2 Synopsis

Trial Registration ID-number NCT01068665	**IND Number –** 76496 **EudraCT number –** 2009-010662-28
Title of Trial Comparison of NN1250[1] with Insulin Glargine in Subjects with Type 2 Diabetes (BEGIN™)	
Investigator(s) [redacted], MD was appointed as signatory investigator.	
Trial Site(s) The trial was conducted at 106 sites in 8 countries: Canada (11 sites), France (6 sites), Ireland (3 sites), Russian Federation (7 sites), South Africa (4 sites), Ukraine (2 sites), United Kingdom (18 sites) and United States (U.S.) (55 sites).	
Publications Results from this trial have not been published at the time of this report.	
Trial Period 01 March 2010 to 26 November 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

- To confirm the efficacy of insulin degludec (IDeg) 200 U/mL once daily (OD) + metformin ± dipeptyl peptidase-4 (DPP-4) inhibitor 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 IDeg 200 U/mL OD + metformin ± DPP-4 inhibitor and insulin glargine (IGlar) OD + metformin ± DPP-4 inhibitor 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 200 U/mL OD + metformin ± DPP-4 inhibitor over IGlar OD + metformin ± DPP-4 inhibitor after 26 weeks of treatment in terms of:

- Treatment-emergent severe or minor hypoglycaemic episodes
- Fasting plasma glucose (FPG) analysed at a central laboratory
- Within-subject variability in pre-breakfast self-measured plasma glucose (SMPG)
- Frequency of responders for HbA_{1c} (< 7.0%) without hypoglycaemic episodes

To compare efficacy and safety in terms of:

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

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

Methodology

The present trial was a confirmatory 26-week randomised, controlled, open-labelled, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of IDeg 200 U/mL and IGlar both administered OD in combination with metformin ± DPP-4 inhibitor in insulin-naïve subjects diagnosed with type 2 diabetes mellitus currently treated with oral antidiabetic drugs (OADs) qualifying for intensified treatment.

Subjects attended a screening visit (Visit 1) in order to assess their eligibility, followed by a randomisation visit (Visit 2) approximately 1 week later. At Visit 2 the subject's current antidiabetic treatment was discontinued except for metformin and DPP-4 inhibitor, if applicable. After discontinuation of all OADs other than metformin ± DPP-4 inhibitor (as applicable) the subjects were randomised to one of two parallel treatment arms consisting of either IDeg 200 U/mL or IGlar (1:1; IDeg:IGlar) and continued metformin ± DPP-4 inhibitor treatment. Subjects were instructed to continue with the same total daily dose of metformin ± DPP-4 inhibitor as before the start of the trial. A follow-up visit (Visit 29) took place no less than 1 week post-treatment for all subjects. This follow-up visit was offered to any subjects withdrawing prematurely at any point during the trial.

Number of Subjects Planned and Analysed

The planned number of subjects to be screened (642), randomised (450) and complete the trial (382) was based on the sample size calculation. The numbers of subjects included in the trial are shown below.

	IDeg 200 U/mL OD N (%)	IGlar OD N (%)	Total N (%)
Screened			697
Screening Failures			237
Withdrawn before Randomisation			0
Randomised	230 (100.0)	230 (100.0)	460 (100.0)
Exposed	228 (99.1)	228 (99.1)	456 (99.1)
Withdrawn at/after Randomisation	30 (13.0)	29 (12.6)	59 (12.8)
Adverse Event	5 (2.2)	4 (1.7)	9 (2.0)
Ineffective Therapy	0 (0.0)	2 (0.9)	2 (0.4)
Non-Compliance With Protocol	5 (2.2)	2 (0.9)	7 (1.5)
Withdrawal Criteria	3 (1.3)	9 (3.9)	12 (2.6)
Other	17 (7.4)	12 (5.2)	29 (6.3)
Completed	200 (87.0)	201 (87.4)	401 (87.2)
Full Analysis Set	228 (99.1)	229 (99.6)	457 (99.3)
PP Analysis Set	201 (87.4)	212 (92.2)	413 (89.8)
Safety Analysis Set	228 (99.1)	228 (99.1)	456 (99.1)

N: Number of subjects
%: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Insulin-naïve 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) ≤ 45.0 kg/m^2 and with current treatment: metformin monotherapy or metformin in any combination with insulin secretagogues (sulphonylurea [SU] or glinide), DPP-4 inhibitor, α-glucosidase-inhibitor (acarbose) with unchanged dosing for at least 3 months prior to Visit 1 were included in the trial.

