2 Synopsis

Trial Registration ID-number NCT01068678	**IND Number –** 76496 **EudraCT number –** 2009-011398-33
Title of Trial A Trial Comparing Efficacy and Safety of NN1250[1] and Insulin Glargine in Subjects With Type 2 Diabetes (BEGIN™: EASY AM)	
Investigators There were 94 principal investigators. [redacted] MD [redacted], was appointed signatory investigator: [redacted]	
Trial Sites The trial was conducted at 94 sites in 7 countries: Canada (14 sites), Czech Republic (5 sites), Israel (4 sites), Slovakia (5 sites), South Africa (3 sites), United Kingdom (8 sites) and United States (54 sites). In addition, 9 sites (United Kingdom (1 site) and United States (8 sites)) were approved, but did not enroll any subjects.	
Publications None	
Trial Period 25 February 2010 to 18 November 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

To confirm the efficacy of insulin degludec 3 times weekly (IDeg 3TW) + metformin ± dipeptidyl 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 was done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment between IDeg 3TW + metformin ± DPP-4 inhibitor and insulin glargine once daily (IGlar OD) + metformin ± DPP-4 inhibitor to a non-inferiority limit of 0.4%, and if non-inferiority was confirmed, to a superiority limit of 0%.

Secondary Objectives:

To confirm superiority of IDeg 3TW + metformin ± DPP-4 inhibitor to 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
- Insulin dose

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

- 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 3TW injected in the morning (from wake-up to before first meal of the day) and IGlar OD (same time each day according to local labelling), both in a population of insulin-naïve subjects with type 2 diabetes mellitus currently treated with 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 type and 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 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			705
Screening Failures			245
Withdrawn before Randomisation			0
Randomised	230 (100.0)	230 (100.0)	460 (100.0)
Exposed	227 (98.7)	229 (99.6)	456 (99.1)
Withdrawn at/after Randomisation	38 (16.5)	24 (10.4)	62 (13.5)
Ineffective Therapy	3 (1.3)	2 (0.9)	5 (1.1)
Non-Compliance With Protocol	5 (2.2)	1 (0.4)	6 (1.3)
Withdrawal Criteria	12 (5.2)	6 (2.6)	18 (3.9)
Other	18 (7.8)	15 (6.5)	33 (7.2)
Completed	192 (83.5)	206 (89.6)	398 (86.5)
Full Analysis Set	229 (99.6)	230 (100.0)	459 (99.8)
PP Analysis Set	201 (87.4)	211 (91.7)	412 (89.6)
Safety Analysis Set	227 (98.7)	229 (99.6)	456 (99.1)

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) by central laboratory analysis, body mass index (BMI) ≤ 45.0 kg/m2 and with current treatment: metformin monotherapy or metformin in any combination with insulin secretagogues (sulphonylurea 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.

Exclusion criteria: Subjects on 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 200 U/mL, 3 mL PDS290 (prefilled pen). IDeg 200 U/mL was to be injected 3 times weekly before first meal of the day (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 levels and an insulin titration guideline. No maximum insulin dose was specified. Batch Numbers: XL70031, YL70001 and YP50490.

Duration of Treatment

The total duration of the trial for each subject was approximately 29 weeks including screening and follow-up visits.

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, SoloStar™ 3 mL. 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 levels and an insulin titration guideline. No maximum insulin dose was specified. Batch Numbers: 40C408, 40C442, 40C531 and 40C712.

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
  - 1-point profile (SPMG)
  - 9-point profile (SPMG) with additional 1-point profile (SPMG)
- PRO questionnaires
- Body weight

Criteria for Evaluation – Safety

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

Statistical Methods

Analysis Sets

The following analysis sets were defined:

- Full analysis set (FAS): included all randomised subjects. 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: included subjects without any major protocol violations that may have affected 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: included all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set were to contribute to the evaluation as 'treated'.

