was a 26-week, randomised, open-label, two-armed, parallel-group, treat-to-target (T-T-T) trial comparing efficacy and safety of IDegAsp OD with IGlar OD, both in combination with metformin ± pioglitazone ± DPP-4 inhibitor in subjects with type 2 diabetes who were inadequately controlled with basal insulin OD + oral antidiabetic drugs (OADs). There was a 1-week follow-up period after the 26 weeks' treatment period for safety follow-up.

Randomisation was carried out in a 1:1 manner to either IDegAsp OD + OADs or IGlar OD + OADs. Randomisation was stratified with respect to previous prioglitazone use. IDegAsp was to be administered with the main evening meal or largest meal and IGlar was to be administered according to labelling. OADs other than metformin, pioglitazone and DPP-4 inhibitor were to be discontinued at the randomisation visit.

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

At selected trial sites, a subpopulation of subjects underwent an assessment of their 24-h IG levels with a CGM device. The assessment was mandatory for all subjects at these trial sites until the required number of subjects was met globally. The assessment was included in the Subject Information/Informed Consent Form.

Number of Subjects Planned and Analysed

Based on the sample size calculation, the planned number of subjects to be screened was 643, to be randomised was 450 and to complete the trial was 382. The actual number of subjects included in the trial is shown below:

	IDegAsp OD N (%)	IGlar OD N (%)	Total N (%)
Screened			717
Screening Failures			252
Withdrawn before Randomisation			0
Randomised	232 (100.0)	233 (100.0)	465 (100.0)
Exposed	230 (99.1)	233 (100.0)	463 (99.6)
Withdrawn at/after Randomisation	36 (15.5)	28 (12.0)	64 (13.8)
Adverse Event	0 (0.0)	1 (0.4)	1 (0.2)
Ineffective Therapy	3 (1.3)	1 (0.4)	4 (0.9)
Non-Compliance With Protocol	6 (2.6)	3 (1.3)	9 (1.9)
Withdrawal Criteria	10 (4.3)	10 (4.3)	20 (4.3)
Other	17 (7.3)	13 (5.6)	30 (6.5)
Completed	196 (84.5)	205 (88.0)	401 (86.2)
Full Analysis Set	230 (99.1)	233 (100.0)	463 (99.6)
PP Analysis Set	211 (90.9)	211 (90.6)	422 (90.8)
Safety Analysis Set	230 (99.1)	233 (100.0)	463 (99.6)

N: Number of subjects; %: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Male or female subjects ≥ 18 years of age, with type 2 diabetes mellitus (diagnosed clinically) for ≥ 6 months, HbA_{1c} 7.0-10.0% (both inclusive) by central laboratory analysis, body mass index (BMI) ≤ 40.0 kg/m^2, treatment with basal

insulin regimen (insulin detemir, IGlar or Neutral Protamine Hagedorn [NPH] insulin) OD for at least 3 months prior to randomisation and ongoing treatment with metformin with or without other OADs for at least 3 months prior to randomisation were included in the trial.

Subjects treated with insulin regimens other than a basal insulin regimen OD (insulin detemir, IGlar or Neutral Protamine Hagedorn [NPH] insulin) within 3 months prior to Visit 1, total daily insulin dose above 1 U/kg, treatment with glucagon-like peptide 1(GLP-1) receptor agonists within 3 months prior to Visit 1, current rosiglitazone users, anticipated significant lifestyle changes during the trial and cardiovascular disease within the last 6 months (defined as stroke, decompensated heart failure New York Heart Association (NYHA) class III or IV, myocardial infarction, unstable angina pectoris, or coronary arterial bypass graft or angioplasty) were excluded from the trial. Subjects in Croatia treated with rosiglitazone, pioglitazone or GLP-1 receptor agonists within 3 months prior to Visit 1 were excluded.

Test Product, Dose and Mode of Administration, Batch Number

IDegAsp was administered with dinner (evening meal) or the largest meal; subjects continued administering IDegAsp with the same meal throughout the trial. Insulin products used were to be injected subcutaneously (s.c.) in either the abdomen, upper arm (deltoid area) or thigh and the injection sites were rotated within the injection areas.

IDegAsp 100 U/mL, 3 mL FlexPen®. Batch number: For all countries XP51553.

Duration of Treatment

Total trial duration for the individual subject was approximately 28 weeks (1 week screening, 26 weeks treatment and 1 week follow-up).

