2 Synopsis

Trial Registration ID-number NCT01169766	**IND Number –** IND 73,198 **EudraCT number –** 2009-015839-33
Title of Trial An Extension Trial Comparing Safety and Efficacy of NN5401[1] with Insulin Glargine in Subjects with Type 2 Diabetes. (BOOST™: START 1) This synopsis contains the results after 52 weeks treatment (26 weeks in the main trial NN5401-3590 and 26 weeks in the present extension trial NN5401-3726).	
Investigators There were 76 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 76 sites in 8 countries: Austria (4 sites), India (7 sites), Republic of Korea (5 sites), Poland (6 sites), Russia (8 sites), Spain (9 sites), Turkey (5 sites), and United States (32 sites). These sites enrolled subjects.	
Publications Results from this trial have not been published at the time of this report.	
Trial Period 26 July 2010 to 4 May 2011	**Development Phase** Phase 3a

Objectives

Primary Objective:

The primary objective was to investigate the long-term safety and tolerability of IDegAsp. This was done by comparing IDegAsp to insulin glargine (IGlar) after 52 weeks of treatment (26 weeks of treatment in trial NN5401-3590 plus 26 weeks of treatment in this extension trial) in terms of the following safety assessments:

- Adverse events
- Hypoglycaemic episodes
- Clinical evaluations
- Central laboratory assessments incl. lipid profile, cardiovascular (CV) risk markers and insulin antibodies
- Body weight
- Insulin dose

Secondary Objectives:

The secondary objective was to compare the efficacy between IDegAsp and IGlar after 52 weeks of treatment in terms of listed efficacy assessments:

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

Methodology

The main trial (NN5401-3590) was a 26-week, 1:1 randomised, parallel-group trial comparing two active treatment groups in subjects with type 2 diabetes: IDegAsp OD + metformin with that of IGlar OD + metformin, and the 26-week extension trial was with the same treatment regimen to ensure the most optimal coverage of both basal and bolus requirements. There was a 1-week follow-up period after the 26 weeks' treatment period for safety follow up.

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

Subjects who consented to participate in the extension trial restarted treatment with IDegAsp OD + metformin or insulin glargine OD + metformin as previously randomly allocated in trial NN5401-3590.

The main 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). There was no further randomisation in the extension trial period.

At randomisation, the subjects' previous oral antidiabetic (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 subjects' 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. 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.

The extension trial included a screening visit to assess eligibility on the same day as the follow-up visit in the main trial (Week 27). Subjects were required to attend a further 7 visits and 7 phone contacts during the 26 weeks of treatment, followed by a follow-up visit one week after discontinuing the trial treatment. All subjects enrolled in the extension trial had previously been participating in the 26-week main trial (NN5401-3590) and received a maximum of 52 weeks of treatment in total.

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

Number of Subjects Planned and Analysed

The planned number of subjects to be screened and complete the main trial was 752 and 446 respectively. The planned number of subjects to be screened and complete the extension trial was 335 and 285, respectively. All subjects enrolled in the extension trial had previously participated in the 26-week main trial (NN5401-3590) and received a maximum of 52 weeks of treatment in total. 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 Main Trial	265 (99.6)	261 (98.9)	526 (99.2)
Withdrawn at/after Randomisation and Before Extension	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 Main Trial	219 (82.3)	232 (87.9)	451 (85.1)
Completed Main Trial, not Screened for extension	27 (10.2)	11 (4.2)	38 (7.2)
Included in Extension	192 (72.2)	221 (83.7)	413 (77.9)
Withdrawn during Extension	13 (4.9)	12 (4.5)	25 (4.7)
Adverse Event	3 (1.1)	3 (1.1)	6 (1.1)
Ineffective Therapy	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance With Protocol	2 (0.8)	3 (1.1)	5 (0.9)
Withdrawal Criteria	2 (0.8)	1 (0.4)	3 (0.6)
Other	6 (2.3)	5 (1.9)	11 (2.1)
Completed Extension	179 (67.3)	209 (79.2)	388 (73.2)
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)
Extension Analysis Set	192 (72.2)	221 (83.7)	413 (77.9)

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 main trial.

Subjects who completed the first 26-week treatment in main trial NN5401-3590 were eligible to participate in the 26-week extension trial.