Analyses of all efficacy endpoints were based on the FAS as were analyses of hypoglycaemia, 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 (Africa, Europe and North America) 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 (IDeg 3TW-IGlar OD) for the mean change in HbA_{1c} was below or equal to 0.4%. 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, body weight was tested to confirm superiority of IDeg 3TW over IGlar OD. 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 this endpoint where the previous hypothesis has 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 HbA1c 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 that used 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 covariates 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 prebreakfast 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 met the titration target 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 PRO 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. 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 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 (56 mg/dL). The number of treatment emergent confirmed and nocturnal 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 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 demographics and baseline characteristics in the treatment groups were similar with only marginal differences between the treatment groups. The population consisted of male and female subjects with type 2 diabetes mellitus, with a mean age of 58.1 years and a mean duration of diabetes of 8.8 years and with a mean HbA_{1c} of 8.2%. Body weight was slightly lower in the IDeg 3TW group (90.8 kg) than in the IGlar OD group (95.7 kg), but the BMI was similar in the two treatment groups (31.9 kg/m^2 and 33.0 kg/m^2, respectively). Approximately 25% of subjects in each treatment group were >65 years of age. The majority of the subjects (~85%) that reported their race were White. Slightly more male subjects were enrolled (56.9%) than females. The pre-trial antidiabetic treatment regimens were evenly distributed in the two treatment groups. The majority (~50%) of the subjects were treated with metformin in combination with insulin secretagogues and/or α-glucosidase inhibitors.

	IDeg 3TW	IGlar OD	Total
Number of Subjects	229	230	459
Age (years)			
N	229	230	459
Mean (SD)	58.4 (9.9)	57.9 (9.7)	58.1 (9.8)
Median	58.2	58.0	58.0
Min ; Max	30.9 ; 81.0	24.1 ; 80.1	24.1 ; 81.0
Age Group (N (%))			
Adults (18-65 years)	169 (73.8)	176 (76.5)	345 (75.2)
Adults (>65 years)	60 (26.2)	54 (23.5)	114 (24.8)
Body Weight (kg)			
N	229	230	459
Mean (SD)	90.8 (18.6)	95.7 (19.0)	93.3 (18.9)
Median	88.9	94.8	91.7
Min ; Max	49.0 ; 150.1	52.0 ; 146.1	49.0 ; 150.1
BMI (kg/m^2)			
N	229	230	459
Mean (SD)	31.9 (5.1)	33.0 (5.4)	32.4 (5.3)
Median	31.3	32.7	32.0
Min ; Max	20.7 ; 45.2	20.0 ; 45.5	20.0 ; 45.5

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	IDeg 3TW	IGlar OD	Total
Duration of Diabetes (years)			
N	229	230	459
Mean (SD)	9.2 (6.4)	8.5 (5.7)	8.8 (6.1)
Median	7.7	7.5	7.7
Min ; Max	0.5 ; 39.7	0.6 ; 29.8	0.5 ; 39.7
HbA1c (%)			
N	229	230	459
Mean (SD)	8.2 (0.8)	8.3 (0.9)	8.2 (0.8)
Median	8.1	8.1	8.1
Min ; Max	6.8 ; 10.2	6.6 ; 10.4	6.6 ; 10.4
FPG (mmol/L)			
N	229	229	458
Mean (SD)	9.3 (2.4)	9.6 (2.4)	9.5 (2.4)
Median	9.0	9.3	9.2
Min ; Max	2.8 ; 15.3	2.7 ; 18.7	2.7 ; 18.7

BMI = Body Mass Index, 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 0.34 %-points $[0.18; 0.51]_{95\%CI}$. The estimated mean change in HbA_{1c} was −0.93 %-point with IDeg 3TW and −1.28 %-points with IGlar OD. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.2 (1.0)% with IDeg 3TW and 6.9 (1.0)% with IGlar OD. As the primary hypothesis could not be confirmed, the hierarchical testing procedure was stopped.

