2 Synopsis

Trial Registration ID-Number NCT01193309	**UTN –** U1111-1114-9426 **IND number –** IND 76496 **EudraCT number –** 2009-015754-38
Title of Trial An Extension Trial to NN1250-3579 Comparing Safety and Efficacy of NN1250 Plus OAD(s) with Insulin Glargine Plus OAD(s) in Type 2 Diabetes [BEGIN™: Once Long] This synopsis contains the results after 104 weeks of treatment (52 weeks in the main trial NN1250-3579 and 52 weeks in the present extension trial NN1250-3643).	
Investigator(s) There were 142 principal investigators who enrolled subjects in this trial. Dr. [redacted] was appointed signatory investigator: [redacted]	
Trial Site(s) The main/extension trial was conducted at 166/142 sites in 12 countries: Austria (6/5), Belgium (5/4), Canada (17/17), Czech Republic (5/5), Denmark (6/6), Finland (6/6), France (7/5), Germany (16/14), Norway (8/8), Serbia (5/5), Spain (9/9), United States (76/58). These sites enrolled subjects.	
Publications None at the time of this report.	
Trial Period Initiation date: 1 September 2009 (main) 9 September 2010 (extension) Completion date: 13 December 2010 (main) 20 December 2011 (extension)	**Development Phase** Phase 3a

Objectives

Primary Objective:

The primary objective was to investigate the long-term safety and tolerability of insulin degludec (IDeg). This was done by comparing IDeg to insulin glargine (IGlar) after 104 weeks of treatment (52 weeks of treatment in NN1250-3579 plus 52 weeks of treatment in this extension trial) in terms of the listed safety assessments from which endpoints were calculated:

- Adverse events (AEs)
- Hypoglycaemic episodes
- Clinical evaluation
- Central laboratory assessments
- Body weight
- Insulin dose

Secondary Objectives:

The secondary objective was to compare the efficacy between IDeg and IGlar after 104 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
- Self-measured plasma glucose for dose adjustments
- Patient Reported Outcome (PRO) Questionnaire

The primary endpoint in the main trial (Trial 3579) was change in HbA_{1c} after 52 weeks of treatment.

Methodology

The main trial (NN1250-3579) was a 52-week, 3:1 randomised, controlled, open-label, active comparator, multicentre, multinational, treat-to-target trial comparing the efficacy and safety of IDeg and IGlar, both injected once daily (OD) in combination with OADs in subjects with type 2 diabetes mellitus currently treated with OAD(s) and who qualified for more intensified treatment. All subjects completing the 52 weeks of treatment were offered to participate in the extension trial NN1250-3643 (also a treat-to-target trial with similar PG targets as Trial 3579) as appropriate.

Subjects who consented to participate in the extension trial restarted treatment as previously randomly allocated in trial NN1250-3579. The main trial NN1250-3579 included a screening visit (Visit 1) to assess eligibility, followed by a randomisation visit (Visit 2) at which time the subject's current antidiabetic treatment was discontinued except for metformin and DPP-4 inhibitor (if applicable according to approved labelling) and subjects were randomised in a 3:1 manner (IDeg:IGlar) in combination with metformin ± DPP-IV inhibitor. In the subsequent 52 weeks of treatment (Visit 3 to Visit 41), the subject's insulin dose was titrated based on SMPG to ensure the enforced titration towards a predefined glycaemic target of FPG <5 mmol/L (90 mg/dL). After 52 weeks of treatment, subjects were switched to NPH and continued with their OAD treatment for a one week wash-out period to assess anti-insulin antibody levels.

The extension trial included a screening visit to assess eligibility on the same day as the follow-up visit in the main trial (Week 53). Subjects were required to attend a further 13 visits and 14 phone contacts during the 52 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 participated in the 52-week main trial (NN1250-3579) and received a maximum of 104 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

In the main trial NN1250-3579, the planned numbers of subjects to be screened (1401), randomised (984) and complete the main trial (736) was based on a planned sample size calculation outlined in the Trial 3579 trial report. The actual number of main trial completers was 804. It was assumed that 75% of the completers in the main trial would continue in the extension trial from which at least 75% were expected to complete the extension trial. The actual number of subjects included in the trial is shown below:

	IDeg OD N (%)	IGlar OD N (%)	Total N (%)
Screened			1597
Screening Failures			567
Withdrawn before Randomisation			0
Randomised	773 (100.0)	257 (100.0)	1030 (100.0)
Exposed Main Trial	766 (99.1)	257 (100.0)	1023 (99.3)
Withdrawn at/after Randomisation and Before extension	166 (21.5)	60 (23.3)	226 (21.9)
Adverse Event	20 (2.6)	5 (1.9)	25 (2.4)
Ineffective Therapy	7 (0.9)	2 (0.8)	9 (0.9)
Non-Compliance	46 (6.0)	18 (7.0)	64 (6.2)
Withdrawal Criteria	9 (1.2)	5 (1.9)	14 (1.4)
Other	84 (10.9)	30 (11.7)	114 (11.1)
Completed Main Trial	607 (78.5)	197 (76.7)	804 (78.1)

	IDeg OD N (%)	IGlar OD N (%)	Total N (%)
Completed Main Trial Not screened for extension	55 (7.1)	23 (8.9)	78 (7.6)
Completed Main Trial screening failure in extension	1 (0.1)		1 (0.1)
Included in Extension	551 (71.3)	174 (67.7)	725 (70.4)
Withdrawn during extension	46 (6.0)	20 (7.8)	66 (6.4)
Adverse Event	12 (1.6)	5 (1.9)	17 (1.7)
Ineffective Therapy	3 (0.4)	1 (0.4)	4 (0.4)
Non-Compliance	2 (0.3)	4 (1.6)	6 (0.6)
Withdrawal Criteria	6 (0.8)	3 (1.2)	9 (0.9)
Other	23 (3.0)	7 (2.7)	30 (2.9)
Completed Extension	505 (65.3)	154 (59.9)	659 (64.0)
Full Analysis Set	773 (100.0)	257 (100.0)	1030 (100.0)
PP Analysis Set	665 (86.0)	221 (86.0)	886 (86.0)
Safety Analysis Set	766 (99.1)	257 (100.0)	1023 (99.3)
Extension Trial Set	551 (71.3)	174 (67.7)	725 (70.4)

N: Number of subjects, %: Proportion of randomised subjects, PP: Per Protocol

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) ≤ 40.0 kg/m^2 and with current treatment: metformin monotherapy or metformin in any combination with insulin secretagogue (sulphonylurea [SU] or glinide), DPP-IV inhibitor, α-glucosidase-inhibitor (acarbose) with unchanged dosing for at least 3 months prior to Visit 1 were included in the main trial. Subjects who completed the first 52-week treatment in main trial NN1250-3579 were eligible to participate in the 52-week extension trial.

Subjects were not eligible for trial participation if they had received treatment with thiazoledinediones (TZDs), exenatide or liraglutide within 3 months prior to Visit 1 of the main trial, anticipated change in concomitant medication known to interfere significantly with glucose metabolism, known or suspected allergy to any of the trial products or related products, 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, pregnancy, breast-feeding, the intention of becoming pregnant or not using adequate contraceptive measures according to local requirements, previous participation in this trial, or noncompliance with any of the eligibility criteria.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number

IDeg 100 U/mL, 3 mL PDS290. IDeg was to be injected subcutaneously OD in the thigh, upper arm (deltoid region) or abdomen.

Batch No.: XL70001, XL70002, XL70003, XL70005, XL70006, XL70007, XL70008, XL70009, XL70012, XL70012_1, XL70019, XL70020, XL70025, YP50300, YP50840, YP50840_2, YP52101, YP52101_2, YP52101_3

Duration of Treatment

The total duration of treatment (main and extension) was 104 weeks for each subject. The total duration of the trial (main and extension) for each subject was approximately 107 weeks including screening and follow-up visits.

