2 Synopsis

Trial Registration ID-number NCT01193322	**IND Number –** 76,496 **EudraCT number –** 2009–015816–17
Title of Trial An Extension Trial Comparing Safety and Efficacy of NN1250[1] With Insulin Glargine Plus Insulin Aspart With/Without Metformin and With/Without Pioglitazone in Type 2 Diabetes (BEGIN™) This synopsis contains the results after 78 weeks treatment (52-weeks in the main trial NN1250-3582 and 26-weeks in the present extension trial NN1250-3667).	
Investigators There were 113 principal investigators (one principal investigator was appointed for each site). The signatory investigator was [redacted], from [redacted].	
Trial Sites A total of 113 sites in 12 countries screened and enrolled subjects: Bulgaria (8 sites), Germany (8 sites), Hong Kong (1 site), Ireland (4 sites), Italy (10 sites), Romania (5 sites), Russian Federation (5 sites), Slovakia (4 sites), South Africa (5 sites), Spain (9 sites), Turkey (3 sites) and United States (51 sites).	
Publications Results from the main trial (NN1250-3582) were presented at the 2011 American Diabetes Association Meeting in San Diego, CA	
Trial Period 01 September 2010 to 10 May 2011	**Development Phase** Phase 3a

Objectives

Primary Objective:

The primary objective was to investigate the long-term safety and tolerability of IDeg in combination with insulin aspart. This was done by comparing IDeg + insulin aspart ± OAD(s) to insulin glargine + insulin aspart ± OAD(s) after 78 weeks of treatment (52 weeks of treatment in NN1250-3582 plus 26 weeks of treatment in this extension trial) in terms of the listed safety assessments from which endpoints were calculated:

- adverse events
- hypoglycaemic episodes
- clinical evaluation
- central laboratory assessments
- body weight
- insulin dose

Secondary Objectives:

The secondary objective was to compare the efficacy between IDeg and insulin glargine, both in combination with insulin aspart ± OAD(s), after 78 weeks of treatment, in terms of the listed efficacy assessments from which endpoints were calculated:

- HbA_{1c} (central laboratory)
- fasting plasma glucose (FPG) measured at a central laboratory
- 9-point self-measured plasma glucose (SMPG) profile
- 4-point self-measured plasma glucose (SMPG) profile

[1] NN1250 is synonymous with insulin degludec and was previously referred to as soluble insulin basal analogue (SIBA)

Methodology

This was a 26-week active controlled open-label multicenter, multinational, two arm parallel groups, treat-to-target safety/efficacy trial. This trial was an extension of a 52-week, 3:1 randomised, active controlled open-label multicenter, multinational, two arm parallel groups, treat-to-target trial comparing the efficacy and safety of once daily (OD) insulin degludec (IDeg) with OD insulin glargine (IGlar) both in a basal/bolus regimen with insulin aspart (IAsp) as mealtime insulin ± metformin ± pioglitazone in subjects with type 2 diabetes mellitus (NN1250-3582).

In the main trial subjects attended a screening visit to assess their eligibility, followed by a randomisation visit, conducted 1 week later. At randomisation (Visit 2), subjects' current antidiabetic treatment was discontinued except for metformin and pioglitazone, if applicable. The randomisation was carried out in a 3:1 manner to IDeg OD or IGlar OD, both with mealtime IAsp ± metformin ± pioglitazone. All subjects were titrated according to the insulin titration guidelines provided in the protocol. The treatment period lasted for 52 weeks. A follow-up visit was offered to any subject withdrawing prematurely at any point during the trial.

All subjects who completed the main trial (Visit 41) and were found eligible for the extension trial (Visit 43) were offered and encouraged to participate in a 26-week extension trial (NN1250-3667). The purpose of the extension trial was to collect safety data. A separate protocol, subject information and informed consent form were prepared for the extension trial. Verbal and written information was provided to the subjects and the informed consent form was signed by the subject and the investigator. Subjects who consented to participate in the extension trial continued receiving treatment with either IDeg + IAsp ± metformin ± pioglitazone or IGlar + IAsp ± metformin ± pioglitazone.

The extension trial included a screening visit to assess eligibility on the same day as the end of treatment visit in trial NN1250-3582. Subjects were required to attend an additional 6 visits and 8 phone contacts during the 26-weeks of treatment and a follow-up visit after discontinuing the trial treatment. The total duration of each subject's participation in this trial was approximately 28 weeks.