Subjects were excluded from the trial for the following reasons: treatment with thiazoledinediones (TZDs), exenatide or liraglutide within 3 months prior to Visit 1, anticipated change in concomitant medication known to interfere significantly with glucose metabolism, previous participation in this trial, known or suspected allergy to any of the trial products or related products and any clinically significant disease or disorder, except for conditions associated with type 2 diabetes, which in the investigator's opinion could have interfered with the results of the trial.

Test Product, Dose and Mode of Administration, Batch Number

IDeg 200 U/mL, 3 mL PDS290 (pre-filled pen). IDeg 200 U/mL was to be injected subcutaneously in the thigh, upper arm (deltoid region) or abdomen. Batch No.: XL70030; XL70031; YP50863; YP50598-1; YP50490; YL70001

Duration of Treatment

Total duration for the individual subjects participating in the trial was approximately 29 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, 3 mL SoloStar™ pen. IGlar was to be injected subcutaneously in the thigh, upper arm (deltoid region) or abdomen. Batch No.: 40C408; 40C442; 40C442_1; 40C712; 40C715; 40C715-1; 40C777

Insulin NPH (Insulatard®/Prothaphane®/Novolin N™) 100 IU/mL, 3 mL FlexPen®. Since insulin NPH is an intermediate acting insulin, it was to be administered BID. The first dose of insulin NPH was to be given at the earliest 24 h after last dose of IDeg 200 U/mL or IGlar. Batch No.: XP52643 and YP50831

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - 1-point profile (SMPG)
  - 9-point profile (SMPG) with additional 1-point profile (SMPG)
- PRO questionnaire

Criteria for Evaluation – Safety

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

Statistical Methods

Analysis Sets:

- Full Analysis Set (FAS): includes all randomised subjects. 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 (ITT) principle and subjects were to contribute to the evaluation "as randomised".
- Per Protocol (PP) Analysis Set: includes subjects without any major protocol violations that may affect 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): includes all subjects who received at least one dose of the investigational product or its comparator. Subjects in the safety set were to contribute to the evaluation "as treated".

Primary Efficacy Analysis

Change from baseline in HbA_{1c} after 26 weeks of treatments was to be analysed using an Analysis of Variance (ANOVA) method with treatment, antidiabetic therapy at screening, sex and region (Europe (France, UK, Ukraine and Russia), North America (Canada and US) and South Africa) as fixed factors, and age and baseline HbA_{1c} as covariates.

Confirmatory Secondary Analyses

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

1. Number of treatment emergent 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
2. Change from baseline in fasting plasma glucose (FPG) after 26 weeks of treatment (analysed at central laboratory)
   - Superiority was considered confirmed if the 95% confidence interval for the treatment difference (investigational product minus comparator) was entirely below zero
3. Within-subject variability as measured by CV% in pre-breakfast SMPG after 26 weeks of treatment
   - Superiority was considered confirmed if the 95% confidence interval for the treatment ratio of within-subject CV% (investigational product / comparator) was entirely below one
4. Responder without hypoglycaemic episodes (HbA_{1c} <7.0% at 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

Supportive Secondary Efficacy Analyses

- The HbA_{1c} responder endpoints 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 (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 primary analysis.
- SMPG values used for dose adjustment: The mean of before meal/before breakfast PG values after 26 weeks of treatment was analysed using an ANOVA method similar to that used for the primary analysis. 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 will assume 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.
- The change in patient reported outcome score from baseline was analysed separately using an ANOVA method similar to that used for the primary analysis.