Secondary Efficacy Endpoints:

Confirmatory Endpoint

- **Body weight:** Please refer to Safety Results and Conclusions

Supportive Efficacy Endpoints

- **Responders for HbA_{1c} (<7.0 %):** The observed proportion of subjects (exposed for at least 12 weeks) achieving HbA_{1c} <7% was 48.0% with IDeg 3TW and 58.3% with IGlar OD. The estimated odds of achieving this target were lower (39%) with IDeg 3TW compared to IGlar OD (estimated odds ratio (IDeg 3TW/IGlar OD) 0.61 $[0.41; 0.92]_{95\%CI}$).
- **Responders for HbA_{1c} (<7.0 %) without confirmed hypoglycaemia:** The observed proportion of subjects (exposed for at least 12 weeks) achieving HbA_{1c} <7% without confirmed hypoglycaemic episodes was 41.7% with IDeg 3TW and 44.9% with IGlar OD. The estimated odds of achieving this target was similar for both treatment groups (estimated odds ratio (IDeg 3TW/IGlar OD) 0.87 $[0.58; 1.32]_{95\%CI}$).
- **Responders for HbA_{1c} (<7.0 %) without severe hypoglycaemia:** The observed proportion of subjects (exposed for at least 12 weeks) achieving HbA_{1c} <7% without severe hypoglycaemic episodes was 53.4% with IDeg 3TW and 61.7% with IGlar OD. There was no statistically significant difference between treatment groups (estimated odds ratio (IDeg 3TW/IGlar OD) 0.66 $[0.43; 1.01]_{95\%CI}$); nonetheless, the estimated odds of achieving this target was numerically lower (34%) with IDeg 3TW compared to IGlar OD.
- **FPG:** FPG decreased during the trial to observed mean (SD) levels of 6.8 (2.8) mmol/L and 6.2 (2.0) mmol/L with IDeg 3TW and IGlar OD, respectively. The decrease in FPG was smaller for subjects in the IDeg 3TW group than in the IGlar OD group; the estimated mean change in FPG was −2.64 mmol/L with IDeg 3TW and −3.35 mmol/L with IGlar OD and the estimated mean treatment difference (IDeg 3TW–IGlar OD) was 0.72 $[0.29; 1.14]_{95\%CI}$.
- **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 (8.30 mmol/L and 7.80 mmol/L, respectively); estimated mean treatment difference was 0.50 mmol/L $[0.16; 0.83]_{95\%CI}$, which was

primarily attributable to differences during the night and early morning hours. No statistically significant difference in PG fluctuation (mmol/L) was seen between treatments (estimated treatment ratio 0.93 [0.84; 1.04]$_{95\%CI}$. After 26 weeks of treatment, the mean increment across all meals was smaller with IDeg 3TW than with IGlar OD; the observed means were 2.1 mmol/L with IDeg 3TW and 2.4 mmol/L with IGlar OD (estimated treatment difference was −0.35 [−0.66; −0.04]$_{95\%CI}$). No statistically significant differences in nocturnal PG were seen between treatments; neither from bedtime to breakfast, from bedtime to 04:00 a.m. nor from 04:00 a.m. to breakfast.

- **1-point prebreakfast SMPG:** The estimated day-to-day variation (CV%) in prebreakfast SMPG was 23.06% with IDeg 3TW and 16.25% with IGlar OD. The estimated mean treatment ratio (IDeg 3TW/IGlar OD) was 1.42 [1.28; 1.55]$_{95\%CI}$). Hence, day-to-day variation was higher with IDeg 3TW compared to 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 small improvement in overall score was seen in both treatment groups. No statististically significant difference between IDeg 3TW and IGlar OD were seen for overall score or for any of the subcategories for the DiabMedSat. For the TRIM-D, statistically significant differences between treatments were identified in 'Total score' and the two subcategories 'Compliance' and 'Diabetes Management', with smaller improvements with IDeg 3TW than with IGlar OD. The estimated treatment differences were: 'Total score': −2.7 [−4.8; −0.5]$_{95\%CI}$, 'Compliance': −2.7 [−5.2; −0.1] $_{95\%CI}$, and 'Diabetes Management': −5.2 [−8.8; −1.5] $_{95\%CI}$. No statistically significant differences were detected in the other PRO assessments.