Number of Subjects Planned and Analysed

The planned number of subjects to be screened (1403), randomised (984) and complete the trial (736) was based on the sample size calculation to meet the primary objective with at least 95% power. The actual number of randomised subjects in the main trial (NN1250-3582) was 1006, and the planned number of completed subjects was revised to 755, of which 75% were expected to continue for this extension trial. The planned numbers of subjects to be screened (566) and complete (481) the extension trial were based on the sample size calculation. All subjects enrolled in the extension trial had previously participated in the 52-week main trial (NN1250-3582) and received maximum 78 weeks of treatment in total. The actual numbers of subjects included in the trial are shown below:

	IDeg OD N (%)	IGlar OD N (%)	Total N (%)
Screened			1440
Screening Failures			434
Withdrawn before Randomisation			0
Randomised	755 (100.0)	251 (100.0)	1006 (100.0)
Exposed	753 (99.7)	251 (100.0)	1004 (99.8)
Completed Main Trial	618 (81.9)	211 (84.1)	829 (82.4)
Withdrawn at/after Randomisation and Before extension	137 (18.1)	40 (15.9)	177 (17.6)
Adverse Event	31 (4.1)	9 (3.6)	40 (4.0)
Ineffective Therapy	3 (0.4)		3 (0.3)
Non-Compliance	23 (3.0)	12 (4.8)	35 (3.5)
Withdrawal Criteria	8 (1.1)	2 (0.8)	10 (1.0)
Other	72 (9.5)	17 (6.8)	89 (8.8)

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	IDeg OD N	(%)	IGlar OD N	(%)	Total N	(%)
Completed Main Trial Not screened for extension	52	(6.9)	20	(8.0)	72	(7.2)
Completed Main Trial screening failure in extension	0	(0.0)	0	(0.0)	0	(0.0)
Included in Extension	566	(75.0)	191	(76.1)	757	(75.2)
Withdrawn during extension	27	(3.6)	8	(3.2)	35	(3.5)
Adverse Event	4	(0.5)			4	(0.4)
Ineffective Therapy	1	(0.1)	1	(0.4)	2	(0.2)
Non-Compliance	5	(0.7)			5	(0.5)
Withdrawal Criteria	6	(0.8)	2	(0.8)	8	(0.8)
Other	11	(1.5)	5	(2.0)	16	(1.6)
Completed Extension	539	(71.4)	183	(72.9)	722	(71.8)
Full Analysis Set	744	(98.5)	248	(98.8)	992	(98.6)
PP Analysis Set	694	(91.9)	233	(92.8)	927	(92.1)
Safety Analysis Set	753	(99.7)	251	(100.0)	1004	(99.8)
Extension Trial Set	566	(75.0)	191	(76.1)	757	(75.2)

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, glycosylated haemoglobin (HbA_{1c}) 7.0-10.0% (both inclusive) by central laboratory analysis, body mass index (BMI) ≤ 40.0 kg/m^2 and current treatment with any insulin regimen (premix, self-mix, basal only, basal-bolus (one or more boluses), bolus only, pump) for at least 3 months ± oral antidiabetics (OADs) before Visit 1 (screening) during the main trial were included in the extension trial. These subjects had completed the 52-week treatment period of the main trial (Visit 41 in trial NN1250-3582).

Subjects for whom any of the following applied were excluded from the main and extension trials: subjects using a glucagon-like peptide 1 (GLP-1) receptor agonist (exenatide, liraglutide) and/or rosiglitazone within the last 3 months before Visit 1 (screening), anticipated change in concomitant medication known to interfere significantly with glucose metabolism, contraindications or restrictions to use of the concomitant antidiabetic medication allowed in the trial (in the last 3 months before randomisation), clinically significant peripheral oedema or contraindications/restrictions to pioglitazone use, cardiovascular disease within the last 6 months before Visit 1 (screening) or uncontrolled treated/untreated severe hypertension, or with any clinically significant disease or disorders.