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, 3 mL SoloStarTM. IGlar was to be injected subcutaneously OD in the thigh, upper arm (deltoid region) or abdomen.
Batch No.: 0F090A, 0F166A, 0F523A, 40C293, 40C296, 40C337, 40C442, 40C474, 40C480, 40C529, 40C715, 40C846, 40U190, 40U212, 40U281

Insulin NPH (Insulatard®/Protaphane®/Novolin N™) 100 IU/mL, 3 mL FlexPen®. Since insulin NPH is an intermediate acting insulin, it was to be administered BID during follow-up, after last dose of IDeg or IGlar.
Batch No.: AP50885, XP51117-1, XP51117-2, XP52523, YP50394

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
- Antibodies
- Physical examination
- Vital signs
- Eye Examination
- Electrocardiogram (ECG)
- Laboratory safety variables
- Body weight

Statistical Methods

The following analysis sets were defined:

- Full Analysis Set (FAS): includes all randomised subjects. The statistical evaluation of the FAS follows the intention-to-treat (ITT) principle and subjects were to contribute to the evaluation "as randomised".
- Per Protocol (PP) Analysis Set includes all subjects in the Full Analysis Set who fulfil the following criteria:
  - Have not violated any inclusion criteria
  - Have not fulfilled any exclusion criteria
  - Have a non-missing HbA_{1c} at screening or randomisation
  - Have at least one non-missing HbA_{1c} after 12 weeks of exposure
  - Have at least 12 weeks of exposure
- Safety Analysis Set (SAS): includes 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): includes all subjects attending Visit 43 in the extension trial.

The analysis sets (FAS, PP and SAS) were defined in the main trial and the assignment of subjects to these analysis sets in the extension trial followed the definition in the main 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 were 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, AEs leading to withdrawal, number of severe and minor treatment emergent hypoglycaemic episodes, antibodies, QTc and central laboratory parameters (ALAT/SGPT, ASAT/SGOT) using the ETS to assess the stability of key results.

In addition, the data for demographic and baseline characteristics, trial product exposure, basal insulin dose, SF-36 and lipids were summarised based on the ETS.

Secondary Efficacy Analysis

- Change from baseline in HbA_{1c} after 104 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. To obtain data for subjects who completed 2-year treatment, a statistical analysis on HbA_{1c} based on the extension completers was included in the full trial report, using the same ANOVA model as the FAS analysis for HbA_{1c} after 104 weeks of treatment.
- HbA_{1c} responder (HbA_{1c} <7% or HbA_{1c} ≤6.5% 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% or HbA_{1c} ≤6.5% at end of trial and no confirmed/severe hypoglycaemic episodes) was a dichotomous endpoint that was defined based on whether a subject had met the American Diabetes Association (ADA) or International Diabetes Federation (IDF) 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 104 weeks of treatment was analysed using an ANOVA method similar to that used for the HbA_{1c} analysis.
- 9-point profile (SMPG): A mixed effect model was fitted to the 9-point profile (SMPG) data, but with a repeated measurement model with the same mean structure without the random subject effect, and with an unstructured residual covariance matrix (a change from the protocol in order to allow for varying variances at different timepoints at varying correlations between the values in the profile). The model included treatment, time, interaction between treatment and time, antidiabetic therapy at screening, sex and region as fixed factors, age and baseline value 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 104 weeks of treatment were analysed separately using an ANOVA method similar to that used for the HbA_{1c} analysis.
- SMPG values used for dose adjustment: The mean of before breakfast PG values after 104 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 mean PG at baseline, 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.
- Aspects of Health Related Quality of Life were assessed by PRO questionnaire using the Short Form 36 version 2 (SF-36 v2), which was completed by trial subjects at baseline and after 26, 52, and 104 weeks of treatment. The changes in score from baseline to 104 weeks were analysed for the questionnaire using an ANOVA model with treatment, sex, region and antidiabetic treatment at screening as fixed effects, and age and baseline response as covariates; missing data was imputed using LOCF.

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 14.1) 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 confirmed hypoglycaemic episodes were analysed separately.
- Antibodies specific for: IDeg 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 104 weeks of treatment was analysed using an ANOVA method similar to that used for the HbA_{1c} 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 demographics and baseline characteristics of the subject population were similar, with only marginal differences between the treatment groups. The population consisted of men and women with type 2 diabetes mellitus. IDeg-treated subjects had a slightly longer mean duration of diabetes than IGlar subjects. Approximately 28% of all subjects were elderly (>65 years of age; 28.7% elderly subjects in the IDeg group and 27.2% in the IGlar group). The majority of subjects were men (60.9% in the IDeg group and 65% in the IGlar group). The largest proportion of subjects was from the US (~37%); 88% of subjects who reported their race were White; 80% were of non-Hispanic/Latino origin. The second-largest race group was Black or African American with 7.4% in the IDeg treatment group and 6.2% in the IGlar group. The largest proportion of subjects at screening used metformin ± [SU or glinides] ± alpha-glucosidase-inhibitors (55.4% of subjects in the IDeg treatment group, and 47.5% of subjects in the IGlar group). The distribution of anti-diabetic regimens at screening was similar between treatment groups. At screening, 133 (17.2%) subjects (122 sitagliptin; 11 vildagliptin) in the IDeg group and 47 (18.3%) subjects (42 sitagliptin; 5 vildagliptin) in the IGlar group were treated with DPP-IV inhibitors. 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 were in accordance with the analysis based on FAS.