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, 3 mL SoloStar™ pen. Batch numbers: 40C630 in Croatia, India, Turkey, Republic of Korea, South Africa, 40C659 in Poland, Sweden, France and 40C368 in the United States.

IGlar was administered according to approved labelling. IGlar was to be injected s.c. in either the abdomen, upper arm (deltoid area) or thigh and the injection sites were to be rotated within the injection areas.

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - 1-point SMPG
  - 9-point SMPG profile with additional 1-point SMPG
- PRO questionnaires
  - Hypoglycaemic questionnaire
- CGM

Criteria for Evaluation – Safety

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

Statistical Methods

Analysis Sets

The following analysis sets were defined:

- Full Analysis Set (FAS): including all randomised subjects. The statistical evaluation of the FAS follows the intention-to-treat (ITT) principle and subjects contribute to the evaluation "as randomised".
- Per Protocol (PP) Analysis Set: including subjects without any major protocol violations that may affect the primary endpoint. Moreover, subjects must be exposed to the investigational product or its comparator for more than 12 weeks and must have a valid assessment necessary for deriving the primary endpoint. Subjects in the PP set contribute to the evaluation "as treated".
- Safety Analysis Set: including all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set contribute to the evaluation "as treated".

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. 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%.

Secondary Confirmatory 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. The consequence of this fixed testing procedure is that superiority can only be confirmed for endpoints where all previous hypotheses have been confirmed. The order of the endpoints defines the testing sequence:

1. Prandial PG increment at main evening meal after 26 weeks of treatment
   - Prandial plasma glucose increment at main evening meal was derived from the 9-point SMPG profile as the difference between PG values available 90 minutes after the meal and immediately before the same meal and was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.
2. Responder without hypoglycaemic episodes (HbA_{1c} <7.0% at end of trial and no confirmed hypoglycaemic episodes during the last 12 weeks of 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 confirmed 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. Fluctuation in nocturnal (00:01-05:59 h) interstitial glucose (IG) after 26 weeks of treatment
   - Logarithmically transformed fluctuation values were analysed using an ANOVA method similar to that used for the analysis of the primary endpoint
4. Number of treatment emergent nocturnal confirmed hypoglycaemic episodes
   - The number of treatment emergent confirmed nocturnal (00:01-05:59 h) 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.
5. Change from baseline in body weight after 26 weeks of treatment
   - Change from baseline in body weight after 26 weeks of treatment was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.

Secondary Supportive Efficacy Analyses

- The HbA_{1c} responder endpoints (HbA_{1c} < 7% or ≤6.5% at end of trial) were analysed separately based on a logistic regression model using same factors and covariates as for the primary analysis.

- Change from baseline in FPG after 26 weeks of treatment was analysed using an ANOVA method similar to the analysis for the primary endpoint.
- 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 analysis of the primary endpoint.
- 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 analysis of the primary endpoint.
  - 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 was calculated from the corresponding residual variance.
- The following endpoints were derived based on continuous glucose measurements: Mean and variation in IG profile, night time characteristics of IG profile, meal characteristics of IG profile as well as number of episodes of low and high IG and the total time spent at low and high IG. Low IG was defined as an IG below 2.5, 3.0, 3.5, and 4.0 (mmol/L). High IG was defined as an IG above 8.0, 9.0 and 12.0 (mmol/L). All endpoints except for the time to the IG meal-peak and the number of episodes of low and high IG were analysed using an ANOVA method similar to that used for the analysis of the primary endpoint. The time to the IG meal-peak was summarised descriptively. The number of episodes of low and high IG were analysed separately for the different targets using a negative binomial regression model with a log-link function and the logarithm to exposure time (year) as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate.
- The change in patient reported outcome score from baseline was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.

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 h (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 (56 mg/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.

- Change from baseline in lipid endpoints was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.
- Remaining laboratory parameters, physical examination, ECG, funduscopy / fundusphotography, vital signs and insulin dose were evaluated based on descriptive statistics.

Hypoglycaemic episodes were categorised according to the ADA classification. In addition, based on the experience of Novo Nordisk with other diabetes development programmes, "minor episodes" with a PG < 3.1 mmol/L (56 mg/dL) were recorded. The pool of severe and minor hypoglycaemic episodes was referred to as confirmed hypoglycaemic episodes.

