2 Synopsis

Trial Registration ID-number NCT01006291	**EudraCT number –** 2008-005771-10
Title of Trial A 26 week randomised, controlled, open-label, multicentre, multinational, three-arm, treat-to-target trial comparing efficacy and safety of three different dosing regimens of either NN1250 [1] or insulin glargine with or without combination with OAD treatment, in subjects with type 2 diabetes mellitus (BEGIN™ FLEX)	
Investigators There were 69 principal investigators. Professor [redacted], MD, [redacted], was appointed signatory investigator: [redacted]	
Trial Sites The trial was conducted at 69 sites in 14 countries: Hungary (3 sites), Macedonia (1 site), Serbia (3 sites), Finland (7 sites), Norway (6 sites), United Kingdom (6 sites), Argentina (4 sites), Mexico (2 sites), South Africa (3 sites), India (10 sites), Malaysia (5 sites), Taiwan (3 sites), Russian Federation (8 sites) and Israel (8 sites). Additional 9 sites were approved, but did not recruit any subjects.	
Publications None	
Trial Period 30 November 2009 to 6 September 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

To confirm the efficacy of insulin degludec (IDeg) ± oral antidiabetic drug(s) (OADs) in a flexible dosing regimen in controlling glycaemia with respect to change from baseline in HbA_{1c} after 26 weeks of treatment. This is done by comparing the difference in change from baseline in glycosylated haemoglobin (HbA_{1c}) after 26 weeks of treatment between IDeg ± OAD(s) in a flexible dosing regimen 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 compare the efficacy of IDeg ± OAD(s) in a flexible regimen to the efficacy of IDeg ± OAD(s) in a fixed regimen in terms of change from baseline in HbA_{1c} after 26 weeks of treatment.
- To compare the efficacy and safety after 26 weeks of treatment between the 3 treatment groups in terms of:
  - Frequency of responders for HbA_{1c}
  - Frequency of responders for HbA_{1c} without hypoglycaemic episodes
  - Fasting plasma glucose (FPG) from central laboratory
  - Hypoglycaemic episodes
  - 9-point profile (self-measured plasma glucose [SMPG])
  - Prandial plasma glucose (PG) increment
  - SMPG for dose adjustments
  - Glucose profile as measured with continuous glucose monitoring (CGM) in a sub-population
  - Insulin dose

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

- Body weight
- Adverse events (AEs)
- Clinical and laboratory assessments
- Insulin antibodies
- Patient reported outcome (PRO)

Methodology

This was a multinational, multicentre, open-labelled, randomised, three-arm, parallel group trial comparing the efficacy and safety of IDeg injected once daily (OD) at defined intervals of approximately 8 to 40 h between doses (IDeg Flex) versus IGlar injected OD according to local labelling at approximately the same time daily in subjects with type 2 diabetes mellitus. Secondarily, the efficacy and safety of IDeg Flex was compared to IDeg injected OD with main evening meal.

The trial was stratified according to treatment prior to randomisation, where the intensity of treatment was used as classification. There were 3 levels in this classification:

- Basal: treatment with basal insulin only, at least OD
- OAD(s): treatment with OAD(s) only (± metformin ± sulphonylureas [SU] ± pioglitazone ± glinide)
- Basal and OAD(s): treatment with any combination of basal insulin at least OD and OAD(s)

All subjects treated with OAD(s) were to continue their current OAD treatment at the stable, pre-randomisation dose level and dosing frequency. The dose and dosing frequency was not to be changed at any time during the 26 weeks treatment period, unless for safety reasons. Metformin was to be taken orally with meals i.e. before the main meals.

The treatment groups consisted of subjects randomised to:

- IDeg Flex: administered OD according to a fixed flexible schedule with 8-40 h intervals between doses:
  - Monday, Wednesday and Friday: Injected in the morning
  - Tuesday, Thursday, Saturday and Sunday: Injected in the evening
- IDeg OD: administered OD at evening meal
- IGlar OD: administered OD according to local labelling

The trial included a screening visit, followed by a randomisation visit to assign treatment group. The subjects were required to attend a total of 15 visits and 14 phone contacts during the 26 weeks of treatment. At Visit 28 (Week 26) subjects switched basal insulin treatment to intermediate acting insulin Neutral Protamine Hagedorn (NPH) to washout the long acting insulin products before antibody measurements at the follow-up visit (Visit 29). Total duration of the individual subjects participating in the trial was approximately 28 weeks.

