2 Synopsis

Trial Registration ID-number NCT01076647	**IND Number –** 76496 **EudraCT number –** 2009-011399-31
Title of Trial A Trial Comparing the Efficacy and Safety of NN1250[1] and Insulin Glargine in Subjects With Type 2 Diabetes (BEGIN™: EASY PM)	
Investigators There were 89 principal investigators. [redacted], MD, [redacted] was appointed as signatory investigator:	
Trial Sites The trial was conducted at 89 sites in 7 countries: Bulgaria (4 sites), Canada (7 sites), France (8 sites), Hungary (5 sites), Netherlands (9 sites), Romania (5 sites), and United States (51 sites). In addition, 17 sites were approved but did not enroll subjects in the trial: France (1 site), Hungary (1 site), Netherlands (1 site), Romania (1 site), United States (13 sites).	
Publications None	
Trial Period 01 March 2010 to 01 December 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

To confirm the efficacy of insulin degludec (IDeg) 200 U/mL 3 times weekly + 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 3 times weekly + metformin ± DPP-4 inhibitor and insulin glargine (IGlar) once daily (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 3 times weekly + metformin ± DPP-4 inhibitor over IGlar OD + metformin ± DPP-4 inhibitor after 26 weeks of treatment in terms of:

- Change from baseline in body weight

To compare efficacy and safety in terms of:

- Frequency of responders for HbA_{1c}
- Fasting plasma glucose (FPG) (analysed by central laboratory)
- 9-point profile (self-measured plasma glucose [SMPG])
- 1-point profile (SMPG) for dose adjustments
- Adverse events (AEs)
- Hypoglycaemic episodes
- Clinical and laboratory assessments

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

- Insulin dose
- Patient reported outcome (PRO)

Methodology

This was a 26-week randomised, confirmatory, controlled, open-label, multicentre, multinational treat-to-target trial comparing efficacy and safety of IDeg three times weekly (3TW) injected in the evening (with the evening meal) on Mondays, Wednesdays and Fridays, and IGlar once daily (OD) (injected at the same time each day according to local labelling), both in a population of insulin-naïve subjects with type 2 diabetes mellitus currently treated with oral antidiabetic drugs (OADs) and 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 to be 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 groups consisting of either IDeg 3TW or IGlar OD and were to continue metformin ± DPP-4 inhibitor treatment. Subjects were randomised in a 1:1 fashion (IDeg 3TW:IGlar OD). Subjects were instructed to continue with the same total daily dose of metformin ± DPP-4 inhibitor as before the start of the trial.

All subjects were titrated according to the insulin dose titration guideline. The treatment period lasted for 26 weeks during which weekly clinic visits or phone contacts with the investigator ensured the enforced titration towards a pre-specified glycaemic target of FPG< 5 mmol/L. 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

Based on the sample size calculation, the planned number of subjects to be screened and randomised was 642 and 450, respectively, while 382 subjects were expected to complete the trial. These targets were met, and the actual numbers of subjects included in the trial are shown below.

	IDeg 3TW N (%)	IGlar OD N (%)	Total N (%)
Screened			677
Screening Failures			210
Withdrawn before Randomisation			0
Randomised	233 (100.0)	234 (100.0)	467 (100.0)
Exposed	233 (100.0)	234 (100.0)	467 (100.0)
Withdrawn at/after Randomisation	25 (10.7)	25 (10.7)	50 (10.7)
Adverse Event	4 (1.7)	1 (0.4)	5 (1.1)
Ineffective Therapy	0 (0.0)	1 (0.4)	1 (0.2)
Non-Compliance With Protocol	7 (3.0)	9 (3.8)	16 (3.4)
Withdrawal Criteria	2 (0.9)	2 (0.9)	4 (0.9)
Other	12 (5.2)	12 (5.1)	24 (5.1)
Completed	208 (89.3)	209 (89.3)	417 (89.3)
Full Analysis Set	233 (100.0)	234 (100.0)	467 (100.0)
PP Analysis Set	222 (95.3)	216 (92.3)	438 (93.8)
Safety Analysis Set	233 (100.0)	234 (100.0)	467 (100.0)

N: Number of subjects; %: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Inclusion criteria: 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), body mass index (BMI) ≤ 45.0 kg/m^2 and with current treatment: metformin as monotherapy or in any combination with insulin secretagogues (sulphonylurea or glinide), DPP-4 inhibitor (minimum half daily max dose), α-glucosidase-inhibitor (acarbose) (minimum half daily max dose) with unchanged dosing for at least 3 months prior to Visit 1 were included in the trial.