Demography of Trial Population

The demographics and baseline characteristics in the two treatment groups were similar, with the exception of a slightly larger proportion of subjects from the U.S. in the IGlar group (34.8%) than in the IDegAsp group (27.0%) and a slightly larger proportion of Asian-Indian subjects in the IDegAsp group (28.7%) compared to the IGlar group (22.3%). One-quarter (25.5%) of all subjects were elderly (> 65 years of age) (23.9% elderly subjects in the IDegAsp group and 27.0% elderly subjects in the IGlar group). More than half (56.6%) of all subjects were men (58.7% men in the IDegAsp group and 54.5% men in the IGlar group). The majority of subjects were White (56%). The majority of subjects were of Non-Latino/Hispanic ethnicity (96%). The demographics and baseline characteristics of all randomised subjects are summarised in the table below. The pretrial insulin + OAD regimens were equally represented in the treatment groups. A total of 41.0% of all subjects used basal insulin plus metformin at the time of screening, 46.9% used basal insulin plus metformin plus other OADs (excluding pioglitazone) and 12.1% used basal insulin plus metformin plus pioglitazone.

	IDegAsp OD	IGlar OD	Total
Number of Subjects	230	233	463
Age (years)			
N	230	233	463
Mean (SD)	57.8 (9.5)	58.4 (10.1)	58.1 (9.8)
Median	58.2	58.6	58.2
Min ; Max	30.7 ; 79.8	27.9 ; 84.3	27.9 ; 84.3
Body Weight (kg)			
N	230	233	463
Mean (SD)	84.7 (19.9)	83.9 (19.2)	84.3 (19.6)
Median	83.0	82.5	83.0
Min ; Max	44.0 ; 137.5	46.1 ; 149.5	44.0 ; 149.5
BMI (kg/m^2)			
N	230	233	463
Mean (SD)	30.1 (5.1)	30.1 (5.3)	30.1 (5.2)
Median	29.7	29.7	29.7
Min ; Max	16.4 ; 40.1	20.2 ; 47.7[a]	16.4 ; 47.7
Duration of Diabetes (years)			
N	230	233	463
Mean (SD)	11.6 (6.8)	11.4 (7.3)	11.5 (7.0)
Median	10.7	10.7	10.7
Min ; Max	0.6 ; 38.5	0.6 ; 55.6	0.6 ; 55.6
HbA_{1c} (%)			
N	230	233	463
Mean (SD)	8.3 (0.8)	8.4 (1.0)	8.3 (0.9)
Median	8.2	8.3	8.3
Min ; Max	6.5 ; 10.5	6.6 ; 11.7[b]	6.5 ; 11.7
FPG (mmol/L)			
N	228	231	459
Mean (SD)	8.0 (2.5)	7.8 (2.8)	7.9 (2.7)
Median	7.5	7.2	7.3
Min ; Max	3.2 ; 14.8	3.3 ; 23.1	3.2 ; 23.1

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG = Fasting Plasma Glucose

The subjects were randomised based on measurements performed at the screening visit (Visit 1). Baseline values were recorded approximately 1 week later at the randomisation visit (Visit 2). The maximum values for HbA_{1c} and BMI in the demographics table are above the limits allowed in the inclusion criteria due to the fact that the body weight or HbA_{1c} of some subjects had increased from Visit 1 to Visit 2. [a]One subject (805004) who had been randomised despite failing to meet the inclusion criterion (BMI ≥40 kg/m^2) was subsequently withdrawn from the trial. [b]One subject (409013) had an HbA_{1c} level of 9.6% at Visit 1 and 11.7% at Visit 2 and therefore met the selection criterion based on the HbA_{1c} evaluated at Visit 1.

Efficacy Results and Conclusions

After 26 weeks of treatment with IDegAsp OD + metformin ± pioglitazone ± DPP-4 inhibitor or IGlar OD + metformin ± pioglitazone ± DPP-4 inhibitor, the following was concluded:

Primary Endpoint

HbA_{1c}: IDegAsp effectively improved glycaemic control, and non-inferiority to IGlar in terms of lowering HbA_{1c} was confirmed; estimated treatment difference (IDegAsp−IGlar): −0.03% points $[-0.20;0.14]_{95\%CI}$. The estimated mean change in HbA_{1c} was −1.00% points with IDegAsp and −0.97% points with IGlar. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.3 (1.1)% with IDegAsp and 7.4 (1.0)% with IGlar.

