2 Synopsis

Trial Registration ID-number NCT01045707	**IND Number –** US only 73,198 **EudraCT number –** 2009-011271-78
Title of Trial A Trial Comparing Efficacy and Safety of NN5401[1] With Insulin Glargine in Insulin Naïve Subjects With Type 2 Diabetes	
Investigators There were 88 principal investigators in this trial. One principal investigator was appointed for each trial site. [redacted] was appointed as a signatory investigator.	
Trial Sites The trial was conducted at 88 sites in 8 countries: Austria (4 sites), India (7 sites), Republic of Korea (5 sites), Poland (6 sites), Russia (10 sites), Spain (11 sites), Turkey (5 sites), and United States (40 sites).	
Publications Results from this trial have not been published at the time of this report.	
Trial Period 11 January 2010 to 26 October 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

- To confirm the efficacy of insulin degludec/insulin aspart (IDegAsp) once daily (OD) with the morning meal + metformin 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} after 26 weeks of treatment between IDegAsp OD + metformin and insulin glargine (IGlar) OD + metformin 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 over IGlar OD + metformin after 26 weeks of treatment in terms of:

- Prandial plasma glucose (PG) increment at breakfast
- Fluctuation in nocturnal interstitial glucose (IG)[a]
- Frequency of responders for HbA_{1c} (< 7.0%) without hypoglycaemic episodes
- Nocturnal hypoglycaemic episodes
- Body weight

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
- Glucose profile as measured with continuous glucose monitoring (CGM) in a sub-population
- Frequency of responders for HbA_{1c}
- Frequency of responders for HbA_{1c} without hypoglycaemic episodes
- Clinical and laboratory assessments
- Beta (β)-cell function
- Cardiovascular risk markers
- Adverse events (AEs)

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

- Hypoglycaemic episodes
- Insulin dose
- Insulin antibodies
- Patient reported outcome (PRO)

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

Methodology

This was a 26-weeks, multinational, multi-centre, open-labelled, randomised 1:1, treat-to-target (TTT), two-arm parallel group, efficacy/safety trial comparing treatment with IDegAsp OD + metformin with that of IGlar OD + metformin in insulin-naïve subjects diagnosed with type 2 diabetes. There was a 1-week follow up period after the 26 weeks' treatment period for safety follow up.

The trial included a screening visit (Visit 1) to assess eligibility, followed by a 1:1 randomisation (Visit 2) into one of the two treatment arms (IDegAsp OD + metformin or IGlar OD + metformin).

At randomization, the subject's previous oral andiabetic (OAD) diabetes treatment was discontinued except for metformin. Subjects treated with a fixed combination of metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors discontinued their treatment with DPP-4 inhibitors and changed to treatment with metformin at a dose level as close to their previous regimen as possible. In the periods between Visit 3 and Visit 28, the subsequent 25 weeks of treatment, the subject's insulin dose was titrated weekly according to the insulin titration guidelines provided in the protocol. At Week 26, during the follow-up period before measurement of antibodies, the subjects discontinued all trial products and were switched to the intermediate acting NPH insulin.

Total duration of the individual subjects participating in this trial was approximately 28 weeks. The weekly contacts between trial site and subjects were a combination of trial site visits and phone contacts. 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 switch from trial insulin treatment to Neutral Protamine Hagedorn (NPH) insulin between end of treatment visit and follow up visit, was done in order to provide basal insulin coverage while reducing the level of exogenous insulin analogue present at antibody sampling and consequently to reduce the possibility for interference with antibody measurements.

Continuous Glucose Monitoring (CGM) was performed in subjects at selected trial sites at certain visits. These subjects were asked to wear the CGM device for a minimum of 72 hours for every recording: 3-4 days just before randomisation (Visit 2), and 3-4 days before Visit 28.

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.