Safety Analyses

- A treatment emergent adverse event (TEAE) was defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. Adverse events were coded using the most recent version (version 13.0) of the Medical Dictionary for Regulatory Activities (MedDRA) coding. Evaluation of TEAEs was based on descriptive statistics. AEs and hypoglycaemic episodes are also presented as the rate of the events per 100 patient years of exposure (PYE).
- A hypoglycaemic episode was defined as treatment emergent using the same definition as for TEAE above. A hypoglycaemic episode with time of onset between 00:01 and 05:59 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 (56mg/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.

- Antibodies specific for: IDeg, 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 26 weeks of treatment was analysed using an ANOVA method similar to that used for the primary analysis.
- Remaining laboratory parameters, physical examination, ECG, funduscopy / fundusphotography and vital signs were evaluated based on descriptive statistics.

Demography of Trial Population

The demographics and baseline characteristics in the two treatment groups were similar with only marginal differences between the treatment groups. The different pretrial regimens were equally represented in the treatment groups. The trial randomized slightly more male subjects than female subjects (53% vs. 47%, respectively). Approximately one-fifth (20.4%) of all subjects were elderly (>65 years of age) (19.3% elderly subjects in the IDeg group and 21.4% in the IGlar group). Most of the subjects who reported their race were White (~78%) and of non-Hispanic/Latino origin (~91%), while the second largest group was Black or African American (~14%).

The baseline demographic and diabetes characteristics are shown in the table below.

	IDeg 200 U/mL OD	IGlar OD	Total
Number of Subjects	228	229	457
Age (years)			
N	228	229	457
Mean (SD)	57.8 (9.0)	57.3 (9.4)	57.5 (9.2)
Median	59.5	58.0	59.0
Min ; Max	33.0 ; 78.0	31.0 ; 78.0	31.0 ; 78.0
Body Weight (kg)			
N	228	229	457
Mean (SD)	92.2 (18.5)	92.7 (18.4)	92.5 (18.4)
Median	89.8	92.5	92.0
Min ; Max	53.7 ; 148.5	50.0 ; 148.7	50.0 ; 148.7
BMI (kg/m^2)			
N	228	229	457
Mean (SD)	32.2 (5.4)	32.7 (5.3)	32.4 (5.4)
Median	31.1	32.5	31.8
Min ; Max	21.8 ; 45.1	21.9 ; 45.1	21.8 ; 45.1
Duration of Diabetes (years)			
N	228	229	457
Mean (SD)	8.4 (6.7)	8.0 (5.6)	8.2 (6.2)
Median	7.5	6.8	6.9
Min ; Max	0.6 ; 59.7	0.5 ; 40.7	0.5 ; 59.7
HbA1c (%)			
N	228	229	457
Mean (SD)	8.3 (1.0)	8.2 (0.9)	8.3 (0.9)
Median	8.2	8.2	8.2
Min ; Max	5.2 ; 10.8	6.7 ; 10.4	5.2 ; 10.8
FPG (mmol/L)			
N	228	226	454
Mean (SD)	9.6 (2.9)	9.7 (2.6)	9.6 (2.7)
Median	9.4	9.5	9.5
Min ; Max	3.5 ; 25.1	4.2 ; 21.0	3.5 ; 25.1

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

Efficacy Results and Conclusions

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

Primary Endpoint

- **HbA_{1c}:** IDeg effectively improved glycaemic control in terms of lowering HbA_{1c} (non-inferiority to IGlar confirmed); estimated mean treatment difference (IDeg−IGlar): 0.04% point $[-0.11; 0.19]_{95\% CI}$. The estimated mean change in HbA_{1c} was -1.18%-points with IDeg and -1.22%-points with IGlar. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.0 (0.9)% with IDeg and 6.9 (1.0)% with IGlar.