	IDeg OD	IGlar OD	Total
Number of Subjects	773	257	1030
Age (years)			
N	773	257	1030
Mean (SD)	59.3 (9.7)	58.7 (9.9)	59.1 (9.8)
Median	59.8	59.3	59.6
Min ; Max	28.8 ; 87.0	21.9 ; 82.7	21.9 ; 87.0
Body Weight (kg)			
N	773	257	1030
Mean (SD)	89.4 (17.7)	91.8 (15.8)	90.0 (17.3)
Median	88.2	90.5	89.0
Min ; Max	49.1 ; 147.2	60.0 ; 136.5	49.1 ; 147.2
BMI (kg/m^2)			
N	773	257	1030
Mean (SD)	30.9 (4.8)	31.6 (4.4)	31.1 (4.7)
Median	30.6	31.3	30.7
Min ; Max	18.3 ; 41.0	22.0 ; 40.5	18.3 ; 41.0

	IDeg OD	IGlar OD	Total
Duration of Diabetes (years)			
N	773	257	1030
Mean (SD)	9.4 (6.3)	8.6 (5.7)	9.2 (6.2)
Median	8.3	8.0	8.2
Min ; Max	0.5 ; 44.4	0.5 ; 30.2	0.5 ; 44.4
HbA_{1c} (%)			
N	773	257	1030
Mean (SD)	8.2 (0.8)	8.2 (0.8)	8.2 (0.8)
Median	8.0	8.1	8.0
Min ; Max	6.4 ; 10.2	6.8 ; 10.1	6.4 ; 10.2
FPG (mmol/L)			
N	762	256	1018
Mean (SD)	9.6 (2.6)	9.7 (2.6)	9.7 (2.6)
Median	9.4	9.4	9.4
Min ; Max	3.6 ; 24.0	4.0 ; 20.4	3.6 ; 24.0

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

Note that subjects were randomised based on measurements performed on Visit 1 and baseline values were recorded approximately 1 week later, at Visit 2. Because some subjects had a decrease or increase in body weight or HbA_{1c} from Visit 1 to Visit 2, the minimum and maximum values for HbA_{1c} and BMI are outside of the limits allowed in the inclusion criteria.

Efficacy Results

After 104 weeks of treatment with IDeg OD or IGlar OD both in combination with metformin ± DPP-IV inhibitor, the following can be concluded with regards to the full analysis set:

Secondary Endpoints

- **HbA_{1c}**: The estimated mean reduction in HbA_{1c} during the trial was 0.96%-points with IDeg and 1.08%-points with IGlar, and the estimated mean difference was 0.12%-points $[-0.01; 0.25]_{95\%CI}$. After 104 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.2 (1.0)% with IDeg and 7.1 (1.0)% with IGlar.
- **Responders for HbA_{1c}:** An observed total of 47.2% of subjects treated with IDeg achieved $HbA_{1c} < 7\%$ compared to the observed proportion of 52.9% for subjects treated with IGlar. The estimated odds ratio of achieving this target with IDeg compared to IGlar was 0.77 $[0.58; 1.04]_{95\% CI}$. An observed total of 27.3% of subjects treated with IDeg achieved $HbA_{1c} \leq 6.5\%$ compared to the observed proportion of 30.0% for subjects treated with IGlar. The estimated odds ratio of achieving this target with IDeg compared to IGlar was 0.88 $[0.64; 1.22]_{95\% CI}$. There was no statistically significant difference between treatment groups in terms of achieving either $HbA_{1c} < 7\%$ or $HbA_{1c} \leq 6.5\%$.
- **Responders for HbA_{1c} without hypoglycaemia:** The observed proportion of subjects achieving $HbA_{1c} < 7\%$ without confirmed hypoglycaemia during the last 12 weeks of treatment was 37.4% with IDeg and 45.3% with IGlar. The odds of achieving HbA_{1c} target < 7% without confirmed hypoglycaemia was statistically significantly greater with IGlar than with IDeg, with an estimated odds ratio (IDeg/IGlar) of 0.72 $[0.53; 0.98]_{95\% CI}$. The observed proportion of subjects achieving $HbA_{1c} < 7\%$ without severe hypoglycaemic episodes during the last 12 weeks of treatment was 50.4% with IDeg and 57.3% with IGlar; the estimated odds ratio (IDeg/IGlar) was 0.73 $[0.54; 1.01]_{95\% CI}$. There was no statistically significant difference between treatment groups in terms of achieving $HbA_{1c} < 7\%$ without severe hypoglycaemia.
- **FPG:** FPG decreased during the trial to observed mean (SD) levels of 6.0 (2.3) mmol/L with IDeg and 6.5 (2.4) mmol/L with IGlar. The estimated mean reduction from baseline in FPG during this trial was statistically significantly greater with IDeg (3.63 mmol/L) compared to IGlar (3.25 mmol/L), with an estimated mean difference (IDeg-IGlar) of -0.38 mmol/L $[-0.70; -0.06]_{95\%CI}$.

- **9-point SMPG profiles:** After 104 weeks of treatment, the estimated mean prandial increment was not statistically significantly different for IDeg compared with IGlar at any measured timepoint. The estimated mean fluctuation was not statistically significantly different with IDeg (1.21 mmol/L) vs. IGlar (1.23 mmol/L); the estimated treatment ratio (IDeg/IGlar) was 0.98 $[0.90; 1.06]_{95\ CI\%}$. After 104 weeks of treatment, the observed mean change in nocturnal PG (bedtime to breakfast) was -1.7 mmol/L with IDeg and -1.6 mmol/L with IGlar, with no statistically significantly difference when evaluated from bedtime to breakfast, from bedtime to 04:00 or from 04:00 to breakfast.
- **SMPG for dosing**: Mean SMPG before breakfast was reduced with both IDeg and IGlar during the trial. There was no statistically significant difference between treatment groups in terms of estimated mean SMPG value before breakfast, within-subject variation (CV%) in prebreakfast SMPG or regarding the time to meet the prebreakfast PG titration target. After 104 weeks of treatment, 39.6% and 38.8% of subjects in IDeg and IGlar treatment groups achieved the prebreakfast SMPG target < 5 mmol/L (90 mg/dL).
- **PRO (SF-36 v2)**: The changes from baseline in overall physical score, physical functioning score and bodily pain score were statistically significantly improved with IDeg compared to IGlar with estimated treatment differences (IDeg-IGlar) of: 1.1 $[0.1; 2.1]_{95\%CI}$, 1.1 $[0.0; 2.3]_{95\%CI}$ and 1.5 $[0.2; 2.9]_{95\%CI}$, respectively. Apart from this, only marginal changes were observed over time in both treatment groups.

Safety Results

After 104 weeks of treatment with IDeg OD + metformin ± DPP-IV inhibitor or IGlar OD + metformin ± DPP-IV inhibitor, the following can be concluded:

Primary Endpoints

- **Adverse events:** The percentages of subjects reporting AEs were 80.5% and 77.0% in the IDeg and IGlar groups, respectively. The observed rate of AEs was 362 events per 100 PYE in the IDeg group and 339 events per 100 PYE in the IGlar treatment group. The majority of AEs were mild or moderate. Few of the AEs were severe in either treatment group; the rate of severe AEs was 14 and 17 events per 100 PYE in the IDeg and IGlar groups, respectively. The rate of AEs considered possibly or probably related to trial product by investigator was 19 events per 100 PYE in both the IDeg and IGlar groups, with no patterns, trends or clustering seen within treatment groups. The most frequently reported adverse events in both treatment groups were nasopharyngitis, reported by 24.2% of all subjects, headache (13.3% of subjects), diarrhoea (10.9% of subjects), back pain (9.7% of subjects), upper respiratory tract infection (9.5% of subjects) and bronchitis (8.8% of subjects). Injection-site reactions were reported by 6.1% of subjects in the IDeg group and 6.6% 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:** Seven treatment-emergent deaths were reported in this trial (4 in the IDeg group and 3 in the IGlar group) and two non-treatment-emergent deaths (1 in the IDeg group and 1 in the IGlar group). A total of 116 (15.1%) and 41 (16.0%) subjects reported 240 serious adverse events in the IDeg (176 events) and IGlar groups (64 events), respectively. The rate of serious adverse events per 100 PYE was 15 in the IDeg group and 17 in the IGlar group. A similar percentage of subjects withdrew from the trial due to AEs (non-serious and serious): 32 (4.2%) in the IDeg group and 10 (3.9%) in the IGlar group. The rate of immunologic reactions was 1 per 100 PYE in both treatment groups; the rate of neoplasms was 5 and 4 per 100 PYE, and the rate of major adverse cardiovascular events was 3 and 1 per 100 PYE in the IDeg and IGlar groups, respectively.
- **Hypoglycaemic episodes:** The percentage of subjects who experienced confirmed hypoglycaemic episodes was similar in the IDeg group (58.0%) compared with the IGlar group (54.9%), with an observed rate of confirmed hypoglycaemic episodes of 172 and 205 per 100 PYE for IDeg and IGlar groups, respectively. The observed rate of nocturnal confirmed hypoglycaemic episodes was 27 and 46 per 100 PYE for IDeg and IGlar groups, respectively. The estimated rate ratio (IDeg/IGlar) for confirmed hypoglycaemic episodes was 0.84 $[0.68; 1.04]_{95\%\ CI}$, whereas the estimated rate of nocturnal confirmed hypoglycaemia was statistically significantly lower by 43% with IDeg than with IGlar; estimated rate ratio (IDeg/IGlar) was 0.57 $[0.40; 0.81]_{95\%\ CI}$. The estimated rate of severe hypoglycaemia was statistically significantly lower with IDeg; estimated rate ratio (IDeg/IGlar) was 0.31 $[0.11; 0.85]_{95\%\ CI.}$ Although the total observed rate of severe hypoglycaemia was low

at 1 and 2 events per 100 PYE with IDeg and IGlar, respectively, the observed rate of nocturnal severe hypoglycaemia per 100 PYE was 0 for IDeg and 1 for IGlar.

- **Insulin dose**: The mean daily insulin dose after 104 weeks was the same in the IDeg and IGlar groups: 60 U (0.63 U/kg) for IDeg and 60 U (0.63 U/kg) for IGlar. The ratio of IDeg/IGlar mean daily insulin dose (U) after 104 weeks was 0.99.
- **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, funduscopy/fundusphotography, physical examination and laboratory values.
- **Insulin antibodies:** The mean level of insulin antibodies cross-reacting between IDeg, IGlar and human insulin and IDeg- and IGlar-specific antibodies remained low throughout the trial.
- **Body weight:** There was no statistically significant difference in weight gain between treatment groups after 104 weeks of treatment; the estimated mean weight gain was 3.0 and 2.6 kg with IDeg and IGlar, respectively, with an estimated treatment difference of 0.37 kg $[-0.35; 1.10]_{95\% CI}$.

Conclusions

This confirmatory, randomised, controlled, 104-week trial investigated the long-term safety and efficacy of treatment with IDeg versus IGlar, both administered once daily with metformin ± DPP-IV inhibitor in insulin-naïve subjects with type 2 diabetes mellitus. The data support the following conclusions:

- In this trial, no safety issues are identified with IDeg during 104 weeks of treatment.
- There is no apparent difference between IDeg and IGlar with respect to AEs and standard safety parameters.
- The rate of confirmed hypoglycaemic episodes is similar with IDeg and with IGlar.
- Subjects treated with IDeg experience a statistically significantly lower rate of nocturnal confirmed hypoglycaemic episodes and severe hypoglycaemia compared to subjects treated with IGlar.
- Antibody development is negligible for both treatment regimens.
- The daily dose of IDeg is the same as the daily dose of IGlar.
- Body weight increase is similar for both treatment regimens.
- Treatment with IDeg effectively improves long-term glycaemic control as measured by HbA_{1c}.

In conclusion, these findings confirm the safety and efficacy of IDeg administered once daily in combination with metformin ± DPP-IV inhibitor, 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 16 January 2012.