Number of Subjects Planned and Analysed

Based on the sample size calculation, the planned number of subjects to be screened was 752, to be randomised was 526, and to complete the trial was 446. The actual number of subjects included in the trial is shown below:

	IDegAsp OD N (%)	IGlar OD N (%)	Total N (%)
Screened			813
Screening Failures			283
Withdrawn before Randomisation			0
Randomised	266 (100.0)	264 (100.0)	530 (100.0)
Exposed	265 (99.6)	261 (98.9)	526 (99.2)
Withdrawn at/after Randomisation	47 (17.7)	32 (12.1)	79 (14.9)
Adverse Event	5 (1.9)	3 (1.1)	8 (1.5)
Ineffective Therapy	4 (1.5)	2 (0.8)	6 (1.1)
Non-Compliance With Protocol	6 (2.3)	5 (1.9)	11 (2.1)
Withdrawal Criteria	22 (8.3)	11 (4.2)	33 (6.2)
Other	10 (3.8)	11 (4.2)	21 (4.0)
Completed	219 (82.3)	232 (87.9)	451 (85.1)
Full Analysis Set	266 (100.0)	263 (99.6)	529 (99.8)
PP Analysis Set	229 (86.1)	244 (92.4)	473 (89.2)
Safety Analysis Set	265 (99.6)	261 (98.9)	526 (99.2)

N: Number of subjects
%: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Male or female insulin naïve subjects age ≥ 18 years, with type 2 diabetes mellitus (diagnosed clinically) ≥ 6 months, HbA_{1c} 7.5-11.0% (both inclusive) by central laboratory analysis, body mass index (BMI) ≤40.0 kg/m^2 and ongoing treatment with metformin and at least one other OAD for at least 3 months prior to randomisation were included in the trial.

Subjects with anticipated change in concomitant medication known to interfere with glucose metabolism, use of glucagon-like peptide-1 (GLP-1) receptor agonists and/or thiazolidinediones (TZDs) within the last 3 months prior to Visit 1 and cardiovascular disease within the last 6 months (defined as stroke, decompensate 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.

Test Product, Dose and Mode of Administration, Batch Number

IDegAsp 100 U/mL, 3 mL PDS290 pen (The IDegAsp drug product consists of two drug substances (70 volume% IDeg + 30 volume% IAsp). Subjects randomised to IDegAsp were instructed to initiate treatment with IDegAsp 10 U OD with the breakfast (morning meal). IDegAsp was administered subcutaneously (s.c.) either in the abdomen, upper arm (deltoid area) or thigh and the injection sites were rotated within the injection areas.
Batch No.: XL70021, XL70010, XL70011

Duration of Treatment

The treatment period was 26 weeks. 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™. Subjects randomised to IGlar were instructed to initiate treatment with IGlar 10 U OD according to approved labelling. IGlar was injected s.c. in either the abdomen, upper arm (deltoid area) or thigh and the injection sites were rotated within the injection areas.
Batch No.: 40C442, 40C458, 40C525, 40C610.

NPH insulin (Insulatard®, Protaphane®, Novolin N™) 100 IU/mL, 3 mL FlexPen®
From end of trial insulin treatment to the follow-up visit, the subjects were instructed to switch from trial insulin treatment to the intermediate acting NPH insulin which was administered twice daily, morning and evening. The NPH dose corresponded to total daily basal dose at end of the treatment period reduced by 20% and divided by two. The first dose of NPH insulin was given 24 h after the last dose of IDegAsp or IGlar.
Batch No.: XP5264, XP5117

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - Prebreakfast SMPG
  - 9-point SMPG profile with 1 additional measurement before breakfast (SMPG)
- PRO questionnaires
- CGM
- Beta-cell function
- Body Weight

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 ≤ 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 formally for endpoints where all previous hypotheses have been confirmed. The

order of the endpoints defines the testing sequence:

1. Prandial PG increment at breakfast (90 min. after start of breakfast as measured by SMPG) after 26 weeks of treatment
   - Superiority was considered confirmed if the 95% confidence interval for the treatment difference (investigational product minus comparator) was entirely below zero
2. Fluctuation in nocturnal (00:01-05:59 a.m.) interstitial glucose (IG) as measured by CGM after 26 weeks of treatment
   - Superiority was considered confirmed if the 95% confidence interval for the treatment ratio (investigational product / comparator) was entirely below one
3. Responder without hypoglycaemic episodes (HbA_{1c} <7.0% at the end of trial and no severe or minor episodes during the last 12 weeks of treatment including only subjects exposed for at least 12 weeks)
   - Superiority was considered confirmed if the 95% confidence interval for the odds ratio (investigational product / comparator) was entirely above one
4. Number of treatment emergent nocturnal (00:01-05:59 a m.) severe or minor hypoglycaemic episodes
   - Superiority was considered confirmed if the 95% confidence interval for the relative risk (investigational product / comparator) was entirely below one
5. Change from baseline in body weight after 26 weeks of treatment
   - Superiority was considered confirmed if the 95% confidence interval for the treatment difference (investigational product minus comparator) was entirely below zero

