2 Synopsis

Trial Registration ID-number NCT00982644	**IND Number – US only** IND 76496 **EudraCT number –** 2008-005776-27
Title of Trial A 52-week Randomised, Controlled, Open Label, Multicentre, Multinational Treat-to-target Trial Comparing the Efficacy and Safety of NN1250 and Insulin Glargine, Both Injected Daily in Combination With Oral Anti-diabetic Drugs (OADs), in Subjects With Type 2 Diabetes Mellitus Currently Treated With OADs and Qualifying for More Intensified Treatment (BEGIN™: Once Long)	
Investigators There were 168 principal investigators who enrolled subjects in this trial. Professor [redacted] was appointed signatory investigator: [redacted]	
Trial Site(s) The trial was conducted at 166 sites in 12 countries: Austria (6 sites), Belgium (5 sites), Canada (17 sites), Czech Republic (5 sites), Denmark (6 sites), Finland (6 sites), France (7 sites), Germany (16 sites), Norway (8 sites), Serbia (5 sites), Spain (9 sites) and United States (76 sites).	
Publications None at the time of this report	
Trial Period 01 September 2009 - 13 December 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

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

- Hypoglycaemic episodes
- Fasting plasma glucose (FPG) measured at a central laboratory
- Within-subject variability in self-measured pre-breakfast plasma glucose (PG)
- Frequency of responders for HbA_{1c} without hypoglycaemic episodes

To compare efficacy and safety after 52 weeks of treatment in terms of:

- 9-point self-measured plasma glucose (SMPG) profile
- SMPG for dose adjustments
- Frequency of responders for HbA_{1c}
- Insulin dose
- Body weight
- Adverse events (AEs)
- Hypoglycaemic episodes
- Clinical and laboratory assessments
- Cardiovascular risk markers
- Insulin antibodies

- Patient reported outcome (PRO)
- CGM (selected sites)

Methodology

This was a 52-week, 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.

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 according to approved labelling) and subjects were randomised in a 3:1 manner (IDeg:IGlar) in combination with metformin ± DPP-4 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 <5nM. 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.

For selected sites, subjects underwent assessment of their 72-hour interstitial glucose levels with a continuous glucose monitoring (CGM) device. All subjects completing the 52-weeks of treatment were offered to participate in an extension trial.

Number of Subjects Planned and Analysed

The planned number of subjects to be screened (1401), randomised (984) and complete the trial (736) was based on the sample size calculation. 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	766 (99.1)	257 (100.0)	1023 (99.3)
Withdrawn at/after Randomisation	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 With Protocol	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	607 (78.5)	197 (76.7)	804 (78.1)
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)

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) ≤ 40.0 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 with 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 were excluded from the trial.

Test 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

Duration of Treatment

Total duration for the individual subjects participating in the trial was approximately 55 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, 3 mL SoloStar™. IGlar was to be injected subcutaneously OD in the thigh, upper arm (deltoid region) or abdomen. Batch No.: 40C293, 40C296, 40C442, 40C474, 40C480, 40C529, 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. The first dose of insulin NPH was to be given at the earliest 24 h after last dose of IDeg or IGlar. Batch No.: 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
- CGM (in a sub population)

Criteria for Evaluation – Safety

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

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 HbA1c at screening or randomisation
  - Have at least one non-missing HbA1c after 12 weeks of exposure
  - Have at least 12 weeks of exposure
- Safety Analysis Set: 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".

All statistical analyses, including analyses of PRO as well as confirmatory analyses of confirmed hypoglycaemia and body weight are based on the FAS. In addition, the analysis of the primary endpoint is repeated based on the PP

analysis set and is considered as supportive evidence.

Primary Efficacy Analysis

Change from baseline in HbA1c 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 HbA1c as covariates. Non-inferiority was to be considered confirmed if the upper bound of the two-sided 95% confidence interval was less than or equal to 0.4%. Superiority was to be considered confirmed if the upper bound of the two-sided 95% confidence interval was <0%.