At selected trial sites, subjects were to undergo assessment of their 24 h interstitial glucose levels with a CGM device for 3 consecutive days at baseline (72 h before Visit 2) and at the end of the trial (Week 26). The assessment was mandatory for all subjects at these trial sites and the assessment was included in the subject information and in the informed consent form.

Number of Subjects Planned and Analysed

Based on the sample size calculation, the planned number of subjects to be screened and randomised was 965 and 675, respectively, while 573 subjects were expected to complete the trial

	IDeg OD FF N (%)	IDeg OD N (%)	IGlar OD N (%)	Total N (%)
Screened				946
Screening Failures				259
Withdrawn before Randomisation				0
Randomised	229 (100.0)	228 (100.0)	230 (100.0)	687 (100.0)
Exposed	230	226	229	685
Withdrawn at/after Randomisation	26 (11.4)	24 (10.5)	27 (11.7)	77 (11.2)
Adverse Event	2 (0.9)	1 (0.4)	2 (0.9)	5 (0.7)
Ineffective Therapy	2 (0.9)	2 (0.9)	1 (0.4)	5 (0.7)
Non-Compliance With Protocol	3 (1.3)	3 (1.3)	3 (1.3)	9 (1.3)
Withdrawal Criteria	5 (2.2)	4 (1.8)	4 (1.7)	13 (1.9)
Other	14 (6.1)	14 (6.1)	17 (7.4)	45 (6.6)
Completed	203 (88.6)	204 (89.5)	203 (88.3)	610 (88.8)
Full Analysis Set	229 (100.0)	228 (100.0)	230 (100.0)	687 (100.0)
PP Analysis Set	211 (92.1)	207 (90.8)	210 (91.3)	628 (91.4)
Safety Analysis Set	230	226	229	685

N: Number of subjects %: Proportion of randomised subjects
FF: Fixed Flexible (IDeg Flex); OD: Once daily; PP: Per protocol

Diagnosis and Main Criteria for Inclusion

Inclusion criteria: Male or female subjects aged ≥ 18 years, with type 2 diabetes mellitus (diagnosed clinically) ≥ 6 months, HbA_{1c} within 7.0-11.0% (both inclusive) for OAD only users and HbA_{1c} within 7.0-10.0% (both inclusive) for basal insulin ± OADs users by central laboratory analysis, BMI ≤ 40.0 kg/m^2 and current treatment with OAD(s) alone, basal insulin alone or the combination of OAD(s) and basal insulin for at least 3 months prior to Visit 1 were included in the trial. The following OADs were allowed with unchanged dosing for at least 3 months prior to visit 1: metformin, insulin secretagogues (sulphonylureas (SU) or glinides), and pioglitazone.

Exclusion criteria: Subjects were excluded from the trial if they had been treated with glucagon-like peptide 1 (GLP-1) receptor agonist (exenatide, liraglutide), rosiglitazone, dipeptyl peptidase-IV (DPP-IV) inhibitors and/or α-glucosidase-inhibitors within the last 3 months prior to Visit 1; had anticipated change in concomitant medication known to interfere significantly with glucose metabolism; had recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic event during the last 12 months) or hypoglycaemic unawareness; had been hospitalised for diabetic ketoacidosis during the previous 6 months; had proliferative retinopathy or maculopathy requiring treatment; or had previously participated in this trial.

A subject was to be withdrawn if the following applied:

- Hypoglycaemia during the treatment period posing a safety problem as judged by the investigator.
- Initiation or significant change of any systemic treatment which in the investigator's opinion could have interfered with glucose metabolism (inhaled corticosteroids were allowed).
- Lack of effect: After Week 12, if the subject had not had reduction in HbA_{1c} and had a pre-breakfast SMPG reading > 13.3 mmol/L (> 240 mg/dL) on 3 consecutive days despite appropriate dose adjustments and no treatable intercurrent cause for the hyperglycaemia was diagnosed.