Secondary Efficacy Endpoints

Confirmatory Endpoints

- **Confirmed hypoglycaemia:** Please see the safety conclusions.
- **FPG:** The estimated mean change in FPG was greater with IDeg (-3.94 mmol/L) than with IGlar (-3.52 mmol/L) with a treatment difference (IDeg-IGlar) of -0.42 mmol/L, $[-0.78; -0.06]_{95\% CI}$. The hierarchical testing was stopped prior to testing this endpoint for superiority. FPG decreased during the trial to mean (SD) levels of 5.9 (1.9) mmol/L with IDeg and 6.3 (2.2) mmol/L with IGlar.
- **Within-subject variability in pre-breakfast PG:** The estimated mean treatment ratio (IDeg/IGlar) for the within-subject variation in prebreakfast SMPG was 0.92 $[0.84; 1.01]_{95\% CI}$.
- **HbA_{1c} <7.0% without confirmed hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% was 45.2% with IDeg and 44.7% with IGlar. The estimated odds ratio (IDeg/IGlar) of achieving this target HbA_{1c} <7.0% without confirmed hypoglycaemic episodes was 1.05 $[0.69; 1.61]_{95\% CI}$.

Supportive Endpoints

- **Responder for HbA_{1c} without severe hypoglycaemia:** A total of 55.7% and 40.5% of subjects treated with IDeg achieved HbA_{1c} <7% and ≤6.5% without severe hypoglycaemic episodes, respectively, compared to the proportion of 58.6% and 45.6% of subjects treated with IGlar. The estimated odds of achieving the target of <7% without severe hypoglycaemic episodes were numerically lower (12%) with IDeg compared to IGlar (odds ratio (IDeg/IGlar): 0.88 $[0.57; 1.38]_{95\% CI}$). The estimated odds of achieving the target of ≤6.5% were numerically lower (21%) with IDeg compared to IGlar (odds ratio (IDeg/IGlar): 0.79 [0.51; 1.23]).
- **9-point SMPG Profiles:** Fluctuation in 9-point profile was 1.2 mmol/L with IDeg and 1.2 mmol/L with IGlar. The mean fluctuation of the 9-point SMPG profile was similar in the IDeg and IGlar groups; the estimated treatment ratio was 1.03 $[0.93; 1.14]_{95\ CI\%}$. The decrease in nocturnal PG (bedtime to breakfast) was numerically lower with IDeg than with IGlar after 26 weeks of treatment; estimated mean difference −0.24 mmol/L $[-0.78; 0.29]_{95\% CI}$.
- **SMPG target <5.0 mmol/L (90 mg/dL):** Approximately 30% of subjects in both treatment groups achieved the prebreakfast SMPG target < 5 mmol/L. Statistical analysis did not identify a difference between the treatment groups; estimated hazard ratio: 1.15 $[0.93; 1.41]_{95\% CI}$.
- **PRO:** The subjects' perception of both 'Bodily Pain' and 'Vitality' as measured by the SF-36 questionnaire improved more with IDeg than with IGlar; estimated treatment difference (IDeg─IGlar): 1.6 $[0.1; 3.2]_{95\% CI}$ and 1.5 $[0.1; 3.0]_{95\% CI}$, respectively.

Safety Results and Conclusions

From the results of this 26-week trial of treatment with IDeg or IGlar, the following can be concluded:

Secondary Endpoints

Confirmatory Safety Endpoint

Hypoglycaemic episodes: The observed rate of confirmed hypoglycaemic episodes was 122 episodes per 100 PYE with IDeg and 142 episodes per 100 PYE with IGlar. The estimated rate of confirmed hypoglycaemia was numerically lower (14%) with IDeg than with IGlar, (estimated rate ratio (IDeg/IGlar) 0.86 $[0.58; 1.28]_{95\% CI}$;

superiority could not be confirmed and the testing procedure was therefore stopped.