Secondary Efficacy Endpoints

Confirmatory Endpoints

- **Prandial increment in SMPG:** Superiority of IDegAsp to IGlar was confirmed in terms of a smaller increment in prandial glucose at the main evening meal; estimated treatment difference (IDegAsp−IGlar): −1.32 mmol/L $[-1.93;-0.72]_{95\%CI}$. After 26 weeks of treatment, the observed mean (SD) prandial glucose increment at the main evening meal was 1.2 (3.7) mmol/L with IDegAsp and 2.6 (2.9) mmol/L with IGlar.
- **Responders without confirmed hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemic episodes was 20.9% with IDegAsp and 23.5% with IGlar. The odds of achieving this target were numerically lower with IDegAsp compared to IGlar; estimated odds ratio (IDegAsp/IGlar): 0.80 $[0.50;1.30]_{95\%CI}$. Superiority of IDegAsp compared to IGlar could not be confirmed as the lower limit of the 95% CI was ≤1. Consequently, the hierarchical testing procedure was stopped. Therefore, superiority could not be confirmed for the remaining confirmatory secondary efficacy and safety endpoints
- **Fluctuation in nocturnal IG:** The observed geometric mean fluctuation (CV of mean) in nocturnal glucose around the mean, as measured by CGM, was 0.7 (77.78) mmol/L in the IDegAsp group and 0.7 (75.71) mmol/L in the IGlar group. The estimated treatment ratio (IDegAsp/IGlar) was 0.97 $[0.74;1.28]_{95\%CI}$. Superiority could not be confirmed as the upper limit of the 95% CI for the treatment ratio was ≥1 and the hierarchical testing procedure was stopped before this endpoint.
- **Nocturnal confirmed hypoglycaemia**: See the Safety Conclusions.
- **Body weight:** See the Safety Conclusions.

Supportive Efficacy Endpoints

- **Responders for HbA_{1c} <7% and ≤6.5%:** An observed proportion of 40.0% and 23.5% subjects treated with IDegAsp achieved HbA_{1c} <7% and ≤6.5%, compared with 36.5% and 18.5% of subjects treated with IGlar, respectively. These analyses were based on the full analysis set. The estimated odds of achieving the target of <7% were numerically higher with IDegAsp compared to IGlar (odds ratio (IDegAsp/IGlar): 1.18 $[0.78;1.78]_{95\%CI}$). The estimated odds of achieving the target of ≤6.5% were numerically higher with IDegAsp compared to IGlar (odds ratio (IDegAsp/IGlar): 1.38 $[0.86;2.24]_{95\%CI}$).
- **Responder for HbA_{1c} ≤6.5% without confirmed hypoglycaemia:**An observed proportion of 12.3% of subjects treated with IDegAsp achieved HbA_{1c} ≤6.5% without confirmed hypoglycaemic episodes during the last 12 weeks, compared with 11.7% of subjects treated with IGlar. The odds of achieving the target of HbA_{1c} ≤6.5% without confirmed hypoglycaemia were not statistically significantly different between treatment groups (odds ratio (IDegAsp/IGlar) 1.00 $[0.54;1.82]_{95\%CI}$). These analyses were based on a subset of subjects who had been exposed to trial products for at least 12 weeks.