Secondary Supportive Efficacy Analyses

- Change from baseline in FPG after 26 weeks of treatment (analysed at central laboratory) was to be analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline FPG as covariates.
- SMPG Values Used for Dose Adjustment
  - The mean of 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.
- 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.
- 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.
- 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.
- Beta (β)-cell Function
  - Change in β-cell-function as measured by 1) HOMA score and 2) pro-insulin from baseline to end of trial was to be analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline value as covariates.

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 13.1) 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 (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 hsCRP, NT-proBNP and lipid endpoints was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.
- Antibodies specific for: IDeg, IAsp and IGlar as well as antibodies cross-reacting to human insulin were measured and their correlation to 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 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) was recorded. The pool of severe and minor hypoglycaemic episodes was referred to as confirmed hypoglycaemic episodes.

Demography of Trial Population

The population consisted of male and female subjects with type 2 diabetes mellitus, with a mean age of 56.9 years and a mean duration of diabetes of 9.2 years (ranging from 0.6 to 39.6 years), with a mean HbA1c of 8.9%, a mean BMI of 30.7 kg/m2, and slightly larger proportion of elderly subjects (> 65 years old) in the IDegAsp group (20.7%) than in the IGlar group (16.3%). There were more men than women in the IGlar group (51.7% men) than in the IDegAsp group (47.0% men). The majority of the subjects reported their ethnicity as non-Hispanic/Latino (68.4%). The trial subjects were White (72.4%) or Asian Indian (14%). The demographics and baseline characteristics of all randomised subjects are summarised in the table below. At screening, the subjects in both treatment groups were insulin-naïve and were treated on OADs only, with the largest proportion of subjects using two OADs. Metformin

+ SU or glinides were the two most commonly used anti-diabetic treatment regimens (about 86% of subjects). Few subjects (14%) were treated with DPP-inhibitors and alpha glucosidase inhibitors. The different pretrial regimens were equally represented in the treatment groups.

	IDegAsp OD	**IGlar OD**	**Total**
Number of Subjects	266	263	529
Age (years)			
N	266	263	529
Mean (SD)	57.4 (9.0)	56.4 (9.2)	56.9 (9.1)
Median	57.3	57.3	57.3
Min ; Max	36.8 ; 78.4	21.8 ; 76.1	21.8 ; 78.4
Body Weight (kg)			
N	266	263	529
Mean (SD)	85.0 (17.9)	85.1 (18.6)	85.0 (18.2)
Median	82.8	84.4	84.0
Min ; Max	50.0 ; 144.2	42.4 ; 139.0	42.4 ; 144.2
BMI (kg/m^2)			
N	266	263	529
Mean (SD)	30.9 (5.1)	30.5 (5.1)	30.7 (5.1)
Median	31.0	30.5	30.7
Min ; Max	20.0 ; 43.8[a]	18.1 ; 40.0	18.1 ; 43.8[a]
Duration of Diabetes (years)			
N	265	263	528
Mean (SD)	8.7 (6.1)	9.6 (6.1)	9.2 (6.1)
Median	7.5	8.8	7.7
Min ; Max	0.6 ; 39.6	0.6 ; 34.7	0.6 ; 39.6
HbA_{1c} (%)			
N	266	263	529
Mean (SD)	8.9 (1.0)	8.9 (0.9)	8.9 (0.9)
Median	8.8	8.8	8.8
Min ; Max	7.0 ; 11.6[b]	7.3 ; 11.1[b]	7.0 ; 11.6[b]
FPG (mmol/L)			
N	261	261	522
Mean (SD)	10.1 (2.9)	10.4 (2.8)	10.2 (2.9)
Median	9.7	10.2	9.9
Min ; Max	3.8 ; 19.6	4.7 ; 20.6	3.8 ; 20.6