Test Product, Dose and Mode of Administration, Batch Number

IDeg 100 U/mL, FlexPen® 3 mL ± OADs was administered OD with alternating morning and evening dosing (IDeg Flex) or OD with the evening meal (IDeg OD). IDeg was to be injected subcutaneously either in the thigh, upper arm (deltoid area) or abdomen. Rotation of injection sites within a given region was recommended. The injection area was not expected to affect the absorption kinetics in a clinically significant way.

Insulin doses were titrated weekly by the investigator based upon the subject's SMPGs and a titration guideline. No maximum insulin dose was specified. Batch Number: XP52063.

Duration of Treatment

The total duration of the trial for each subject was approximately 28 weeks including screening and follow-up visits.

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, SoloStar™ 3 mL (OD according to local labelling) ± OADs was administered. IGlar was to be administered according to local labelling. Batch Numbers: 40C458, 40U394 and 40C525.

Insulin NPH (Insulatard®/Protaphane®/Novolin N™) 100 IU/mL, FlexPen® 3 mL. BID morning and evening. Batch Number: XP52034.

All insulin products were to be injected subcutaneously either in the thigh, upper arm (deltoid area) or abdomen. Rotation of injection sites within a given region was recommended.

Insulin doses were titrated weekly by the investigator based upon the subject's SMPGs and a titration guideline. No maximum insulin dose was specified.

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - SMPG measurements (1-point profile)
  - 9-point profile (SMPG)
- CGM
- PRO questionnaire

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes (overall and nocturnal)
- 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): 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 as fixed factors, and age and baseline HbA_{1c} as covariates. The antidiabetic therapy at screening was a factor with the following five levels: treatment with one OAD (metformin or secretagogues or pioglitazone), combination of two OADs, combination of three OADs, basal

insulin alone, basal insulin and at least one OAD. The region was a factor with four levels: Europe (Hungary, Macedonia, Serbia, Finland, Norway, United Kingdom, Israel and Russian Federation), South America (Argentina and Mexico), Africa (South Africa) and Asia (India, Malaysia and Taiwan). Non-inferiority was to be considered confirmed if the upper bound of the two-sided 95% confidence interval for the treatment difference (IDeg Flex – 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 below 0%.

Supportive Secondary Efficacy Analyses

- The treatment difference for the comparison of HbA_{1c} after 26 weeks between IDeg Flex and IDeg OD was analysed in the same way as for the primary endpoint
- The HbA_{1c} responder endpoints (proportion of subjects reaching the HbA_{1c} targets with or without hypoglycaemia) were analysed separately based on a logistic regression model using same factors and covariates as for the primary analysis
- Change from baseline in FPG after 26 weeks of treatment (analysed at a central laboratory) 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 and baseline values 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(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 following endpoints were derived based on continuous glucose measurements (CGM): Mean and variation in interstitial glucose (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 episodes of low and high IG were analysed separately for the different targets using a negative binomial regression model with a log-link function and the logarithm to duration of the profile as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate.
- The change in patient reported outcome score from baseline was analysed separately using an ANOVA method similar to that used for the primary analysis.

Safety Analyses

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

nocturnal. Hypoglycaemic episodes were classified according to the ADA classification into the following five categories based on BG measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia. Furthermore, confirmed hypoglycaemic episodes were defined as episodes of severe hypoglycaemia and minor hypoglycaemic episodes with a confirmed PG value of less than 3.1 mmol/L (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.

- 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 26 weeks of treatment was analysed using an ANOVA method similar to that used for the primary analysis.
- Remaining laboratory parameters, physical examination, ECG, fundoscopy / fundusphotography and vital signs 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 majority of the subjects that reported their race were White and of non-Hispanic/Latino origin. The baseline demographic and diabetes characteristics are shown in the table below. The pre-trial anti-diabetic treatment regimens were evenly distributed in the two treatment groups. The majority (57.9%) of the subjects were treated with OADs only, while 38.7% were treated with basal insulin plus at least one OAD. Of the subjects treated with OADs only, the majority were treated with 2 OADs. With basal insulin, the most common treatment was basal insulin plus 2 OADs.