- **Responder for HbA_{1c} <7% and ≤6.5% without severe hypoglycaemia:** An observed proportion of 43.1% and 25.6% of subjects treated with IDegAsp achieved HbA_{1c} <7% and ≤6.5% without severe hypoglycaemic episodes during the last 12 weeks, compared with 38.5% and 19.2% of subjects treated with IGlar, respectively. The estimated odds of achieving the target of <7% without severe hypoglycemia were numerically higher with IDegAsp compared to IGlar (odds ratio (IDegAsp/IGlar): 1.22 $[0.80;1.87]_{95\%CI}$). The estimated odds of achieving the target of ≤6.5% were numerically higher with IDegAsp compared to IGlar (odds ratio (IDegAsp/IGlar): 1.47 $[0.90;2.41]_{95\%CI}$). These analyses were based on a subset of subjects who had been exposed to trial products for at least 12 weeks.
- **FPG:** Mean FPG (SD) values decreased by 1.7 (3.0) mmol/L with IDegAsp and 1.9 (3.0) mmol/L with IGlar to similar observed mean FPG values of 6.3 (2.5) mmol/L with IDegAsp and 6.0 (2.5) mmol/L with IGlar; estimated treatment difference (IDegAsp−IGlar): 0.33 mmol/L $[-0.11;0.77]_{95\%CI}$.
- **9-point SMPG Profiles:** The mean prandial increment across all meals was lower with IDegAsp after 26 weeks; estimated treatment difference (IDegAsp−IGlar): −0.65 mmol/L $[-1.00;-0.30]_{95\%CI}$. The observed geometric mean fluctuation (CV of mean) in 9-point profile was 1.4 (53.31) mmol/L with IDegAsp and 1.5 (49.24) mmol/L with IGlar. There was no statistically significant difference in the fluctuation in profiles between treatment groups; estimated treatment ratio (IDegAsp/IGlar) 0.98 $[0.89;1.08]_{95\%CI}$. The observed reduction in nocturnal PG (bedtime to breakfast) was smaller with IDegAsp (2.6 mmol/L) than with IGlar (4.2 mmol/L) after 26 weeks of treatment; estimated difference: 1.66 mmol/L $[1.06;2.27]_{95\%\ CI}$.
- **SMPG for dosing:** A total of 23.0% in the IDegAsp group and 36.1% in the IGlar group achieved the prebreakfast SMPG target of <5 mmol/L. Subjects who had not achieved the titration target at a given visit had a lower chance of achieving the target at the next visit when treated with IDegAsp compared to subjects in the IGlar group; estimated hazard ratio (IDegAsp/IGlar): 0.67 $[0.54;0.83]_{95\%CI}$.
- **CGM-related endpoints**: At baseline, the mean (SD) value of the IG profile was 9.4 (2.4) mmol/L with IDegAsp and 10.1 (2.0) mmol/L with IGlar. The mean (SD) IG decreased slightly during the trial to 8.2 (2.1) mmol/L in the IDegAsp group and 8.2 (2.0) mmol/L in the IGlar group, with no statistically significant difference in mean IG profiles between treatment groups. The variation in IG profiles was assessed by fluctuation and CV%. The mean fluctuation and mean CV% were 1.8 mmol/L and 29.4% with IDegAsp and 1.9 mmol/L and 29.3% with IGlar, respectively. Statistical analysis did not identify a difference in mean fluctuations and mean CV% between the treatments. The mean (SD) nocturnal IG concentration was 7.4 (3.4) mmol/L with IDegAsp and 7.3 (2.7) mmol/L with IGlar. There was a smaller observed decline in IG during the night with IDegAsp compared to IGlar; this was indicated by the less steep slope for the IDegAsp group. Statistical analysis did not detect any statistically significant differences in nocturnal IG profiles between the treatments; estimated treatment difference (IDegAsp−IGlar): 0.30 mmol/L $[-0.71;1.30]_{95\%CI}$.
- **PRO:** The results related to PRO appeared similar between the treatment groups with only marginal changes over time. Statistical analysis showed a treatment difference in the change from baseline in the 'Burden' category of the DiabMedSat Questionnaire, the 'bodily pain' score of the SF-36 v2 Questionnaire and the 'social functioning score' of the SF-36 v2 Questionnaire; estimated treatment difference (IDegAsp−IGlar): −2.5 $[-4.9;-0.1]_{95\%CI}$, −1.7 $[-3.4;-0.1]_{95\%CI}$) and −1.9 $[-3.5;-0.4]_{95\%CI}$, respectively.

Safety Results and Conclusions

From the results of this 26-week trial of treatment with IDegAsp OD + metformin ± pioglitazone ± DPP-4 inhibitor or IGlar OD + metformin ± pioglitazone ± DPP-4 inhibitor, the following can be concluded:

Secondary Endpoints

Confirmatory Safety Endpoints

- **Nocturnal Confirmed Hypoglycaemic Episodes:** The observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was 82 episodes for IDegAsp and 101 episodes for IGlar. The estimated rate ratio (IDegAsp/IGlar) was 0.80 $[0.49;1.30]_{95\%CI.}$ This difference was not statistically significant and superiority of IDegAsp over IGlar could not be confirmed as the upper limit of the 95% CI for the estimated rate ratio (IDegAsp/IGlar) was ≥1 and the hierarchical testing procedure was stopped before this endpoint.
- **Body Weight:** Body weight increased during the trial to mean (SD) values of 85.9 (20.6) kg with IDegAsp and 84.9 (19.7) kg with IGlar. The estimated mean change was 1.74 kg with IDegAsp and 1.41 kg with IGlar. The

estimated treatment diffference (IDegAsp−IGlar) was 0.33 kg $[-0.17;0.83]_{95\%CI}$. Superiority could not be confirmed as the upper limit of the 95% CI for the treatment difference (IDegAsp−IGlar) was ≥ 0 and the hierarchical testing procedure was stopped before this endpoint.