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 (Subject [redacted]) with BMI [redacted] kg/m^2) had been randomised despite failing to meet the inclusion criterion (BMI ≤40 kg/m^2) was subsequently withdrawn from the trial and was excluded from the PP analysis. [b] One subject ([redacted]) had a HbA_{1c} level of [redacted]% at Visit [redacted] and [redacted]% at Visit [redacted]. Another subject ([redacted]) had a HbA_{1c} level of [redacted]% at Visit [redacted] and [redacted]% at Visit [redacted]. Both subjects met the selection criterion based on the HbA_{1c} evaluated at Visit 1 and completed the study.

Efficacy Results and Conclusions

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

Primary Endpoint

- **HbA_{1c}**: IDegAsp effectively improved long-term glycaemic control as measured by HbA_{1c} (non-inferior to

IGlar). The estimated treatment difference (IDegAsp-IGlar) was 0.03%-points [-0.14; 0.20]$_{95\%\ CI}$. The estimated mean change in HbA_{1c} was -1.72%-points with IDegAsp and -1.75%-points with IGlar. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} with IDegAsp and IGlar was the same i.e. 7.2 (1.0) %.

Secondary Efficacy Endpoints

Confirmatory Endpoints

- **Prandial increment in SMPG:** Superiority of IDegAsp to IGlar was confirmed in terms of a smaller increment in the mean prandial glucose at breakfast; estimated treatment difference (IDegAsp-IGlar) was -1.40 mmol/L [-1.92; -0.88]$_{95\%CI}$. The estimated mean prandial glucose increment at breakfast was 1.99 mmol/L with IDegAsp and 3.39 mmol/L with IGlar.
- **Fluctuation in nocturnal IG:** The estimated mean fluctuation in nocturnal glucose as measured by CGM was 0.58 mmol/L with IDegAsp and 0.85 mmol/L with IGlar after 26 weeks. The fluctuation (mmol/L) in nocturnal IG was numerically (31%) lower in the IDegAsp group compared to the IGlar group and the estimated mean treatment ratio (IDegAsp/IGlar) was 0.69 [0.25; 1.92]$_{95\%\ CI}$. Superiority could not be confirmed and consequently, the hierarchical testing procedure was stopped. Therefore, superiority could not be confirmed for the remaining confirmatory efficacy and safety endpoints.
- **Responders with HbA_{1c} <7.0% without confirmed hypoglycaemia**: The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemic episodes was 23.6% with IDegAsp and 30.7% with IGlar. Superiority could not be confirmed as the lower limit of the 95% CI for the treatment ratio was <1 and the hierarchical testing procedure were stopped prior to testing this endpoint for superiority.
- **Nocturnal confirmed hypoglycaemia:** – Please see safety results and conclusions.
- **Change in body weight** – Please see safety results and conclusions.