Secondary Confirmatory 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. A hierarchical testing procedure was used to control the overall Type 1error. A consequence of this fixed testing procedure is that 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 confirmed hypoglycaemic episodes
   - Superiority was to be 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 52 weeks of treatment (analysed at central laboratory)
   - Superiority was to be 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 self-measured FPG after 52 weeks of treatment
   - Superiority was to be 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 confirmed hypoglycaemic episodes during the last 12 weeks of treatment including only subjects exposed for at least 12 weeks)
   - Superiority was to be considered confirmed if the 95% confidence interval for the odds ratio (investigational product / comparator) was entirely above one

Secondary Supportive Endpoints

- The HbA1c responder endpoints (HbA1c < 7% 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 data. The model was to include 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 the model mean profile by treatment and relevant treatment differences were to be estimated and explored.
  - Mean and logarithmically transformed fluctuations (mmol/L) in the 9-point profile (SMPG), prandial PG increment and nocturnal PG endpoints after 52 weeks of treatment were analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.
- SMPG Values Used for Dose Adjustment
  - The mean of before breakfast PG values was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.
  - Survival endpoints (time until subject met titration target for the first time and time subject met the target and stayed on target for the remaining treatment period) were analysed separately in a Cox proportional hazards model including treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as covariate.
  - The following endpoints were derived based on continuous glucose measurements: mean and variation in IG profile, night time characteristics of IG profile, meal characteristics of IG profile as well as number of episodes

of low and high IG and the total time spent at low and high IG. . All endpoints except for the time to the IG meal-peak and the number of episodes of low and high IG were analysed using an ANOVA method similar to that used for the analysis of the primary endpoint. The time to the IG meal-peak was summarised descriptively. The number of low and high IG episodes was to be analysed separately for the different targets - the offset used in the analysis of low (near-hypo) and high (near-hyper) episodes of interstitial glucose was the duration of the profile (entire or nocturnal part), and not duration of exposure as stated in the protocol. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate.

– The change from baseline in patient reported outcome scores 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. AEs were coded using the most recent version (version 13.1) 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 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 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. The statistical analysis for severe hypoglycaemic episodes was not performed since only one episode was reported.
- Change from baseline in hsCRP, NT-proBNP and lipid endpoints was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint
- Antibodies specific for IDeg and IGlar as well as cross-reacting antibodies to human insulin and the correlation to insulin dose and HbA1c were investigated using descriptive statistics and graphs.
- Change from baseline in QTc was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint
- Change from baseline in body weight after 52 weeks of treatment was analysed 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

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, with a mean age of 59.1 years and a mean duration of diabetes of 9.2 years (ranging from 0.5 to 44.4 years), with a mean HbA1c of 8.2% and a mean BMI of 31.1 kg/m2. 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 majority of subjects in both treatment groups were insulin-naïve at screening, with the largest proportion of subjects using 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.

	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
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
HbA1c (%)			
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 1and baseline values were recorded approximately 1 week later, at Visit 2. Because some subjects had an increase in body weight or HbA1c from Visit 1 to Visit 2, the maximum values for HbA1c and BMI are above the limits allowed in the inclusion criteria; see Section 9.3.

Efficacy Results

After 52 weeks of treatment with IDeg OD or IGlar OD both in combination with OAD(s), the following was concluded:

Primary Endpoint

- **HbA_{1c}:** IDeg effectively improved glycaemic control, and non-inferiority to IGlar in terms of lowering HbA_{1c} was confirmed; estimated mean treatment difference (IDeg -IGlar) 0.09 percentage points [-0.04; 0.22] $_{95\% CI}$. The estimated mean change in HbA_{1c} was -1.06 percentage points with IDeg and -1.15 percentage points with IGlar. After 52 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.1 (1.0)% with IDeg and 7.0 (1.0)% with IGlar.