Supportive Safety Endpoints

- **Hypoglycaemic episodes:** The rate of confirmed hypoglycaemia was higher with IDegAsp than with IGlar, whereas the rate of nocturnal hypoglycaemia was numerically lower with IDegAsp than with IGlar. The observed rate of confirmed hypoglycaemic episodes per 100 PYE was 431 for IDegAsp and 320 for IGlar. The estimated rate ratio for confirmed hypoglycaemia (IDegAsp/IGlar) was 1.43 per 100 PYE $[1.07;1.92]_{95\%CI}$. The main period of increased frequency of confirmed hypoglycaemic episodes occured between 20:00 and 24:00 h in the IDegAsp group, compared with 04:00 to 08:00 h in the IGlar group. No episodes of severe hypoglycaemia were reported for IDegAsp. Four (4) episodes of severe hypoglycaemia per 100 PYE were reported in the IGlar group. No episodes of nocturnal severe hypoglycaemia were reported for IDegAsp or IGlar.
- **Adverse events:** The percentage of subjects reporting treatment-emergent AEs was similar in the IDegAsp (57.8%) and IGlar (62.7%) groups. The event rate for AEs was numerically lower in the IDegAsp group (351 events per 100 PYE) than in the IGlar group (431 events per 100 PYE). Few of the AEs in either treatment group were severe, and the rate of severe AEs per 100 PYE was 10 events in the IDegAsp group and 17 events in the IGlar group. The most frequently reported AEs in both groups were headache, nasopharyngitis, diarrhoea, upper respiratory tract infection and peripheral oedema.
- **Deaths, serious adverse events and other significant adverse events:** No deaths were reported in this trial. A total of 10 (4.3%) subjects reported 10 serious adverse events in the IDegAsp group, while 8 (3.4%) subjects reported 9 serious adverse events in the IGlar group. The event rate per 100 PYE of serious adverse events was similar in the IDegAsp (10) and IGlar (8) groups. No SAEs were reported with a frequency of ≥5% or ≥1% in either treatment group. One subject (from the IGlar group) was withdrawn from the trial before completing 12 weeks of treament because of an AE (haemorrhage).
- **Vital signs, ECG, fundoscopy, physical examination and laboratory values:** No clinically relevant differences from baseline to end of treatment or between the treatment groups were observed.
- **Insulin dose:** The mean daily IDegAsp and IGlar dose after 26 weeks was similar in the treatment groups: 60 U (0.69 U/kg) for IDegAsp and 60 U (0.69 U/kg) for IGlar. The ratio of IDegAsp/IGlar mean daily insulin dose (U) after 26 weeks was 1.01.

Conclusions

The results of this confirmatory, randomised, controlled, 26-week trial demonstrate the efficacy and safety of IDegAsp versus IGlar, both administered once daily in combination with metformin ± pioglitazone ± DPP-4 inhibitors in subjects with type 2 diabetes mellitus.

- IDegAsp effectively improves long-term glycaemic control as measured by HbA_{1c} (non-inferior to IGlar) and the data confirm superiority of IDegAsp to IGlar with respect to a smaller prandial glucose increment in relation to the evening meal.
- FPG decreases to a similar level in both treatment groups, while IDegAsp is associated with a smaller mean prandial glucose increment across all meals.
- The fluctuation in nocturnal glucose, as measured by continuous glucose monitoring, is similar with IDegAsp and IGlar; superiority of IDegAsp cannot be confirmed.
- Superiority of IDegAsp compared to IGlar cannot be demonstrated for subjects achieving the treatment target (HbA_{1c} < 7%) without confirmed hypoglycaemia.
- IDegAsp is associated with a higher rate of confirmed hypoglycaemia compared to IGlar. The rate of nocturnal confirmed hypoglycaemia is numerically lower with IDegAsp than with IGlar, but superiority of IDegAsp cannot be confirmed.
- Body weight increases slightly in both treatment groups and superiority of IDegAsp cannot be confirmed.
- In this trial, no safety issues are identified with IDegAsp; IDegAsp and IGlar are similar with respect to AEs and standard safety parameters.

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 12-Nov-2010.