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

Test Product, Dose and Mode of Administration, Batch Number

IDeg 100 U/mL, 3 mL FlexPen® was injected OD with IAsp as mealtime insulin ± metformin ± pioglitazone (metformin and pioglitazone were not trial products). IDeg was to be taken OD with the evening meal. IDeg was to be administered subcutaneously in the abdomen, upper arm (deltoid region) or thigh. At the end of the trial, the subjects were to discontinue all trial products and were switched to a suitable marketed treatment at the discretion of the investigator. The batch numbers for IDeg were XP50551, XP52063, XP52237 and YP50742.

Duration of Treatment

The total duration of the trial for each subject was approximately 78 weeks including screening and follow-up visits (52 weeks in main trial NN1250-3582 and 26 weeks in extension trial NN1250-3667).

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, 3 mL SolarStar™ was administered OD according to approved labelling and dosed according to titration guidelines provided in the protocol. At the end of the trial, subjects were to discontinue all trial products and were switched to a suitable marketed treatment at the discretion of the investigator. The batch numbers for IGlar were 40C506, 40C426, 0F166A, 40C296, 40C337, 40C359 and 40C777.

IAsp (NovoRapid®/NovoLog®) 100 U/mL, 3 mL FlexPen® was to be injected in the abdomen before breakfast, lunch and the main evening meal. Additional IAsp could be administered with a fourth meal. The dose of IAsp was titrated according to titration guidelines. At the end of the trial, the subjects were to discontinue all trial products and were switched to a suitable marketed treatment at the discretion of the investigator. The batch numbers for IAsp were XP50716, XP52657, XP52945, YP51172, XP50729, YP50957, YP51142 and YP51225.

Criteria for Evaluation – Efficacy

- HbA_{1c}
- Fasting plasma glucose (FPG)
- Self-measured plasma glucose (SMPG)
  - 4-point SMPG profile (pre-breakfast, pre-lunch, pre-evening meal and bedtime)
  - 9-point SMPG profile with additional 4-point SMPG profiles

Criteria for Evaluation – Safety

- Adverse events (AEs)
- Hypoglycaemic episodes
- Physical examination
- Funduscopy / Fundusphotography (Eye Examination)
- 12-lead Electrocardiogram (ECG)
- Vital signs
- Laboratory safety parameters
- Insulin dose
- Body Weight

Statistical Methods

Analysis Sets

The following analysis sets were defined:

- Full Analysis Set (FAS): includes all randomised subjects in the main trial. In exceptional cases, subjects from the FAS could be eliminated. In such cases the elimination was to be justified and documented. The statistical evaluation of the FAS was to follow the intention-to-treat principle and subjects were to 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 were to 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".
- Extension Trial Set (ETS): included subjects receiving at least one dose of the investigational product or its comparator in the extension trial.

Analyses of all efficacy endpoints were based on the FAS as were analyses of hypoglycaemia, body weight and lipids. All other endpoints related to safety were based on the Safety Analysis Set. Analyses were repeated for the number of severe and minor treatment emergent hypoglycaemic episodes (overall and nocturnal), central laboratory parameters (ALAT/SGPT, ASAT/SGOT) and HbA_{1c} using the ETS to assess the stability of key results. The analyses of HbA_{1c} were repeated on the PP Analysis Set.

Primary Safety Analysis

- 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. AEs were coded using the most recent version (version 14.0) of the Medical Dictionary for Regulatory Activities (MedDRA) coding. Evaluation of TEAEs was based on descriptive statistics. AEs were 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 American Diabetes Association (ADA) classification into the following 5 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 plasma glucose (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. Nocturnal confirmed hypoglycaemic episodes were analysed separately. Nocturnal severe hypoglycaemic episodes were not analysed due to few number of episodes.
- Change from baseline in body weight was to be analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline body weight as covariates.
- Remaining laboratory parameters, physical examination, ECG, funduscopy/fundusphotography, vital signs and insulin dose were evaluated based on descriptive statistics.

Secondary Supportive Efficacy Analyses

- The HbA_{1c} responder endpoints ($HbA_{1c} < 7\%$ or $\leq 6.5\%$ at end of trial) with or without hypoglycaemic episodes were analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} as covariates.
- 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 fluctuation in the 9-point profile (SMPG), prandial PG increment and nocturnal PG endpoints were to be analysed separately using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and the relevant baseline value as covariates. Fluctuation in the 9-point profile (SMPG) was to be logarithm transformed before analysed.
- 4-point Profile SMPG Values Used for Dose Adjustment
  - The mean of before breakfast PG values was to be analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and country/region as fixed factors, and age and the corresponding mean PG at baseline as covariates.
  - 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.