	IDeg OD FF	IDeg OD	IGlar OD	Total
Number of Subjects	229	228	230	687
Age (years)				
N	229	228	230	687
Mean (SD)	56.2 (10.3)	56.5 (9.6)	56.7 (8.8)	56.4 (9.6)
Median	58.2	57.3	57.0	57.5
Min ; Max	23.1 ; 78.6	22.9 ; 80.9	32.5 ; 80.1	22.9 ; 80.9
Height (m)				
N	229	228	230	687
Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.6 (0.1)	1.7 (0.1)
Median	1.7	1.7	1.6	1.7
Min ; Max	1.4 ; 1.9	1.4 ; 1.9	1.4 ; 1.9	1.4 ; 1.9
BMI (kg/m^2)				
N	229	228	230	687
Mean (SD)	29.3 (4.6)	29.4 (4.9)	30.0 (4.7)	29.6 (4.7)
Median	29.0	29.4	29.4	29.3
Min ; Max	17.7 ; 40.8	16.2 ; 40.0	19.5 ; 39.8	16.2 ; 40.8
Duration of Diabetes (year)				
N	229	228	230	687
Mean (SD)	10.8 (6.9)	10.3 (6.7)	10.8 (6.4)	10.6 (6.7)
Median	9.5	9.3	9.7	9.5
Min ; Max	0.8 ; 40.4	0.6 ; 40.6	0.5 ; 39.5	0.5 ; 40.6
HbA1c (%)				
N	229	228	230	687
Mean (SD)	8.5 (1.0)	8.4 (0.9)	8.4 (0.9)	8.4 (0.9)
Median	8.4	8.2	8.4	8.3
Min ; Max	6.2 ; 11.1	6.5 ; 11.1	6.8 ; 11.1	6.2 ; 11.1
FPG (mmol/L)				
N	226	228	225	679
Mean (SD)	9.0 (2.6)	8.8 (2.8)	9.0 (2.8)	8.9 (2.7)
Median	8.8	8.5	8.8	8.7
Min ; Max	3.9 ; 20.0	3.3 ; 19.9	3.7 ; 19.3	3.3 ; 20.0

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

Efficacy Results and Conclusions

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

Primary Endpoint (HbA_{1c})

- **HbA_{1c}**: IDeg Flex was noninferior to IGlar OD in terms of lowering HbA_{1c} with an estimated treatment difference (IDeg Flex – IGlar OD) of 0.04 %-points, $[-0.12; 0.20]_{95\%CI}$. The estimated change in mean HbA_{1c} was -1.17 %-points with IDeg Flex and -1.21 %-points with IGlar OD. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.2 (0.9) % with IDeg Flex, 7.3 (1.0) % with IDeg OD and 7.1 (0.9) % with IGlar OD.