Secondary Endpoints

Confirmatory Endpoints

- **Confirmed hypoglycaemia:** see conclusion in Safety Section below
- **FPG:** The observed mean change in FPG was greater with IDeg (-3.76 mmol/L) than with IGlar (-3.30 mmol/L) with an estimated mean treatment difference (IDeg-IGlar) of -0.43 mmol/L, [-0.74; -0.13]95% CI. FPG decreased during the trial to observed mean (SD) levels of 5.9 (2.2) mmol/L with IDeg and 6.4 (2.3) mmol/L with IGlar.
- **Within-subject variability (CV%) in pre-breakfast SMPG:** The estimated day-to-day variability (CV%) in self-measured FPG was 16.57% with IDeg and 16.74% with IGlar. There was no statistically significant difference between treatment groups; the estimated mean treatment ratio (IDeg/IGlar) was 0.99 [0.92; 1.06]$_{95\% CI}$.
- **HbA_{1c} <7% without confirmed hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemic episodes was 42.1% with IDeg and 45.7% with IGlar. There was no statistically significant difference between treatment groups; the estimated odds ratio (IDeg/IGlar) was 0.86 [0.63; 1.17]$_{95\% CI}$.

Supportive Efficacy Endpoints

- **Responders for HbA_{1c}:** The observed proportion of subjects achieving HbA_{1c} <7% was 51.7% with IDeg and 54.1% with IGlar. There was no statistically significant difference between treatment groups; the estimated odds ratio (IDeg/IGlar) was 0.88 [0.65; 1.19]$_{95\% CI}$.
- **Responders for HbA_{1c} without hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} ≤6.5% without confirmed hypoglycaemia was 25.2% with IDeg and 28.9% with IGlar. There was no statistically significant difference between treatment groups in the proportion of subjects achieving HbA_{1c} ≤6.5% without confirmed hypoglycaemia; the estimated odds ratio (IDeg/IGlar) was 0.82 [0.58; 1.17]$_{95\% CI}$. There was no statistically significant difference between treatment groups in the proportion of subjects achieving HbA_{1c} targets of ≤6.5% or <7% without severe hypoglycaemia; for the <7% target, the estimated odds ratio (IDeg/IGlar) was 0.85 [0.62; 1.17], for the ≤6.5% target, the estimated odds ratio (IDeg/IGlar) was 0.79 [0.57; 1.10].
- **9-point SMPG profiles:** Overall, the 9-point profiles appeared similar between IDeg and IGlar after 52 weeks. There was no statistically significant difference between treatment groups in any of the endpoints related to 9-point SMPG profiles with the exception of a greater mean prandial increment at lunch with IDeg (estimated treatment difference IDeg-IGlar 0.43 [0.00*; 0.86]$_{95\%CI}$ and a greater reduction in nocturnal increment from 04:00 to breakfast with IDeg (estimated treatment difference IDeg-IGlar -0.34 [-0.63; -0.06]$_{95\%CI}$). *This value is actually 0.0016.
- **SMPG for Dosing:** There was no statistically significant difference between treatment groups for any SMPG-related endpoint.
- **CGM:** There were no statistically significant differences between IDeg and IGlar for any CGM-related endpoints.
- **PRO:** The change from baseline in overall physical score and physical functioning score (SF-36 v2) was greater with IDeg compared to IGlar (treatment contrast estimate for overall physical score 1.0 [0.1; 2.0]$_{95\%CI}$; treatment contrast estimate for physical functioning 1.4 [0.3; 2.4]$_{95\%CI}$). Apart from this, there were no statistically significant differences and the results of the PRO appear to be similar between the two treatment groups, with only marginal changes over time.

Safety Results

From the results of this 52-week trial of treatment with IDeg OD or IGlar OD both in combination with OAD(s), the following can be concluded:

Secondary Endpoints

Confirmatory Safety Endpoints

- **Confirmed hypoglycaemic episodes:** The observed rate of confirmed hypoglycaemic episodes per 100 PYE was 152 episodes with IDeg and 185 episodes with IGlar. The estimated rate of confirmed hypoglycaemia was numerically lower (18%) with IDeg than with IGlar, (estimated rate ratio (IDeg/IGlar) 0.82 $[0.64; 1.04]_{95\% CI}$.

