2 Synopsis

Trial Registration ID-number NCT00972283	**IND Number** 76,496 **EudraCT number** 2008-005777-35
Title of Trial Comparison of NN1250[1] With Insulin Glargine Plus Insulin Aspart With/Without Metformin and With/Without Pioglitazone in Type 2 Diabetes (BEGIN™)	
Investigators There were 124 principal investigators in this trial. Dr. [redacted], from [redacted], [redacted], [redacted], [redacted], was appointed signatory investigator.	
Trial Sites A total of 123 sites in 12 countries enrolled subjects: Bulgaria (8 sites), Germany (8 sites), Hong Kong (1 site), Ireland (4 sites), Italy (11 sites), Romania (5 sites), Russia (6 sites), Slovakia (4 sites), South Africa (5 sites), Spain (9 sites), Turkey (3 sites) and the United States (U.S.) (59 sites).	
Publications Results from this trial have not been published at the time of this report.	
Trial Period 01 September 2009 to 28 October 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

To confirm the efficacy of insulin degludec (IDeg) + insulin aspart (IAsp) ± oral antidiabetic drugs (OADs) in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA_{1c}) after 52 weeks of treatment. This was done by comparing the difference in change from baseline in HbA_{1c} after 52 weeks of treatment between IDeg + IAsp ± OAD(s) and insulin glargine (IGlar) + IAsp ± OAD(s) 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 IDeg + IAsp ± OAD(s) to IGlar + IAsp ± OAD(s) after 52 weeks of treatment in terms of:

- Hypoglycaemic episodes
- Fasting plasma glucose (FPG) from central laboratory
- Within-subject variability in prebreakfast self-measured plasma glucose (SMPG)
- Frequency of responders for HbA_{1c} without hypoglycaemic episodes

To compare efficacy and safety in terms of:

- Frequency of responders for HbA_{1c}
- 9-point profile (SMPG)
- 4-point profile (SMPG) for dose adjustments
- Insulin dose
- Body weight
- Adverse events (AEs)
- Hypoglycaemic episodes
- Clinical and laboratory assessments
- Cardiovascular risk markers
- Patient reported outcomes (PRO)

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

Methodology

This was a confirmatory 52-week, multicentre, multinational, open-label, randomised, active controlled, treat-to-target, parallel-group trial comparing the efficacy and safety of IDeg and IGlar in a basal-bolus regimen with IAsp as mealtime insulin ± metformin ± pioglitazone in subjects with type 2 diabetes mellitus.

The subjects attended a screening visit (Visit 1) in order to assess their eligibility. If found eligible, the subjects were randomised 3:1 into 1 of the 2 treatment arms (IDeg or IGlar) at Visit 2 (Week 0). At Visit 2 (Week 0) previous diabetes treatments, except metformin or pioglitazone were to be discontinued. Stratification was carried out according to the insulin regimen at screening (basal-bolus [basal insulin at least 1/day and bolus insulin at least 2/day, or pump], basal only [basal insulin at least 1/day and no bolus insulin], or other [any other insulin regimen not mentioned above, including regimen with premixed insulin preparations]). In the period between Visit 3 (Week 1) and Visit 28 (Week 26), the subject's insulin dose was titrated weekly and in the period between Visit 28 (Week 26) to Visit 41 (Week 52) the subject's insulin dose was titrated every 2 weeks. Insulin titration was according to the insulin titration guideline provided in the protocol. The contacts between trial site and subjects were a combination of trial site visits and phone contacts.

For subjects that withdrew from the trial early or who chose not to continue in an additional 26-week extension trial (separate protocol and informed consent), a follow-up visit (Visit 42 [Week 53]) at least 7 days after end of trial treatment was to be performed to ensure assessment of any safety issues related to treatment discontinuation.

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 subjects included in the trial is 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)
Withdrawn at/after Randomisation	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)	0 (0.0)	3 (0.3)
Non-Compliance With Protocol	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)
Completed	618 (81.9)	211 (84.1)	829 (82.4)
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)

N: Number of subjects
%: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Male or female subjects aged ≥ 18 years, with type 2 diabetes mellitus (diagnosed clinically) ≥ 6 months, 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 ± OADs prior to Visit 1 (screening) were included in the trial.

Subjects using glucagon-like peptide 1 (GLP-1) receptor agonist (exenatide, liraglutide) and/or rosiglitazone within

the last 3 months prior to 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 prior to randomisation), clinically significant peripheral oedema or contraindications/restrictions to pioglitazone use, cardiovascular disease within the last 6 months prior to Visit 1 (screening) or uncontrolled treated/untreated severe hypertension, or with any clinically significant disease or disorders were excluded from the trial.