Subjects were excluded from the main trial if they had an 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/or 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).

Subjects were not eligible for participation in the extension trial if they had an anticipated change in concomitant medication known to interfere with glucose metabolism, anticipated significant lifestyle changes/ highly variable eating habits during the trial, and/or pregnancy, breast-feeding, the intention of becoming pregnant or not using adequate contraceptive measures according to local requirements.

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

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

Test Product, Dose and Mode of Administration, Batch Number

IDegAsp 100 U/mL, 3 mL PDS290 pen (The IDegAsp drug product consists of two drug substances (70 volume% IDeg + 30 volume% IAsp). During the first 26 weeks (main trial; NN5401-3590), subjects randomised to IDegAsp were instructed to initiate treatment with IDegAsp 10 U OD with breakfast (morning meal). During the extension, the possibility of moving the IDegAsp OD dose to the largest meal was permitted. 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.: YP50611

Duration of Treatment

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

Reference Therapy, Dose and Mode of Administration, Batch Number

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.: 40C764, 40C368, 40C408, 40C777, OF166A

NPH insulin (Insulatard®, Protaphane®, Novolin N™) 100 IU/mL, 3 mL FlexPen®
From end-of-trial insulin treatment to the follow-up visit in the main trial and in the extension trial, 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 the 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.: YP50831

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - Prebreakfast SMPG
  - 9-point SMPG profile with 1 additional measurement before breakfast (SMPG)

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes#
- Antibodies
- Insulin dose
- Physical examination

- Vital signs
- Body weight
- 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 (SAS): included all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set were to contribute to the evaluation "as treated".
- Extension Trial Set (ETS): included subjects receiving at least one dose of the investigational product or its comparator in the extension trial.

Safety endpoints were summarised and analysed using the SAS. Efficacy endpoints were summarised and analysed using the FAS. All formal statistical analyses (including statistical analyses on hypoglycaemic episodes, body weight and lipids) used LOCF and are based on the FAS, which consisted of all subjects randomised during the main trial. The analysis of secondary endpoint HbA_{1c} was repeated on the PP and the ETS analysis sets. Analyses were repeated for serious treatment emergent AEs, number of severe and minor treatment emergent hypoglycaemic episodes, antibodies, central laboratory parameters (ALAT/SGPT, ASAT/SGOT) and HbA_{1c} using the ETS to assess the stability of key results.

Secondary Efficacy Analysis

- Change from baseline in HbA_{1c} after 52 weeks of treatment was analysed using an analysis of variance (ANOVA) method with treatment, antidiabetic therapy at screening, sex and region as fixed factors and age and baseline HbA_{1c} as covariates.
- HbA_{1c} responder (HbA_{1c} <7% at end of trial) was a dichotomous endpoint. The HbA_{1c} responder endpoint was analysed based on a logistic regression model using same factors and covariates as for the HbA_{1c} analysis.
- Responder without hypoglycaemic episodes (HbA_{1c} <7.0% at end of trial and no confirmed/severe hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks) was a dichotomous endpoint that was defined based on whether a subject had met the American Diabetes Association (ADA) HbA_{1c} target at end of trial without confirmed/severe hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after last randomised treatment. Responder analysis was based on a logistic regression model using the same factors and covariates as for the primary analysis.
- Change from baseline in FPG after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the primary analysis.
- 9-point profile (SMPG): A mixed effect model was fitted to the 9-point profile (SMPG) data. The model included treatment, time, interaction between treatment and time, antidiabetic therapy at screening, sex and region as fixed factors, age as covariate and subject as random effect. From this model, mean profile by treatment and relevant treatment differences were estimated and explored.
- Mean and logarithmically transformed fluctuations (mmol/L) in the 9-point profile (SMPG), prandial PG increment and nocturnal PG endpoints after 52 weeks of treatment were analysed separately using an ANOVA

method similar to that used for the primary analysis.

- SMPG values used for dose adjustment: The mean of before meal/before breakfast PG values after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the HbA_{1c} analysis. The time from randomisation until the date a subject met 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.