Secondary Efficacy Endpoints

- **HbA_{1c}:** IDeg Flex was noninferior to IDeg OD in terms of lowering HbA_{1c} with an estimated treatment difference (IDeg Flex – IDeg OD) of -0.13 %-points, $[-0.29; 0.03]_{95\%}$CI
- **Responder for HbA_{1c} (<7.0 %):** The observed proportion of subjects who achieved HbA_{1c} < 7% was 38.9%, 40.8% and 43.9% with IDeg Flex, IDeg OD and IGlar OD. The estimated odds of achieving this target were 0.55 with IDeg Flex, 0.55 with IDeg OD and 0.67 with IGlar OD, with no significant difference between treatments; estimated odds ratio (IDeg Flex/IGlar OD) 0.82 $[0.54; 1.23]_{95\%CI}$ and (IDeg Flex/IDeg OD) 1.00 $[0.66 ; 1.51]_{95\%CI}$.
- **Responder for HbA_{1c} (<7.0 %) without severe hypoglycaemia:** The observed proportion of subjects (exposed for at least 12 weeks) who achieved HbA_{1c} < 7.0% without severe hypoglycaemic episodes (during the last 12 weeks of treatment) was 40.8%, 44.3% and 46.9% with IDeg Flex, IDeg OD and IGlar OD. The estimated odds of achieving this target were 0.63 with IDeg Flex, 0.63 with IDeg OD and 0.78 with IGlar OD, with no significant difference between treatments; estimated odds ratio (IDeg Flex/IGlar OD) 0.82 $[0.53 ;1.25]_{95\%CI}$ and (IDeg Flex/IDeg OD) 1.01 $[0.65; 1.55]_{95\%CI}$.
- **Responder for HbA_{1c} (<7.0 %) without confirmed hypoglycaemia:** The observed proportion of subjects (exposed for at least 12 weeks) who achieved HbA_{1c} <7.0% without confirmed hypoglycaemic episodes (during the last 12 weeks of treatment) was 26.5%, 30.0% and 32.2% with IDeg Flex, IDeg OD and IGlar OD. The estimated odds of achieving this target were 0.35 with IDeg Flex, 0.37 with IDeg OD and 0.44 with IGlar OD, with no significant difference between treatments; estimated odds ratio (IDeg Flex /IGlar OD) 0.80 $[0.51; 1.26]_{95\%CI}$ and (IDeg Flex/IDeg OD) 0.96 $[0.61; 1.53]_{95\%CI}$
- **FPG:** After 26 weeks of treatment, the observed mean (SD) FPG was 5.8 (2.0) mmol/L with IDeg Flex, 5.8 (2.4) mmol/L with IDeg OD and 6.2 (2.4) mmol/L with IGlar OD. The estimated treatment difference (IDeg Flex - IGlar OD) was -0.42 mmol/L $[-0.82 ;-0.02]_{95\%CI}$ and (IDeg OD Flex - IDeg OD) 0.05 mmol/L $[-0.45 ; 0.35]_{95\%CI}$. Hence, the estimated reduction in FPG was greater with IDeg Flex than with IGlar OD with the upper bound of the 95% confidence interval below 0.
- **9–point SMPG profiles:** The observed fluctuation in 9-point profile after 26 weeks was 1.3, 1.4 and 1.4 (mmol/L) with IDeg Flex, IDeg OD and IGlar OD, with no treatment difference; estimated treatment ratio (IDeg Flex / IGlar OD) 0.97 $[0.88 ; 1.06]_{95\%CI}$ and (IDeg Flex/IDeg OD) 0.94 $[0.86 ; 1.04]_{95\%CI}$. There were no marked changes in prandial SMPG increments with any of the three treatment groups, for any of the meals.
- **Prebreakfast SMPG:** The estimated day-to-day variation (CV%) in prebreakfast SMPG was 19.22% with IDeg Flex, 18.46% with IDeg OD and 17.25% with IGlar OD. The estimated treatment ratio (IDeg Flex/ IGlar OD) was 1.11 $[1.01; 1.22]_{95\%CI}$, and (IDeg Flex/ IDeg OD) 1.04 $[0.94; 1.14]_{95\%CI}$. Hence, day-to-day variation was lower with IGlar OD compared to IDeg Flex.
- **CGM-related endpoints in subpopulation:** After 26 weeks, the observed mean of the nocturnal IG profile was 8.1 mmol/L with IDeg Flex, 7.8 mmol/L with IDeg OD and 7.3 mmol/L with IGlar OD. The observed fluctuation in the nocturnal IG profile was 0.8 mmol/L for all three groups. Apart from the number of nocturnal episodes of IG > 9 mmol/L being higher with IDeg Flex than with IGlar (estimated treatment ratio 1.56 $[1.09; 2.23]_{95\%CI}$, no statistically significant treatment differences (IDeg Flex - IGlar OD) could be identified for the CGM endpoints. For the comparison of IDeg Flex vs. IDeg OD, the mean profile of IDeg Flex was lower. In addition, statistically significant differences in other CGM endpoints were identified, but these are of minor clinical importance.
- **PRO:** Statistical analysis indicated a higher perception of compliance with IDeg OD than with IDeg Flex based on the TRIM-D questionnaire; estimated treatment difference (IDeg Flex – IDeg OD) was -2.9 $[5.7; 0.0]_{95\%CI}$. Apart from this, the results related to PRO appear to be similar between the treatment groups, with only marginal changes over time.