Supportive Endpoints

- **FPG:** After 26 weeks of treatment, IGlar resulted in a greater reduction in FPG than IDegAsp. The estimated mean change in FPG was -4.02 mmol/L with IGlar and -3.5 mmol/L with IDegAsp; estimated treatment difference (IDegAsp-IGlar) was 0.51 mmol/L [0.09; 0.93]$_{95\%CI}$ The FPG decreased during the trial to a mean (SD) level of 6.3 (2.7) mmol/L with IGlar and 6.8 (2.2) mmol/L with IDegAsp.
- **SMPG for dosing**: The mean prebreakfast SMPG for dose adjustment was lower with IGlar than with IDegAsp with an estimated treatment difference (IDegAsp-IGlar) of 0.91 mmol/L [0.62; 1.21]$_{95\%\ CI}$ The proportion of subjects who met the prebreakfast SMPG titration target <5 mmol/L (90 mg/dL) was 13.9% with IDegAsp and 28.5% with IGlar. Subjects who had yet not achieved the prebreakfast target at a given visit had a 0.45 [0.36 ; 0.56]$_{95\%\ CI}$ times lower chance of achieving the target at the next visit when treated with IDegAsp compared to subjects in the IGlar group.
- **9-point SMPG Profiles:** The estimated mean prandial increment across all meals was lower for IDegAsp than with IGlar (2.30 Vs 2.87 mmol/L; estimated treatment difference was -0.58 mmol/L [-0.90; -0.26]$_{95\%CI}$ Fluctuation (mmol/L) in the 9-point profile was lower with IDegAsp than with IGlar, with an estimated treatment ratio of 0.89 [0.81; 0.98]$_{95\%CI}$ The decrease in nocturnal PG was smaller with IDegAsp than with IGlar from bedtime to breakfast; the estimated treatment difference (IDegAsp-IGlar) was 0.97 mmol/L [0.45; 1.48]$_{95\%\ CI}$.
- **Responder for HbA_{1c} <7% and HbA_{1c} ≤ 6.5%:** The observed proportion of subjects who achieved HbA_{1c} <7% was 45.9% with IDegAsp and 45.6% with IGlar; estimated odds ratio (IDegAsp/IGlar) 0.95 [0.66; 1.35]$_{95\%\ CI}$. The proportion achieving HbA_{1c} ≤6.5% was 27.8% with IDegAsp and 25.9% with IGlar; estimated odds ratio (IDegAsp/IGlar) 1.07 [0.72; 1.58]$_{95\%\ CI}$.
- **Within-subject variability in fasting SMPG**: The day-to-day variability in prebreakfast SMPG was lower with IDegAsp compared to IGlar as measured by within-subject variation (CV%). The estimated treatment ratio (IDegAsp/IGlar) was 0.86 [0.79; 0.94]$_{95\%\ CI}$.
- **CGM related endpoints**: The mean (SD) interstitial glucose after 26 weeks of treatment decreased to 8.4 (2.4) mmol/L with IDegAsp and 8.1 (2.1) mmol/L with IGlar. No statistically significant differences were identified between the two treatment groups with respect to the number or duration of low or high IG readings, irrespective of the threshold used. After 26 weeks of treatment, the mean prandial IG increment at 90 and 120 minutes after breakfast were lower with IDegAsp than with IGlar; estimated difference (IDegAsp-IGlar) was

-1.06 mmol/L [-1.85;-0.28]$_{95\% CI}$ and -1.47 mmol/L [-2.29; -0.65]$_{95\% CI}$; respectively.

- **Beta-cell function:** The mean proinsulin after 26 weeks of treatment was 15.27 pmol/L with IDegAsp and 12.76 pmol/L with IGlar. The change in beta-cell function as measured by the change in proinsulin from baseline to 26 weeks of treatment was numerically greater with IDegAsp (-23.57 pmol/L) than with IGlar (-17.46 pmol/L). The estimated treatment difference (IDegAsp-IGlar) for the proinsulin was 0.30 pmol/L [-2.69; 3.30]$_{95\% CI}$.
- **Patient reported outcome (PRO):** The results related to PRO appeared similar between the treatment groups with only marginal changes over time. The estimated mean score for "TRIM-D Total" "Diabetes Management," and "Psychological Health" improved more in the IGlar group than in the IDegAsp; estimated treatment difference (IDegAsp-IGlar) -2.4 [-4.4; -0.3]$_{95\% CI}$, -6.7 [-10.2 ;-3.1],$_{95\% CI}$, and -2.7 [-5.2 ;-0.3]$_{95\% CI}$, respectively

Safety Results and Conclusions

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

Secondary Endpoints

Confirmatory Safety Endpoint

- **Nocturnal Confirmed Hypoglycaemic Episodes:** The observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was 19 episodes for IDegAsp and 46 episodes for IGlar. The rate of nocturnal confirmed hypoglycaemia was 71% lower with IDegAsp than with IGlar; estimated rate ratio (IDegAsp/IGlar) was 0.29, [0.13; 0.65]$_{95\% CI}$. The hierarchical testing was stopped prior to testing this endpoint for superiority.
- **Body Weight:** Body weight increased during the trial to similar mean (SD) levels: 87.5 kg (18.1) with IDegAsp and 86.3 kg (18.7) with IGlar. IDegAsp was associated with more weight gain than IGlar after 26 weeks of treatment as the upper limit of the 95% CI for the estimated treatment difference (IDegAsp-IGlar) (1.31 kg [0.72; 1.89]$_{95\% CI}$) was > 0. The hierarchical testing was stopped prior to testing this endpoint for superiority.