Demography of Trial Population

The demographics and baseline characteristics in the two treatment groups were similar across treatment groups. The extension population consisted of male (54.2%) and female (45.8%) subjects with type 2 diabetes mellitus. They had a mean age of 58.9 years (ranging from 23 to 86 years of age), mean duration of diabetes of 13.5 years (ranging from 0.6 to 57.2 years), mean HbA_{1c} of 8.3%, and a mean BMI of 32.2 kg/m^2. The majority of subjects were White (82.9%), while the second-largest racial group was Black or African American (9.5%). The majority of subjects were non-Hispanic/Latino (88.0%).

	IDeg OD	IGlar OD	Total
Number of Subjects	744	248	992
Age (years)			
N	744	248	992
Mean (SD)	59.2 (9.1)	58.1 (10.0)	58.9 (9.3)
Median	60.0	58.2	59.6
Min ; Max	23.1 ; 82.1	29.1 ; 86.3	23.1 ; 86.3
Body Weight (kg)			
N	744	248	992
Mean (SD)	92.6 (17.9)	92.2 (17.2)	92.5 (17.7)
Median	92.0	91.1	91.7
Min ; Max	45.1 ; 149.6	54.0 ; 143.8	45.1 ; 149.6
BMI (kg/m^2)			
N	744	248	992
Mean (SD)	32.3 (4.7)	31.9 (4.5)	32.2 (4.6)
Median	32.5	31.6	32.4
Min ; Max	18.4 ; 41.1	19.6 ; 40.4	18.4 ; 41.1
Duration of Diabetes (years)			
N	744	248	992
Mean (SD)	13.6 (7.4)	13.4 (6.9)	13.5 (7.3)
Median	12.2	12.5	12.2
Min ; Max	0.6 ; 57.2	1.1 ; 36.2	0.6 ; 57.2
HbA_{1c} (%)			
N	744	248	992
Mean (SD)	8.3 (0.8)	8.4 (0.9)	8.3 (0.8)
Median	8.2	8.2	8.2
Min ; Max	6.7 ; 10.4	6.9 ; 12.2	6.7 ; 12.2
FPG (mmol/L)			
N	740	248	988
Mean (SD)	9.2 (3.0)	9.2 (3.2)	9.2 (3.1)
Median	8.8	9.0	8.8
Min ; Max	2.8 ; 21.4	2.8 ; 18.2	2.8 ; 21.4

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

Efficacy Results and Conclusions

After 78-weeks of treatment with IDeg + IAsp ± metformin ± pioglitazone or IGlar + IAsp ± metformin ± pioglitazone, the following was concluded:

Secondary Endpoint

- **HbA_{1c}**: The estimated mean reduction in HbA_{1c} during the trial was -1.03%-points with IDeg and -1.19%-points with IGlar with an estimated mean difference of 0.16%-point $[0.02;0.30]_{95\%\ CI}$ (FAS) after 78 weeks of treatment, which was statistically significant. After 78 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.3 (1.1) % with IDeg and 7.2 (1.0) % with IGlar. All statistical analyses done with change in HbA_{1c} as the endpoint, resulted in an upper bound of the 95% CI below the pre-specified non-inferiority margin of 0.4%.

- **Responders for HbA_{1c}:** A total of 39.1% of subjects treated with IDeg achieved HbA_{1c} <7.0% compared to 44.0% for subjects treated with IGlar. The estimated odds of achieving this target was 0.64 with IDeg compared to 0.88 with IGlar; estimated odds ratio (IDeg/IGlar) was 0.73 $[0.54;1.00]_{95\%\ CI}$. The difference between treatment groups was not statistically significant, as the 95% CI for the estimated odds ratio (IDeg/IGlar) contained 1.

- **Responders for HbA_{1c} without hypoglycaemia:** The proportion of subjects achieving HbA_{1c} < 7% without confirmed hypoglycaemic episodes was 20.7% with IDeg and IGlar. The estimated odds ratio (IDeg/IGlar) of achieving this target was 0.96 $[0.66;1.40]_{95\%\ CI.}$ The proportion of subjects achieving HbA_{1c} < 7% without severe hypoglycaemic episodes was 40.3% with IDeg and 45.1% with IGlar. The estimated odds of achieving this target

were numerically lower (by 25%) with IDeg than with IGlar. The estimated odds ratio (IDeg/IGlar) was 0.75 $[0.55;1.03]_{95\%\ CI}$.