Test Product, Dose and Mode of Administration, Batch Number

IDeg 100 U/mL, 3 mL FlexPen® was administered once-daily (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. Batch numbers.: XP50551 and XP52237

Duration of Treatment

The treatment period was 52 weeks.

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, the subjects were to discontinue all trial products and were switched to a suitable marketed treatment at the discretion of the investigator. Batch numbers: 40C426, 40C296, 40C337, 40C359, and 40C506.

IAsp (NovoRapid®/NovoLog®) 100 U/mL, 3 mL FlexPen® was to be injected in the abdomen prior to breakfast, lunch and 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. Batch numbers: XP50716 and XP50729.

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - 4-point SMPG profile (pre-breakfast, pre-lunch, pre-evening meal and bedtime)
  - 9-point profile (SMPG) with additional 4-point Profiles (SMPG)
- PRO questionnaire

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes
- Body weight
- 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".

Analyses of all efficacy endpoints were based on the FAS as were analyses of hypoglycaemia, body weight, lipids, and cardiovascular risk markers. All other endpoints related to safety were based on the Safety Analysis Set. The robustness of the results for the primary endpoint was explored by additional analysis on the PP Analysis Set.

Primary Efficacy Analysis

Change from baseline in HbA_{1c} after 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 value as covariates. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval (CI) for the treatment difference (investigational product–comparator) for the mean change in HbA_{1c} was below or equal to 0.4%. Superiority was confirmed if the upper bound of the two-sided 95% CI was < 0%.

Secondary Confirmatory Analyses

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

1. Number of treatment emergent confirmed (severe or minor [PG < 3.1 mmol/L]) hypoglycaemic episodes
   - The number of treatment emergent confirmed hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate.
2. Change from baseline in FPG after 52 weeks of treatment (analysed at central laboratory)
   - Change from baseline in FPG after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.
3. Within-subject variability in pre-breakfast SMPG
   - 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 assumes independent within- and between-subject errors with variances depending on treatment. Within-subject variability as measured by CV% for a treatment can be calculated from the corresponding residual variance.
4. Responder without hypoglycaemic episodes (HbA_{1c} <7.0% at end of trial and no confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks)
   - Responder without hypoglycaemic episodes is a dichotomous endpoint (responder/non-responder) that is defined based on whether a subject has met the American Diabetes Association (ADA) HbA_{1c} target at end of trial (HbA_{1c} < 7.0% at end of trial) without confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after last randomised treatment. Responder analysis was based on a logistic regression model using the same factors and covariates as for the primary analysis.

Secondary Supportive Efficacy Analyses

- The HbA_{1c} responder endpoints (HbA_{1c} < 7.0% 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.

- 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 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 analysis of the primary endpoint.
- SMPG values used for dose adjustment
  - The mean of before meal and before bedtime PG values after 52 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 (pre-breakfast SMPG < 5 mmol/L) 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.
- The change in patient reported outcome score from baseline was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.

Safety Analyses

- A Treatment Emergent Adverse Event (TEAE) was defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. Adverse Events were coded using 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 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 nocturnal confirmed hypoglycaemia 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 confirmed hypoglycaemic episodes were analysed separately.
- Change from baseline in hsCRP, NT-proBNP, lipid endpoints, and body weight were analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.
- Remaining laboratory parameters, physical examination, ECG, funduscopy / fundusphotography, vital signs and insulin dose were evaluated based on descriptive statistics.

Demography of Trial Population

In general, the two groups were comparable in baseline characteristics, with only marginal differences between the treatment groups. The population consisted of male and female subjects with type 2 diabetes mellitus, with a mean age of 58.9 years and a mean duration of diabetes of 13.5 years (ranging from 0.6 to 57.2 years), with a mean HbA_{1c}

of 8.3% and a mean BMI of 32.2 kg/m^2. The majority of trial subjects were White (82.9%) or Black or African American (9.5%).

	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
HbA1c (%)			
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 52 weeks of treatment with IDeg + IAsp ± metformin ± pioglitazone or IGlar + IAsp ± metformin ± pioglitazone, the following was concluded:

Primary Endpoint

- **HbA_{1c}**: IDeg effectively improved glycaemic control (non-inferiority to IGlar in terms of lowering HbA_{1c} was confirmed); estimated mean treatment difference (IDeg–IGlar) was 0.08 % points $[-0.05; 0.21]_{95\% CI}$. The estimated mean change in HbA_{1c} was −1.1 % points with IDeg and −1.2 % points with IGlar. After 52 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.1 (1.0)% with IDeg and 7.1 (1.0)% with IGlar.