Exclusion criteria: treatment with thiazoledinediones (TZDs), exenatide or liraglutide within 3 months prior to Visit 1, anticipated changes 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, or 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 3 times weekly with the main evening meal (Mondays, Wednesdays, Fridays), subcutaneously in the thigh, upper arm (deltoid region) or abdomen. Insulin doses were titrated weekly by the investigator based upon the subject's SMPG and a titration guideline. No maximum insulin dose was specified. Batch Numbers: XL70031, YL70001, YP50490.

Duration of Treatment

Total duration for the individual subjects participating in the trial was approximately 29 weeks, including screening and follow-up visits.

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, 3 mL SoloStar™ pen. IGlar was to be injected once daily at the same time each day, according to local labelling, subcutaneously in the thigh, upper arm (deltoid region) or abdomen. Insulin doses were titrated weekly by the investigator based upon the subject's SMPG and a titration guideline. No maximum insulin dose was specified. Batch Numbers: 40C368, 40C442, 40C700, 40C712, 40C715.

All subjects were instructed to continue on metformin and on DPP-4 inhibitor (if applicable) as before the start of the trial. Dose and frequency of metformin and DPP-4 inhibitor, if applicable, should not be changed during the trial unless for safety reasons. Metformin and DPP-4 inhibitors were not considered trial products and were not supplied by Novo Nordisk A/S.

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - Fasting SMPG measurements for dose adjustment
  - 9-point profile (SPMG)
- PRO questionnaire
- Body Weight

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes
- Insulin dose
- Physical examination
- Vital signs
- Fundoscopy/Fundusphotography
- 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 have affected 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 hypoglycaemic episodes, body weight and lipids. 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 26 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. 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%. If non-inferiority was confirmed, superiority of the investigational product over the comparator would be investigated. Superiority was considered 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, the following confirmatory secondary endpoint was 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. The consequence of this fixed testing procedure is that superiority can only be confirmed for endpoints where all previous hypotheses have been confirmed:

- Change from baseline in body weight after 26 weeks of treatment was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.

Secondary Supportive Efficacy Analyses

- The HbA_{1c} responder endpoints (proportion of subjects reaching the HbA_{1c} targets < 7% or ≤6.5% at end of trial with or without hypoglycaemia) were analysed separately based on a logistic regression model using the same factors and covariates as for the primary analysis.
- Change from baseline in FPG after 26 weeks of treatment was analysed using an ANOVA method similar to the analysis for the primary endpoint.
- 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 analysis of the primary endpoint.
- SMPG Values Used for Dose Adjustment
    - The mean of before breakfast PG values after 26 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(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 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.

- 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 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 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 plasma glucose measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia. Furthermore, confirmed hypoglycaemic episodes were defined as episodes of severe hypoglycaemia and minor hypoglycaemic episodes with a confirmed plasma glucose 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 severe nocturnal hypoglycaemic episodes were analysed separately
- Laboratory safety parameters, physical examination, ECG, fundoscopy / fundusphotography, vital signs and insulin dose were evaluated based on descriptive statistics

Demography of Trial Population

The trial population was well matched 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 57.4 years and a mean duration of diabetes of 8.8 years, with a mean HbA_{1c} of 8.3 % and a mean BMI of 32.1 kg/m^2. The majority of subjects (~90%) were White; 12.4% of subjects were of Hispanic or Latino ethnicity. Approximately 47% of subjects enrolled were from North America (United States (39.8%) and Canada (7.5%)), while the remaining 53% of subjects were distributed between five European countries. Slightly more male subjects were enrolled (57.2%) than females. Approximately 23% of subjects were >65 years of age. The majority (60.8%) of the subjects had been treated with metformin in combination with insulin secretagogues and/or alpha-glucosidase inhibitors, while 16.1% also received DPP-4 inhibitors; 64.9% of subjects were on 2 OADs at screening, the most common regimen being metformin in combination with a sulphonylurea, most frequently glimepiride (21.2%), gliclazide (14.8%) or glibenclamide (13.1%).