- **FPG:** FPG decreased during the trial by 2.18 mmol/L in the IDeg group and by 2.05 mmol/L in the IGlar group after 78 weeks of treatment. The estimated mean reduction from baseline in FPG during this trial was similar (IDeg: -2.30 mmol/L and IGlar: -2.17 mmol/L); estimated mean treatment difference after 78 weeks of treatment was -0.13 mmol/L $[-0.50; 0.24]_{95\%CI}$. There was no statistically significant difference between treatment groups at the end of the trial.

- **9-point SMPG profiles:** The 9-point mean SMPG value was statistically significantly higher in the IDeg group compared with the IGlar group for all time points except at 90 minutes after the start of lunch and 90 minutes after the start of the main evening meal. After 78 weeks of treatment, the observed mean fluctuation in 9-point SMPG was 0.9 mmol/L in the IDeg group and 0.8 mmol/L in the IGlar group, estimated treatment ratio (IDeg/IGlar) was 1.07 $[0.97; 1.18]_{95\%\ CI}$. The estimated mean change in nocturnal PG (04:00 h to breakfast) was statistically significantly greater in the IDeg group (-0.43 mmol/L) than in the IGlar group (-0.09 mmol/L); estimated treatment difference (IDeg-IGlar) was -0.34 $[-0.64;-0.04]_{95\%CI}$.

- **SMPG for dosing:** Mean SMPG before breakfast, lunch, main evening meal and bedtime were reduced in both the IDeg and IGlar groups during the trial. The estimated mean SMPG value before breakfast, before lunch, and before the evening meal at Week 78 were greater in the IDeg group than in the IGlar group. After 78 weeks of treatment, 19.3% in the IDeg group and 21.9% in the IGlar group achieved the prebreakfast SMPG target < 5 mmol/L. The within-subject variability in SMPG was significantly lower for IDeg compared to IGlar; estimated treatment ratio [IDeg/IGlar]; 0.93 $[0.86;1.00]_{95\%CI}$, when the 95% CI values [0.860;0.998] are not rounded up, the upper limit of the 95% CI is shown to be less than 1.

Safety Results and Conclusions

After 78-weeks of treatment with IDeg + IAsp ± metformin ± pioglitazone or IGlar + IAsp ± metformin ± pioglitazone, the following was concluded:

Primary Endpoints

- **Adverse events:** A similar percentage of subjects reported adverse events in the IDeg and IGlar groups (83.7% and 82.9%, respectively). The rate of all adverse events was similar for the IDeg and IGlar groups (411 and 403 events per 100 PYE, respectively). The rates of severe adverse events were reported at similar rates in both groups (24 and 20 events per 100 PYE in the IDeg and IGlar groups, respectively).

  The rates of adverse events probably or possibly related to trial drug were similar in both groups (9 and 15 events per 100 PYE in the IDeg group, and 6 and 11 events per 100 PYE in the IGlar group). The most frequently reported adverse events in both treatment groups were upper respiratory tract infection, nasopharyngitis and headache. A small proportion of subjects in each treatment group reported injection-site reactions (4.2% in the IDeg group and 3.2% in the IGlar group).

- **Deaths, serious adverse events and other significant adverse events:** Three (3) deaths (brain stem haemorrhage, unknown cause, metastases to central nervous system [bronchial carcinoma]) occurred during this extension trial, all in the IDeg treatment group. Overall, 13 deaths (11 in the IDeg treatment group and 2 in the IGlar group) occurred in both main and extension trials.

  A total of 139 (18.5%) subject reported 194 SAEs in the IDeg group while 53 (21.1%) subjects reported 63 SAEs in the IGlar group. The rate of serious adverse events was the same in both groups (20 events per 100 PYE). In both groups, the most frequently reported SAEs (frequency ≥ 1%) were hypoglycaemia (1 event per 100 PYE in both groups), coronary artery disease (1 event per 100 PYE in both groups), cardiac failure (< 1 and 1 event per 100 PYE in the IDeg and IGlar groups, respectively), and chronic obstructive pulmonary disease (< 1 and 1 event per 100 PYE in the IDeg and IGlar groups, respectively).