Primary Safety Analyses

- A treatment emergent adverse event (TEAE) was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 14.0) coding. Evaluation of TEAEs was based on descriptive statistics. AEs and hypoglycaemic episodes are also presented as the rate of the events per 100 patient years of exposure (PYE).
- A hypoglycaemic episode was defined as treatment emergent using the same definition as for TEAE above. A hypoglycaemic episode with time of onset between 00:01 and 05:59 a.m. (both included) was considered nocturnal. Hypoglycaemic episodes were classified according to the ADA classification into the following five categories based on PG measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia. Furthermore, confirmed hypoglycaemic episodes were defined as episodes of severe hypoglycaemia and minor hypoglycaemic episodes with a confirmed PG value of less than 3.1 mmol/L (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 nocturnal hypoglycaemic episodes were analysed separately.
- Antibodies specific for: IDeg, IAsp and IGlar as well as antibodies cross-reacting to human insulin were measured and their correlation to total insulin dose and HbA_{1c} were investigated using descriptive statistics.
- Change from baseline in body weight after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the primary analysis.
- Remaining laboratory parameters, insulin dose, physical examination, ECG, funduscopy / fundusphotography and vital signs were evaluated based on descriptive statistics.

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 (ranging from 22 to 78 years), and a mean duration of diabetes of 9.2 years (ranging from 7.2 months to 40 years), with a mean HbA_{1c} of 8.9% and a mean BMI of 30.7 kg/m^2. The demographics and baseline characteristics were similar with only marginal differences between the treatment groups: the IDegAsp group had 20.7% subjects over 65 years of age and 53.0% who were female, while the IGlar group had 16.3% subjects above 65 years and 48.3% who were female. The majority of the subjects (~72%) reported their race as White. The second-largest race group (~14%) consisted of Asian-Indian subjects. Approximately 22% of subjects reported their ethnicity as Hispanic or Latino. The demographics and baseline characteristics of all randomised subjects (FAS) are summarised in the table below. The demographic and baseline characteristics of subjects who participated in the extension trial were also evaluated using the ETS and results were in accordance with the analysis based on FAS.

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-4 inhibitors or 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	18.1 ; 40.0	18.1 ; 43.8
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	7.3 ; 11.1	7.0 ; 11.6
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 into the main trial 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 846008 with BMI 43.8 kg/m^2) who 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 (103010) had an HbA_{1c} level of 9.1% at Visit 1 and 11.5% at Visit 2. Another subject (828008) had an HbA_{1c} level of 10.6% at Visit 1 and 11.6% at Visit 2. 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 52-week trial of treatment with IDegAsp OD + metformin or IGlar OD + metformin, the following can be concluded with regards to the full analysis set:

Secondary Endpoints

- **HbA_{1c}:** IDegAsp effectively improved long−term glycaemic control, as measured by HbA_{1c}. The estimated mean reduction in HbA_{1c} during the trial was 1.48 %-points with IDegAsp and 1.40 %-points with IGlar, and the estimated mean difference was -0.08 %-points $[-0.26; 0.09]_{95\%CI}$. After 52 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.5 (1.0) % with IDegAsp and 7.6 (1.1) % with IGlar.
- **Responders for HbA_{1c}:** There was no statistically significant difference between treatment groups in terms of achieving either $HbA_{1c} < 7\%$ or $HbA_{1c} \leq 6.5\%$. An observed total of 33.1% of subjects treated with IDegAsp achieved $HbA_{1c} < 7\%$ compared to the observed proportion of 29.7% for subjects treated with IGlar. The estimated odds ratio of achieving this target with IDegAsp compared to IGlar was 1.13 $[0.77; 1.66]_{95\% CI}$. An observed total of 17.3% of subjects treated with IDegAsp achieved $HbA_{1c} \leq 6.5\%$ compared to the observed proportion of 17.5% for subjects treated with IGlar. The estimated odds ratio of achieving this target with IDegAsp compared to IGlar was 0.94 $[0.59; 1.50]_{95\% CI}$.
- **Responders for HbA_{1c} without hypoglycaemia:** There was no statistically significant difference between treatment groups in terms of achieving either HbA_{1c} target without confirmed or severe hypoglycaemia. The observed proportion of subjects achieving $HbA_{1c} < 7\%$ without confirmed hypoglycaemia was 23.6% with IDegAsp and 20.9% with IGlar; the estimated odds ratio (IDegAsp/IGlar) was 1.15 $[0.73; 1.81]_{95\% CI}$. The observed proportion of subjects achieving $HbA_{1c} < 7\%$ without severe hypoglycaemic episodes was 36.9% with IDegAsp and 31.1% with IGlar; the estimated odds ratio (IDegAsp/IGlar) was 1.26 $[0.84; 1.88]_{95\% CI}$. The observed proportion of subjects achieving $HbA_{1c} \leq 6.5\%$ without confirmed hypoglycaemia was 11.2% with IDegAsp and 12.7% with IGlar; the estimated odds ratio (IDegAsp/IGlar) was 0.83 $[0.47; 1.47]_{95\% CI}$. The observed proportion of subjects achieving $HbA_{1c} \leq 6.5\%$ without severe hypoglycaemic episodes was 18.9% with IDegAsp and 18.4% with IGlar; the estimated odds ratio (IDegAsp/IGlar) was 0.97 $[0.60; 1.57]_{95\% CI}$.
- **FPG:** FPG decreased during the trial to similar levels; observed mean 7.0 mmol/L with IDegAsp and 6.7 mmol/L with IGlar. The estimated mean reduction from baseline in FPG during this trial was 3.50 mmol/L with IDegAsp compared to 3.77 mmol/L with IGlar, with an estimated mean difference (IDegAsp-IGlar) of 0.28 mmol/L $[-0.14; 0.69]_{95\%CI}$.
- **9-point SMPG profiles:** After 52 weeks of treatment, the estimated mean prandial increment was statistically significantly smaller for IDegAsp compared with IGlar both across all meals and at breakfast; estimated difference IDegAsp-IGlar -0.34 $[-0.64; -0.04]_{95\%CI}$ with respect to all meals and -0.97 $[-1.42; -0.51]_{95\%CI}$ with respect to breakfast. Estimated mean SMPG values before breakfast, at 4 a.m., and before breakfast the next day were higher with IDegAsp compared to IGlar, the estimated mean treatment differences (IDegAsp-IGlar) were 0.81 mmol/L $[0.46; 1.17]_{95\% CI}$, 0.53 mmol/L $[0.10; 0.95]_{95\% CI}$, and 0.89 mmol/L $[0.56; 1.23]_{95\% CI}$, respectively. There was statistically significantly less fluctuation in PG with IDegAsp compared to IGlar based on the 9-point SMPG profiles; the estimated treatment ratio (IDegAsp/IGlar) was 0.89 $[0.80; 0.99]_{95\ CI\%}$. After 52 weeks of treatment, the observed mean change in nocturnal PG (bedtime to breakfast) was smaller with IDegAsp (-2.2 mmol/L) than with IGlar (-3.1 mmol/L); estimated mean difference 0.75 mmol/L $[0.24; 1.27]_{95\%CI}$.
- **SMPG for dosing:** Mean SMPG before breakfast was reduced with both IDegAsp and IGlar during the trial. The estimated mean SMPG value before breakfast was statistically significantly higher with IDegAsp (estimated mean difference 0.83 mmol/L $[0.49; 1.16]_{95\%CI}$). There was a statistically significant difference in the within-subject variation (CV%) in pre-breakfast SMPG with IDegAsp compared to IGlar, in favour of IDegAsp (estimated treatment ratio [IDegAsp/IGlar] was 0.84 $[0.77; 0.92]_{95\%CI}$). After 52 weeks of treatment, 20.3% and 33.8% of subjects in IDegAsp and IGlar treatment groups achieved the prebreakfast SMPG target < 5 mmol/L. There was a statistically significant difference regarding the time to meet the prebreakfast PG titration target between treatment groups, in favour of IGlar (estimated mean difference 0.48 $[0.39; 0.58]_{95\% CI}$).