Safety Results and Conclusion

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. Mean (SD) body weight at baseline was 91.1 (18.8) kg in the IDeg 3TW group and 95.9 (18.9) kg in the IGlar OD group. After 26 weeks, body weight increased in both treatment groups to mean (SD) levels; 91.7 (18.4) kg with IDeg 3TW and 96.8 (18.9) kg with IGlar OD. The estimated mean change in body weight was 0.77 kg with IDeg 3TW and 1.18 kg with IGlar OD and the estimated mean treatment difference (IDeg 3TW − IGlar OD) was −0.41 [−1.08; 0.26]$_{95\%CI}$.
- **Hypoglycaemic episodes:** The observed rate of confirmed hypoglycaemic episodes per 100 PYE was 134 episodes with IDeg 3TW and 119 episodes with IGlar OD; estimated rate ratio (IDeg 3TW/IGlar OD) was 1.04 [0.69; 1.55]$_{95\%CI}$. The observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was higher with IDeg 3TW than with IGlar OD (38 and 18 episodes, respectively); the estimated rate ratio (IDeg 3TW/IGlar OD) was 2.12 [1.08; 4.16]$_{95\%CI}$. Severe hypoglycaemia was reported by 1 subject in each treatment group (1 episode each). Nocturnal severe hypoglycaemia was reported by 1 subject in the IDeg 3TW group (1 episode).
- **Adverse events:** A similar percentage of subjects reported adverse events in the IDeg 3TW and IGlar OD groups (61.7% and 65.9%, respectively). The rate of all adverse events was similar for the IDeg 3TW and IGlar OD groups (488 and 513 events per 100 PYE, respectively) as was the rate of severe adverse events (28 and 27 events per 100 PYE, respectively). The most frequent adverse events in both treatment groups were headache, diarrhoea and nasopharyngitis. The rates of adverse events possibly or probably related to investigational product were similar with IDeg 3TW and IGlar OD (81 and 76 events per 100 PYE); the most frequent were injection site haematoma, injection site reaction and headache. The percentage of subjects with injection site reactions was similar for the IDeg 3TW and IGlar OD groups (11.9% and 13.1%, respectively).
- **Deaths, serious adverse events and other significant adverse events:** No deaths were reported in the trial. A total of 11 (4.8%) and 4 (1.7%) subjects reported SAEs in the IDeg 3TW and IGlar OD groups, respectively. The rate of SAEs per 100 PYE was 12 in the IDeg 3TW group and 5 in the IGlar OD group. None of the preferred terms reported as SAEs occurred in more than one subject, except for 2 cases of unstable angina in the IDeg 3TW group. A single SAE was considered probably related to investigational product (IDeg 3TW; hypoglycaemia). No AEs were reported as leading to withdrawal in this trial.
- **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 group than in the IGlar OD group: 50 U (0.53 U/kg) for IDeg 3TW and 62 U (0.63 U/kg) for IGlar OD. The dose ratio of mean calculated daily insulin dose (U) was 0.81 for IDeg 3TW/IGlar OD. Mean actual doses administered on injection days were 116 U (1.24 U/kg) and 62 U (0.63 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 morning 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.
- The rate of confirmed hypoglycaemia does not differ between treatments. Subjects treated with IDeg 3TW experience more nocturnal confirmed hypoglycaemic episodes than subjects treated with IGlar OD.
- No safety issues are identified with IDeg 3TW; there is no apparent difference between IDeg 3TW and IGlar OD with respect to AEs, standard 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 10 December 2010.