Secondary Endpoints

Confirmatory Endpoints

- **Confirmed hypoglycaemia:** Please see Safety Results and Conclusions
- **FPG:** FPG decreased during the trial to similar observed mean (SD) levels; 6.8 (2.5) mmol/L with IDeg and 7.1 (2.7) mmol/L with IGlar. The estimated mean reduction in FPG was −2.25 mmol/L with IDeg and −1.96 mmol/L

with IGlar, and the estimated mean treatment difference (IDeg–IGlar) was −0.29 mmol/L $[-0.65; 0.06]_{95\%CI}$. Superiority could not be confirmed and consequently, the hierarchical testing procedure was stopped.

- **Within-subject variability (CV%) in prebreakfast SMPG:** The estimated treatment ratio (IDeg/IGlar) was 0.94 $[0.87; 1.01]_{95\% CI}$, meaning that there was no statistically significant difference in the day-to-day variability in prebreakfast SMPG.
- **HbA_{1c} < 7.0% without confirmed hypoglycaemia**: The observed proportion of subjects achieving HbA_{1c} < 7.0% without confirmed hypoglycaemic episodes was 24.4% with IDeg and 23.2% with IGlar. The estimated odds of achieving this target were similar between IDeg and IGlar; odds ratio (IDeg/IGlar) was 1.02 $[0.72; 1.47]_{95\% CI}$.

Supportive Efficacy Endpoints

- **Responders for HbA_{1c}:** The observed proportion of subjects achieving HbA_{1c} < 7.0% was 49.5% with IDeg and 50.0% with IGlar, and the observed proportion of subjects achieving HbA_{1c} ≤6.5% was 30.8% with IDeg and 33.1% with IGlar. The estimated odds of achieving these targets were similar between treatments (HbA_{1c} < 7.0% odds ratio (IDeg/IGlar) 0.88 $[0.65; 1.21]_{95\% CI}$; HbA_{1c} ≤ 6.5% odds ratio (IDeg/IGlar) 0.83 $[0.60; 1.15]_{95\% CI}$).
- **9-point SMPG profiles:** The estimated overall mean of the 9-point profile was higher with IDeg than with IGlar, with an estimated treatment difference (IDeg–IGlar) of 0.44 $[0.20; 0.69]_{95\% CI}$. There was no statistically significant difference for fluctuation in 9-point SMPG profiles, changes in prandial PG increments, and changes between nocturnal SMPG measurements between IDeg and IGlar.
- **SMPG for dosing**: After 52 weeks, the proportion of subjects who achieved the pre-specified prebreakfast SMPG titration target of <5 mmol/L was 18.7% with IDeg and 21.1% with IGlar. The observed median time to achieve the prebreakfast SMPG titration target for the first time was 12 weeks for both IDeg and IGlar.
- **PRO:** Overall, the results related to PRO appeared similar between the two treatment groups, with only marginal changes over time. The Work Productivity score improved more with IDeg than with IGlar based on the Diabetes Productivity Measure (DPM); estimated treatment difference (IDeg–IGlar) was 2.7 points $[0.3; 5.1]_{95\%CI}$. The Bodily Pain score based on the SF-36, v2 form deteriorated less with IDeg compared with IGlar (meaning less bodily pain); estimated treatment difference (IDeg–IGlar) was 1.4 points $[0.1; 2.7]_{95\%CI}$.

Safety Results and Conclusions

From the results of this 52-week trial of treatment with IDeg + IAsp ± metformin ± pioglitazone or IGlar + IAsp ± metformin ± pioglitazone, the following can be concluded:

Secondary Safety Endpoints

Confirmatory Safety Endpoint

- **Confirmed hypoglycaemic episodes:** Superiority of IDeg to IGlar was demonstrated in terms of a lower rate of confirmed hypoglycaemic episodes; estimated rate ratio (IDeg/IGlar) 0.82, $[0.69; 0.99]_{95\% CI}$. The estimated rate of confirmed hypoglycaemia was 18% lower with IDeg than with IGlar. The observed rate of confirmed hypoglycaemic episodes per 100 PYE was 1109 episodes for IDeg and 1363 episodes for IGlar.