Supportive Safety Endpoints

- **Nocturnal confirmed hypoglycaemic episodes:** The observed rate of nocturnal confirmed hypoglycaemia was 18 episodes per 100 PYE for IDeg and 28 episodes per 100 PYE for IGlar. The estimated rate ratio for nocturnal confirmed hypoglycaemia was numerically lower (36%) with IDeg than with IGlar, (estimated rate ratio (IDeg/IGlar) 0.64 $[0.30; 1.37]_{95\% CI}$. No statistically significant difference was detected between the treatment groups.
- **Body weight:** Body weight increased during the trial to similar mean (SD) values at Week 26: 94.1 kg (18.6) with IDeg and 94.0 kg (18.5) with IGlar. The observed body weight gain from baseline to the end of the trial was 1.9 kg in the IDeg treatment group and 1.5 kg in the IGlar treatment group. The estimated treatment difference (IDeg−IGlar) was 0.44 kg $[-0.20; 1.08]_{95\%CI}$. However, no statistically significant difference was detected between the treatment groups with respect to body weight gain between IDeg and IGlar after 26 weeks of treatment.
- **Adverse events:** The percentage of subjects reporting treatment-emergent AEs was similar in the IDeg (64.5%) and IGlar (68.4%) groups. The event rate for AEs was numerically lower in the IDeg (451 events per 100 PYE) treatment group than in the IGlar group (486 events per 100 PYE). The rate of AEs possibly or probably related to trial product was numerically lower with IDeg than with IGlar (38 and 52 events per 100 PYE, respectively). The most frequently reported AEs in both treatment groups were headache, diarrhoea, and nasopharyngitis. The percentage of subjects experiencing injection site reactions was similar in both treatment groups (6.6% in the IDeg group, 5.3% in the IGlar group).
- **Deaths, serious adverse events and other significant adverse events:** Two deaths were reported in this trial in the IGlar treatment group (myocardial ischaemia/suspected sudden death and acute myocardial infarction/pneumonia) and none in the IDeg group. A total of 15 (6.6%) subjects reported 23 SAEs in the IDeg group while 10 (4.4%) subjects reported 14 SAEs in the IGlar group. The rate of SAEs was numerically higher with IDeg (22 events per 100 PYE) than with IGlar (13 events per 100 PYE). There was no clustering of SAEs at any timepoint during the trial. The most frequently reported SAE was chest pain in the IDeg treatment group (of these 4 SAEs, one was adjudicated as a MACE). A total of 9 (2.0%) subjects reported 9 treatment-emergent AEs leading to withdrawal in this trial: 5 (2.2%) subjects in the IDeg group and 4 (1.7%) subjects in the IGlar group.
- **Insulin antibodies:** After 26 weeks of treatment, the mean level of cross-reacting insulin antibodies remained low in the IDeg group (0.4%B/T) and increased slightly in the IGlar group (2.2%B/T).
- **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.
- **Insulin dose:** The mean daily basal insulin dose after 26 weeks was similar between treatment groups (IDeg group: 59 U [0.62 U/kg]; IGlar group: 63 U [0.66 U/kg]). The insulin dose ratio at Week 26 (IDeg/IGlar) in U was 0.95.

Overall Conclusions

The results of this confirmatory, randomised, controlled, 26-week trial demonstrate the efficacy and safety of IDeg 200 U/mL vs. IGlar dosed once-daily with metformin ± DPP-IV inhibitor in insulin-naïve subjects with type 2 diabetes mellitus who were not in glycaemic control.

- IDeg effectively improves long-term glycaemic control as measured by HbA_{1c} (non-inferiority to IGlar confirmed).
- IDeg reduces FPG more than IGlar, while day-to-day variation in prebreakfast plasma glucose is similar.
- The proportion of subjects achieving the treatment target (HbA_{1c} <7%) without confirmed hypoglycaemia is similar with IDeg and IGlar.
- The overall rate of hypoglycaemia is low with no statistically significant difference between treatments.
- The daily dose of IDeg (200 U/mL) is similar to the daily dose of IGlar (100 U/mL).
- In this trial, no safety issues are identified with IDeg 200 U/mL; there are no apparent differences between IDeg and IGlar with respect to AEs and standard safety parameters.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (refer to applicable edition).

The results presented reflect data available in the clinical database as of 21 Dec 2010.