Supportive Safety Endpoints

- **Hypoglycaemic episode:** One episode of severe hypoglycaemia was reported in each treatment group. The observed rate of confirmed hypoglycaemic episodes per 100 patient year exposure (PYE) was 423 with IDegAsp and 185 with IGlar. The estimated rate ratio (IDegAsp/IGlar) for confirmed hypoglycaemia was 2.17 [1.59; 2.94]$_{95\% CI}$. The majority of hypoglycaemic episodes reported with IDegAsp occurred approximately between 10:00 and 14:00 h.
- **Adverse events:** The percentage of subjects reporting treatment-emergent AEs was 54.7% in the IDegAsp and 48.3% in the IGlar treatment group. The event rate for AEs was numerically higher in the IDegAsp (352 events per 100 PYE treatment group than in the IGlar group (269 events per 100 PYE). The rate of adverse events possibly or probably related to IDegAsp and IGlar was 24 and 19 events per 100 PYE, respectively. The most frequently reported AEs in both treatment groups were nasopharyngitis, headache, and hypertension.
- **Deaths, serious adverse events and other significant adverse events:** Two deaths were reported in this trial in the IDegAsp treatment group (hepatic metastatic cancer and sudden cardiac death) and none in the IGlar group. A total of 17 (6.4%) subjects reported 19 serious adverse events in the IDegAsp group while 4 (1.5%) subjects reported 6 serious adverse events in the IGlar group. The event rate per 100 PYE of serious adverse events was numerically higher with IDegAsp (16 events) than with IGlar (5 events). The most frequently reported SAE was thrombophlebitis (3 and 0 events per 100 PYE in IDegAsp and IGlar, respectively). A total of 8 (1.5%) subjects reported 11 treatment-emergent AEs leading to withdrawal in this trial: 5 (1.9%) subjects in the IDegAsp group and 3 (1.1%) subjects in the IGlar group.
- **Insulin antibodies:** After 26 weeks of treatment, the mean level of antibodies cross-reacting to human insulin remained low in the IDegAsp (2.4%) group and increased slightly in the IGlar (3.9%) group.
- **Vital signs, ECG, funduscopy, physical examination and laboratory values:** No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed.
- **Insulin dose:** The mean daily insulin dose after 26 weeks was numerically higher in the IDegAsp group: 66 U (0.75 U/kg) than in the IGlar group: 59 U (0.67 U/kg). The insulin dose ratio (IDegAsp/IGlar) in U was 1.12.

Conclusions

The results of this confirmatory, randomised, controlled, 26-week trial demonstrate the efficacy and safety of IDegAsp versus IGlar, both administered once daily with metformin in insulin-naïve 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 confirms superiority of IDegAsp to IGlar with respect to a smaller prandial glucose increment at breakfast.
- IGlar reduces FPG more than IDegAsp, while IDegAsp is associated with a smaller mean prandial glucose increment across all meals.
- Plasma glucose is more stable with IDegAsp compared to IGlar as measured both by a lower pre-breakfast day-to-day variation and by less fluctuation in daily self-measured plasma glucose. Fluctuation in nocturnal glucose, as measured by continuous glucose monitoring, is numerically lower with IDegAsp, but superiority can not be confirmed.
- Superiority of IDegAsp compared to IGlar can not be demonstrated for subjects achieving the treatment target ($HbA_{1c} < 7\%$) without confirmed hypoglycaemia and the odds of achieving this target is lower with IDegAsp than with IGlar.
- IDegAsp is associated with a higher rate of confirmed hypoglycaemia compared to IGlar, while subjects treated with IDegAsp experience a lower rate of nocturnal confirmed hypoglycaemia.
- Body weight increases more in the IDegAsp treatment group compared to the IGlar group.
- In this trial, no safety issues are identified with IDegAsp; there are no clinically relevant differences in the AE pattern between IDegAsp and IGlar 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 23-Nov-2010