Supportive Safety Endpoints

- **Hypoglycaemic episodes:**
  - There were fewer nocturnal confirmed hypoglycaemic episodes with IDeg compared with IGlar. The observed rate of nocturnal confirmed hypoglycaemic episodes, per 100 PYE was 139 for IDeg and 184 for IGlar. There was a statistically significantly lower rate of nocturnal confirmed hypoglycaemia with IDeg compared with IGlar; estimated rate ratio (IDeg/IGlar) for nocturnal confirmed hypoglycaemia were 0.75 $[0.58; 0.99]_{95\% CI}$.
  - The observed rates of severe and nocturnal severe hypoglycaemic episodes per 100 PYE were 6 (41 episodes) and 2 (14 episodes) for IDeg and 5 (12 episodes) and 1 (3 episodes) for IGlar, respectively.
- **Body weight:** There was no statistically significant difference in weight gain between IDeg and IGlar; estimated treatment difference in change in body weight (IDeg–IGlar) was −0.31 kg $[-0.98; 0.37]_{95\% CI}$. The mean (SD) body weight at baseline and at the end of the trial was 92.6 kg (17.8) and 96.2 (19.2) in the IDeg group and 92.1

kg (17.1) and 96.0 kg (18.6) in the IGlar group, respectively.

- **Adverse events:** A numerically similar percentage of subjects reported AEs in the IDeg and IGlar groups (81.0% and 79.3%, respectively). The observed rate of all AEs was similar for the IDeg and IGlar groups (438 and 431 events per 100 PYE, respectively). The observed rate of AEs possibly or probably related to investigational product was higher with IDeg than with IGlar (31 and 20 events per 100 PYE, respectively). The most frequently reported AEs in both treatment groups were nasopharyngitis and upper respiratory tract infection. The most frequently reported AEs possibly or probably related to investigational product were increased weight and hypoglycaemia in both treatment groups. The percentage of subjects with injection-site reactions was low in both treatment groups (3.6% [27 subjects, 36 events] and 2.8% [7 subjects, 7 events], in the IDeg and IGlar groups, respectively).
- **Deaths, serious adverse events and other significant adverse events:** 10 deaths were reported in this trial: 8 (arteriosclerosis and hypertensive heart disease in 1 subject, myocardial infarction [2 deaths], haemorrhage intracranial, cardio-respiratory arrest, haematemesis, cardiac arrest, and road traffic accident) in the IDeg group and 2 (metastatic neoplasm, myocardial infarction) in the IGlar group, in line with the 3:1 randomisation. A total of 112 (14.9%) subjects reported 140 SAEs in the IDeg group while 40 (15.9%) subjects reported 46 SAEs in the IGlar group. The observed event rate per 100 PYE of SAEs was similar with IDeg (21) and with IGlar (20). The most-frequently reported SAE was hypoglycaemia in both treatment groups. A similar percentage of subjects withdrew from the trial due to AEs in the IDeg (4.1% [31 subjects, 41 events]) and the IGlar (3.6% [9 subjects, 9 events]) groups. The most frequently reported AE leading to withdrawal was increased weight.
- **Vital signs, ECG, funduscopy**, **physical examination and laboratory values**: No apparent differences from baseline to end of treatment or between the two treatment groups were observed.
- **Insulin dose:** The mean daily basal insulin dose after 52 weeks was 74 U (0.75 U/kg) for the IDeg group and 67 U (0.69 U/kg) for the IGlar group. The mean total daily bolus insulin dose after 52 weeks was 70 U (0.72 U/kg) for the IDeg group and 73 U (0.74 U/kg) for the IGlar group. The ratio of IDeg/IGlar mean daily insulin dose (U) after 52 weeks of treatment was 1.09 for basal insulin, 0.97 for bolus insulin, and 1.03 for total insulin, meaning that observed mean doses were similar between the two treatment groups.

Conclusions

This confirmatory, randomised, controlled, 52-week trial demonstrates the efficacy and safety of 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:

- IDeg effectively improves long-term glycaemic control as measured by HbA_{1c} (non-inferiority to IGlar confirmed).
- FPG decreases to a similar level in both treatment groups. The day-to-day variation in self-measured prebreakfast plasma glucose is similar with IDeg and IGlar.
- The proportion of subjects achieving the treatment target ($HbA_{1c} < 7.0\%$) without confirmed hypoglycaemia is similar with IDeg and IGlar.
- IDeg is superior to IGlar in terms of a lower rate of confirmed hypoglycaemic episodes. In addition, subjects treated with IDeg experience a lower rate of nocturnal confirmed hypoglycaemic episodes compared to IGlar.
- No safety issues are identified with IDeg with respect to AEs and standard safety parameters in this trial.

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 26 November 2010.