A similar percentage of subjects withdrew from the trial due to AEs in the IDeg 31 (4.1%) and the IGlar 9 (3.6%) group in the main trial and 4 (0.5%) subjects in the IDeg group and none in the IGlar group in the extension trial. The most frequently reported AE leading to withdrawal was weight increase (0.8% and 1.2% of subjects in the IDeg and IGlar groups, respectively).

- **Hypoglycaemic episodes:** The observed rate of confirmed and nocturnal confirmed hypoglycaemic episodes, per 100 PYE was 1039 and 134 for IDeg and 1271 and 176 for IGlar. The estimated rate ratio (IDeg/ IGlar) for confirmed hypoglycaemic episodes was 0.85 $[0.70;1.02]_{95\% CI}$, whereas the estimated rate of nocturnal confirmed hypoglycaemia was significantly lower with IDeg (24%) than with IGlar; estimated rate ratio (IDeg/ IGlar) was was 0.76 $[0.58 ; 1.00]_{95\% CI}$, when the 95% CI values [0.579;0.996] were not rounded up, the upper limit of the 95% CI was shown to be less than 1.

  The observed rates of severe and nocturnal severe hypoglycaemia per 100 PYE were 5 and 2 for IDeg and 6 and 1 for IGlar, respectively. The estimated rate ratio (IDeg/ IGlar) for severe hypoglycaemia was $0.83 [0.43;1.61]_{95\% CI}$.

- **Vital signs, ECG, Funduscopy**, **physical examination and laboratory values**: No apparent changes from baseline to end of treatment or differences between the two treatment groups were observed.

- **Body weight:** IDeg was associated with a numerically smaller weight gain than IGlar after 78 weeks of treatment (the estimated treatment difference (IDeg-IGlar) was -0.34 kg $[-1.05;0.38]_{95\% CI}$. The mean (SD) body weight at baseline and at the end of the trial was 92.6 (17.8) kg and 96.6 (19.3) kg in the IDeg group and 92.1 (17.1) kg and 96.5 (18.7) kg in the IGlar group, respectively.

- **Insulin Dose:** For most of the duration of the 78-week trial, the mean total daily (basal and bolus) insulin doses were numerically higher in the IDeg group than in the IGlar group; whereas at Week 78 the mean total daily insulin doses were similar for IDeg and IGlar (147 U [1.50 U/kg]). The mean daily basal insulin dose after 78 weeks was 75 U (0.76 U/kg) for IDeg and 70 U (0.71 U/kg) for IGlar. The mean total daily bolus insulin dose after 78 weeks was 73 U (0.75 U/kg) for the IDeg group and 77 U (0.78 U/kg) for the IGlar group. After 78 weeks, the insulin dose ratio (U) of IDeg/IGlar was 1.00 for total daily insulin dose, 1.08 for total daily basal insulin dose and 0.94 for total daily bolus insulin dose, hence mean basal and bolus doses were 8% higher and 6% lower with IDeg compared with IGlar, respectively.

Conclusions

This confirmatory, randomised, controlled, 78-week trial investigated the long-term safety and efficacy of treatment with IDeg versus IGlar both administered once daily in a basal-bolus regimen with IAsp as mealtime insulin ± metformin, ± pioglitazone in subjects with type 2 diabetes mellitus. The data support the following conclusions:

- In this trial, no safety issues are identified with IDeg + IAsp after 78 weeks of treatment.
- There is no apparent difference between IDeg + IAsp and IGlar + IAsp with respect to AEs and standard safety parameters.
- The rate of confirmed hypoglycaemic episode is numerically lower with IDeg + IAsp than with IGlar + IAsp.
- Subjects treated with IDeg + IAsp experience a lower rate of nocturnal confirmed hypoglycaemic episodes compared to subjects treated with IGlar + IAsp.
- The average total daily insulin dose is similar in subjects treated with IDeg + IAsp and subjects treated with IGlar + IAsp.
- Treatment with IDeg + IAsp effectively improves long-term glycaemic control as measured by HbA_{1c}.

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 27-May-2011; 1 December 2011 (relates to update of a single event for one subject); and 22 December 2011 (relates to update of a single event for another subject).