Safety Results and Conclusions

From the results of this 52-week trial of treatment with IDegAsp OD + metformin or IGlar OD + metformin, the following can be concluded:

Primary Endpoints

- **Adverse events:** The percentages of subjects reporting AEs were 64.2% and 61.7% in the IDegAsp and IGlar groups, respectively. The observed rate of AEs was numerically higher in the IDegAsp group compared with the IGlar treatment group, 313 and 238 events per 100 PYE, respectively. The majority of AEs were mild or moderate. Few of the AEs were severe in either treatment group; the rate of severe AEs was 9 and 10 events per 100 PYE in the IDegAsp and IGlar groups, respectively. The rates of AEs considered possibly or probably related to trial product by investigator were 18 and 13 events per 100 PYE in the IDegAsp and IGlar groups, respectively. The most frequently reported adverse event in both treatment groups was nasopharyngitis, reported by 13.5% of all subjects. Injection-site reactions were reported by 3.8% of subjects in the IDegAsp group and 1.5% of subjects in the IGlar group. The majority of subjects in both treatment groups recovered from the AEs at the end of trial.
- **Deaths, serious adverse events and other significant adverse events:** Five deaths were reported in this trial; 4 in the IDegAsp group and 1 in the IGlar group. A total of 30 (11.3%) and 15 (5.7%) subjects reported 56 serious adverse events in the IDegAsp (36 events) and IGlar groups (20 events), respectively. The rate of serious adverse events per 100 PYE was slightly higher the IDegAsp group (IDegAsp: 17, IGlar: 9). A similar percentage of subjects withdrew from the trial due to AEs: 5 (1.9%) in the IDegAsp group and 3 (1.1%) in the IGlar group in the main trial and 3 (1.1%) in the IDegAsp group and 3 (1.1%) in the IGlar group in the extension trial.
- **Hypoglycaemic episodes:** The percentage of subjects who experienced confirmed hypoglycaemic episodes was similar in IDegAsp group (57.7%) compared with the IGlar group (52.1%), with an observed rate of confirmed hypoglycaemic episodes of 419 and 211 per 100 PYE for IDegAsp and IGlar groups, respectively. The observed rate of nocturnal confirmed hypoglycaemic episodes was 19 and 53 per 100 PYE for IDegAsp and IGlar groups, respectively. The estimated rate ratio (IDegAsp/IGlar) for confirmed hypoglycaemic episodes was 1.86 $[1.42; 2.44]_{95\% CI}$, whereas the estimated rate of nocturnal confirmed hypoglycaemia was 75% lower with IDegAsp than with IGlar; estimated rate ratio (IDegAsp/IGlar) was 0.25 $[0.14; 0.47]_{95\% CI}$. The observed rate of severe and nocturnal severe hypoglycaemia per 100 PYE was 1 and 0 for IDegAsp and 1 and 0 for IGlar, respectively. No significant difference was seen between treatment groups in terms of achieving target HbA_{1c} levels < 7% and ≤ 6.5% without confirmed or severe hypoglycaemia.
- **Insulin dose:** The mean daily insulin dose after 52 weeks was numerically higher in the IDegAsp group compared with the IGlar group: 70 U (0.78 U/kg) for IDegAsp and 62 U (0.70 U/kg) for IGlar. The ratio of IDegAsp/IGlar mean daily insulin dose (U) after 52 weeks was 1.13.
- **Vital signs, ECG, fundoscopy, physical examination and laboratory values:** No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed for vital signs, ECG, fundoscopy/fundusphotography, physical examination and laboratory values.
- **Insulin antibodies:** The mean level of insulin antibodies cross-reacting between IDegAsp, IGlar and human insulin and IDeg-, IGlar- and IAsp-specific antibodies remained low with IDegAsp and IGlar after 52 weeks of treatment.
- **Body weight:** The observed mean (SD) body weights at baseline and at the end of the trial were 85.1 kg (18.0) and 88.7 kg (18.3) in the IDegAsp group and 85.2 kg (18.6) and 87.4 kg (18.9) in the IGlar group, respectively.

Overall Conclusions

This confirmatory, randomised, controlled, 52-week trial investigated the long-term safety and efficacy of treatment with IDegAsp versus IGlar, both administered once daily with metformin in insulin-naïve subjects with type 2 diabetes mellitus. The data support the following trial conclusions:

- In this trial, no safety issues are identified with IDegAsp after 52 weeks of treatment.
- There are no clinically relevant differences between IDegAsp and IGlar with respect to the AE pattern and standard safety parameters.
- In this trial, 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.
- Treatment with IDegAsp effectively improves long-term glycaemic control as measured by $HbA_{1c.}$
- 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.

In conclusion, these findings confirm the safety and efficacy of once-daily treatment with IDegAsp administered once daily at breakfast or largest meal, in subjects with type 2 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 06-Jul-2011