Supportive Safety Endpoints

- **Hypoglycaemic episodes:** In total, seven episodes of severe hypoglycaemia were reported (IDeg: 2, IGlar: 5). All subjects recovered. The rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was 25 for IDeg and 39 for IGlar. IDeg was associated with a 36% lower rate of nocturnal confirmed hypoglycaemic episodes than IGlar; estimated mean rate ratio (IDeg/IGlar) was 0.64 (IDeg: 24.02; IGlar: 37.62) with 95% CI: [0.42; 0.98]). A single episode of nocturnal severe hypoglycaemia was reported during the trial in the IDeg treatment group.
- **Body weight:** The estimated increase in mean body weight was similar in the IDeg and IGlar groups (2.4 and 2.1 kg, respectively), with a mean treatment difference (IDeg-IGlar) 0.28 [-0.32; 0.88]95% CI). The mean (SD) body weight at baseline and at the end of the trial was 89.6 kg (17.7) and 91.8 kg (18.4) in the IDeg group and 91.9 kg (15.7) and 93.9 kg (16.8) in the IGlar group, respectively.
- **Adverse events:** There was no clinically relevant difference between the treatment groups in the reporting of AEs. A similar percentage of subjects reported adverse events in the IDeg and IGlar groups (74.7% and 70.8%, respectively). The rate of all adverse events was similar for the IDeg and IGlar groups (403 and 384 events per 100 PYE, respectively) as were the rates of adverse events possibly or probably related to investigational product (26 and 29 events per 100 PYE, respectively). Few of the AEs in either treatment group were severe (IDeg: 88 events; IGlar 40 events), and the percentage of subjects experiencing of severe AEs was numerically lower in the IDeg group (8.1% vs. 10.1% in the IGlar group). The most frequently reported adverse events in both treatment groups were nasopharyngitis, headache, diarrhoea and back pain. The percentage of subjects with injection site reactions was low in both treatment groups (5.6% and 6.2%, in the IDeg and IGlar groups, respectively).
- **Deaths, serious adverse events and other significant adverse events:** Two deaths were reported in this trial: urosepsis (IGlar group; treatment-emergent) and sudden cardiac death (IDeg group; non-treatment-emergent). A total of 62 (8.1%) subjects in the IDeg group reported 78 serious adverse events, whereas and 26 (10.1%) subjects in the IGlar group reported 33 serious adverse events. No SAEs were reported with a frequency ≥5% or ≥ 1% in either treatment group. A similar percentage of subjects withdrew from the trial due to AEs in the IDeg (2.6%) and IGlar (1.9%) groups. There appeared to be no difference between the treatment groups in the pattern of AEs leading to withdrawal.
- **Insulin antibodies:** A modest increase in cross-reacting insulin antibody levels was detected in the IDeg and IGlar treatment groups from baseline to Week 53. The mean level of insulin degludec-specific antibodies was very low at baseline and remained low after 52 weeks of treatment with IDeg.
- **Vital signs, ECG, funduscopy**, **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 52 weeks was similar in the treatment groups: 56 U (0.59 U/kg) for IDeg and 58 U (0.60 U/kg) for IGlar. The ratio of IDeg/IGlar mean daily insulin dose after 52 weeks is 0.97, indicating that mean doses are similar in the two treatment groups.

Conclusions

The results of this confirmatory, randomised, controlled, 52-week trial demonstrate the efficacy and safety of IDeg 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 pre-breakfast 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 rate of confirmed hypoglycaemic episodes is numerically lower with IDeg compared to IGlar, but superiority of IDeg cannot be demonstrated. Furthermore, subjects treated with IDeg experience a lower rate of nocturnal

confirmed hypoglycaemic episodes than subjects treated with IGlar. • The daily dose of IDeg is similar to the daily dose of IGlar. • In this trial, no safety issues are identified with IDeg; 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.

The results presented reflect data available in the clinical database as of 17-Jan-2011.