	IDeg 3TW	IGlar OD	Total
Number of Subjects	233	234	467
Age (years)			
N	233	234	467
Mean (SD)	57.3 (9.6)	57.5 (10.7)	57.4 (10.2)
Median	57.4	58.2	57.7
Min ; Max	23.0 ; 80.9	29.0 ; 85.5	23.0 ; 85.5
Age Group (N (%))			
Adults (18-65 yrs)	180 (77.3)	181 (77.4)	361 (77.3)
Adults >65 years	53 (22.7)	53 (22.6)	106 (22.7)

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	IDeg 3TW	IGlar OD	Total
Body Weight (kg)			
N	233	234	467
Mean (SD)	92.3 (18.3)	91.4 (18.7)	91.8 (18.5)
Median	91.0	89.5	90.0
Min ; Max	44.0 ; 138.2	50.8 ; 150.0	44.0; 150.0
BMI (kg/m^2)			
N	233	234	467
Mean (SD)	32.3 (5.1)	31.9 (5.5)	32.1 (5.3)
Median	31.7	31.5	31.6
Min ; Max	18.7 ; 44.9	19.7 ; 45.2	18.7 ; 45.2
Duration of Diabetes (years)			
N	233	234	467
Mean (SD)	8.4 (6.2)	9.2 (6.0)	8.8 (6.1)
Median	7.1	7.9	7.7
Min ; Max	0.5 ; 49.7	0.6 ; 34.7	0.5 ; 49.7
HbA1c (%)			
N	233	234	467
Mean (SD)	8.3 (0.8)	8.3 (0.8)	8.3 (0.8)
Median	8.1	8.4	8.2
Min ; Max	6.9 ; 10.5	6.6 ; 10.3	6.6 ; 10.5
FPG (mmol/L)			
N	229	230	459
Mean (SD)	9.9 (2.2)	9.9 (2.4)	9.9 (2.3)
Median	9.5	9.8	9.7
Min ; Max	3.9 ; 18.5	4.6 ; 17.4	3.9 ; 18.5

BMI = Body mass index; FPG = Fasting plasma glucose; N = Number of subjects; SD = Standard deviation

Efficacy Results and Conclusions

After 26 weeks of treatment with IDeg 3TW + metformin ± DPP-4 inhibitor or IGlar OD + metformin ± DPP-4 inhibitor, the following can be concluded:

Primary Endpoint (HbA_{1c})

- **HbA_{1c}**: Long-term glycaemic control as measured by HbA_{1c} was improved in both treatment groups, but non-inferiority to IGlar OD could not be confirmed. The estimated treatment difference (IDeg 3TW − IGlar OD) was 0.26 %-points $[0.11; 0.41]_{95\%CI}$. The estimated mean change in HbA_{1c} was −1.09 %-points with IDeg 3TW and −1.35 with IGlar OD. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.2 (0.9)% with IDeg 3TW and 7.0 (0.9)% with IGlar OD. As the primary hypothesis could not be confirmed, the hierarchical testing procedure was stopped.

Secondary Efficacy Endpoints

Confirmatory Endpoints

- **Body weight** (see Safety Results and Conclusions)

Supportive Efficacy Endpoints

- **Responders for HbA_{1c}**: The observed proportion of subjects (exposed for at least 12 weeks) achieving HbA_{1c} <7% was 45.9% with IDeg 3TW and 54.3% with IGlar OD. The estimated odds of achieving this target were lower (38%) with IDeg 3TW compared to IGlar OD (estimated odds ratio (IDeg 3TW/IGlar OD) 0.62 $[0.42; 0.92]_{95\%CI}$).
- **Responders for HbA_{1c} without confirmed hypoglycaemia:** The observed proportion of subjects (exposed for at least 12 weeks) achieving HbA_{1c} <7% without confirmed hypoglycaemic episodes was 33.2% with IDeg 3TW and 45.7% with IGlar OD. The estimated odds of achieving this target were lower (51%) with IDeg 3TW compared to IGlar OD (estimated odds ratio (IDeg 3TW/IGlar OD) 0.49 $[0.32; 0.74]_{95\% CI}$).
- **Responders for HbA_{1c} without severe hypoglycaemia:** The observed proportion of subjects (exposed for at

least 12 weeks) achieving HbA_{1c} <7% without severe hypoglycaemic episodes was 46.6% with IDeg 3TW and 57.5% with IGlar OD. The estimated odds of achieving this target were lower (46%) with IDeg 3TW compared to IGlar OD (estimated odds ratio (IDeg 3TW/IGlar OD) 0.54 $[0.36; 0.81]_{95\%CI}$).

- **FPG:** FPG decreased during the trial to observed mean (SD) levels of 6.7 (2.3) mmol/L and 6.2 (2.1) mmol/L with IDeg 3TW and IGlar OD, respectively. The reduction in FPG was smaller for subjects in the IDeg 3TW group than in the IGlar OD group; the estimated mean change in FPG was −3.18 mmol/L with IDeg 3TW and −3.68 mmol/L with IGlar OD, and the estimated treatment difference (IDeg 3TW–IGlar OD) was 0.50 mmol/L $[0.10; 0.90]_{95\%CI}$.
- **9-point SMPG profiles**: Plasma glucose decreased during the trial in both treatment groups. The estimated overall mean of the 9-point SMPG profile was higher with IDeg 3TW than with IGlar OD (7.92 mmol/L and 7.49 mmol/L, respectively); estimated mean treatment difference 0.43 mmol/L $[0.12; 0.74]_{95\%CI}$, which was primarily attributable to differences during the night and early morning hours. No statistically significant differences in PG fluctuation (mmol/L) were seen between treatments (estimated treatment ratio 0.94 mmol/L $[0.85; 1.05]_{95\%CI}$). No statistically significant difference in prandial increment across all meals was observed between IDeg 3TW and IGlar OD groups (estimated treatment difference −0.19 mmol/L $[-0.53; 0.16]_{95\%CI}$. No statistically significant differences in nocturnal PG changes were seen between treatments for the nocturnal period as a whole (estimated treatment difference −0.13 [−0.66; 0.41]), nor for the period between bedtime and 04:00 a.m. For the period between 04:00 a.m. and breakfast, there was a greater decline in PG levels with IDeg 3TW than with IGlar OD (estimated mean difference: −0.35 $[-0.67; -0.04]_{95\%CI}$.
- **1-point Pre-breakfast SMPG:** The estimated day-to-day variation (CV%) in pre-breakfast SMPG was 21.55% with IDeg 3TW and 15.89% with IGlar OD. The estimated treatment ratio (IDeg 3TW/IGlar OD) was 1.36 $[1.23; 1.48]_{95\%CI}$. Hence day-to-day variation was higher with IDeg 3TW than with IGlar OD.
- **PRO**: The results of the PRO assessments, assessed on a scale of 1−100, were generally similar for the two treatments. For the DiabMedSat, a smaller improvement in overall score was seen in the IDeg 3TW group than in the IGlar OD group (estimated treatment difference of −2.5 $[-4.7; -0.2]_{95\%CI}$), with a slight worsening in subcategory 'Symptoms' with IDeg 3TW compared to IGlar OD (estimated treatment difference −4.7 $[-7.6; -1.9]_{95\%CI}$). For the TRIM-D, differences between treatments were identified in two subcategories: 'Compliance', with greater improvement with IDeg 3TW than IGlar OD (estimated treatment difference 3.5 $[0.7; 6.3]_{95\%CI}$), and 'Diabetes Management', with smaller improvement with IDeg 3TW than IGlar OD (estimated treatment difference −4.9 $[-8.4; -1.3]_{95\%CI}$). No other statistically significant differences were detected in the PRO assessments, for overall scores or subcategories.

Safety Results and Conclusions

From the results of this 26-week trial of treatment with IDeg 3TW and IGlar OD, the following can be concluded:

- **Body weight:** Body weight was defined in the protocol as a confirmatory secondary endpoint. As non-inferiority of IDeg 3TW compared to IGlar OD in terms of HbA_{1c} could not be confirmed (upper limit of the 95% CI > 0.4), the hierarchical testing procedure was stopped. Body weight increased during the trial to similar mean (SD) levels, 93.1 (18.8) kg with IDeg 3TW and 91.9 (19.0) kg with IGlar OD. The mean change in body weight was 0.8 kg with IDeg 3TW and 0.5 kg with IGlar OD. The estimated mean treatment difference (IDeg 3TW − IGlar OD) was 0.27 kg $[-0.42; 0.96]_{95\%CI}$.
- **Hypoglycaemic episodes:** The observed rate of confirmed hypoglycaemic episodes per 100 PYE was higher with IDeg 3TW than with IGlar OD (158 and 100, respectively). The estimated rate ratio (IDeg 3TW/IGlar OD) for confirmed hypoglycaemia was 1.58 $[1.03; 2.43]_{95\%\,CI.}$ The observed rate of nocturnal confirmed hypoglycaemic episodes was similar with IDeg 3TW and IGlar OD (24 and 23 episodes per 100 PYE, respectively). The estimated rate ratio (IDeg 3TW/IGlar OD) for nocturnal confirmed hypoglycaemia was 0.60 per 100 PYE $[0.21; 1.69]_{95\%\,CI.}$ Severe hypoglycaemia was reported by 1 subject in the IDeg 3TW group (1 episode). No subjects had any nocturnal severe hypoglycaemia episodes.
- **Adverse events:** Adverse events were reported by 59.7% and 50.9% of subjects in the IDeg 3TW group and the IGlar OD groups, respectively. The rate of all adverse events was numerically higher for the IDeg 3TW group than the IGlar OD group (404 and 279 events per 100 PYE, respectively), while the rates of severe adverse events were similar in the two groups (13 and 12 events per 100 PYE, respectively). The majority of events in both treatment groups were mild in severity. The most frequent adverse events in both treatment

groups were diarrhoea, headache and nasopharyngitis. The rates of adverse events possibly or probably related to investigational product were numerically higher with IDeg 3TW than with IGlar OD (70 and 22 events per 100 PYE), and the most frequent were injection site haematoma and injection site pain. The percentage of subjects with injection site reactions was 6.4% and 3.0% in the IDeg 3TW and IGlar OD groups, respectively.

- **Deaths, serious adverse events and other significant adverse events:** No deaths were reported in this trial. A total of 13 (5.6%) and 12 (5.1%) subjects reported serious adverse events (SAEs) in the IDeg 3TW and IGlar OD groups, respectively. The rate of SAEs per 100 PYE was similar in the two treatment groups (IDeg 3TW: 13, IGlar OD: 15). None of the SAEs occurred in more than one subject, except for 2 cases in the IGlar OD group (erysipelas). A single SAE was considered by the investigator to be probably related to the trial treatment (IDeg 3TW; hypoglycaemia). In all, 5 subjects withdrew from the trial due to an adverse event: 4 (1.7%) with IDeg 3TW and 1 (0.4%) with IGlar OD.
- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values**: Overall, no clinically relevant changes from baseline to end of treatment were seen in either treatment group. No clinically relevant differences between the treatment groups were observed for vital signs, ECG, fundoscopy/fundusphotography, physical examination and laboratory values.
- **Insulin dose:** The mean calculated daily basal insulin dose after 26 weeks was numerically lower in the IDeg 3TW than the IGlar OD treatment group: 51 U (0.54 U/kg) and 56 U (0.59 U/kg) for IGlar OD. The dose ratio of mean calculated daily insulin (U) was 0.92 for IDeg 3TW/IGlar OD. Mean actual doses administered on injection days were 119 U (1.25 U/kg) and 56 U (0.59 U/kg) for IDeg 3TW and IGlar OD, respectively.

Overall Conclusions

This confirmatory, randomised, controlled, 26-week trial compares the efficacy and safety of treatment with IDeg three times weekly injected in the evening versus IGlar injected once daily in subjects with type 2 diabetes mellitus. The data support the following conclusions:

- Glycaemic control as measured by HbA_{1c} improves in both treatment groups by approximately 1 %-point, however non-inferiority of IDeg 3TW to IGlar OD cannot be confirmed.
- Subjects treated with IDeg 3TW experience more confirmed hypoglycaemic episodes than subjects treated with IGlar OD. The rate of nocturnal hypoglycaemia is not statistically significantly different between IDeg 3TW and IGlar OD.
- No safety issues are identified with IDeg 3TW; although a higher rate of adverse events is observed in the IDeg 3TW group, no particular clinical pattern emerges. There is no apparent difference between IDeg 3TW and IGlar OD with respect to other safety parameters or body weight 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 20 December 2010.