Safety Results and Conclusions

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

- **Hypoglycaemic episodes:** There was no difference between treatment groups in the rate of confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes, or episodes of severe or nocturnal severe hypoglycaemia. The observed rate of confirmed hypoglycaemic episodes was numerically similar between the IDeg Flex, IDeg OD and IGlar OD treatment groups (364, 363 and 348 episodes per 100 PYE). Few (2) episodes of severe hypoglycaemia were reported in each of the three treatment groups. Of these, 3 were nocturnal severe hypoglycaemia episodes (IDeg Flex: 2 and IGlar OD:1). The percentage of subjects who experienced nocturnal confirmed hypoglycaemic episodes during the treatment period was numerically lower with IDeg Flex and IDeg OD than with IGlar OD (13.5%, 10.5% and 21.4%, respectively). Statistical analysis of confirmed hypoglycaemic episodes indicated that there was no difference between treatment groups as the estimated rate ratios (IDeg Flex/IGlar and IDeg Flex/IDeg OD) for confirmed hypoglycaemia were 1.03 $[0.75; 1.40]_{95\% CI}$ and 1.10 $[0.79; 1.52]_{95\% CI}$, respectively.
- **Body weight:** All three treatment groups were associated with a numerically similar weight gain after 26 weeks as the 95% CI of the estimated treatment difference included 0 (IDeg Flex – IGlar OD: 0.27 kg $[-0.25; 0.79]_{95\% CI}$; IDeg Flex - IDeg OD: 0.00 kg $[-0.53; 0.52]_{95\% CI}$). Mean (SD) body weight at baseline and at the end of the trial was 81.3 (16.3) kg and 82.7 (16.6) kg in the IDeg Flex group, 81.8 (17.1) kg and 83.4 (17.7) kg in the IDeg OD group and 82.1 (16.6) kg and 83.3 (16.7) kg in the IGlar OD group, respectively.
- **Adverse events:** There was no clinically relevant difference between the three treatment groups in reported adverse events. A similar percentage of subjects reported adverse events in the IDeg Flex, IDeg OD and IGlar OD groups (53%, 57% and 56%, respectively). The rates of all adverse events were numerically similar for the IDeg Flex, IDeg OD and IGlar OD groups (402, 394 and 383 events per 100 PYE, respectively) as were the rates of severe adverse events (7, 12 and 8 events per 100 PYE, respectively). The rates of adverse events possibly or probably related to investigational product were numerically similar with IDeg Flex, IDeg OD and IGlar OD (34, 25 and 23 events per 100 PYE). The most frequent adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infection and headache. The most frequent adverse events considered by the investigator to be possibly/probably related to trial products were diabetic retinopathy, headache and hypoglycaemia. The percentage of subjects with injection site disorders was low in all three treatment groups: 1.3% (5 events), 3.5% (12 events) and 1.7% (5 events), in the IDeg Flex, IDeg OD and IGlar OD groups, respectively.
- **Deaths, serious adverse events and other significant adverse events:** Two deaths were reported in this trial: 1 (anaemia and myelodysplastic syndrome) in the IDeg OD group and 1 (cause of death unknown) in the IGlar OD group. A total of 6 (2.6%), 8 (3.5%) and 4 (1.7%) subjects reported SAEs in the IDeg Flex, IDeg OD and IGlar OD groups, respectively. The rate of SAEs per 100 PYE was low in all treatment groups (IDeg Flex: 8, IDeg OD: 11; IGlar OD: 4). A similar percentage of subjects withdrew from the trial due to AEs in the IDeg Flex, IDeg OD and IGlar OD treatment groups (0.9%, 0.4% and 0.9%, respectively).
- **Insulin antibodies:** The mean level of insulin antibodies cross-reacting between insulin degludec (respective comparator) and human insulin was low at baseline and remained low after 26 weeks of treatment.
- **Vital signs, ECG, fundoscopy, physical examination and laboratory values:** No clinically relevant differences from baseline to end of treatment or between the three treatment groups were observed for vital signs, ECG, fundoscopy/fundusphotography, physical examination and laboratory values.
- **Insulin dose:** The mean daily basal insulin dose after 26 weeks was similar in the treatment groups: 46 U (0.55 U/kg) for IDeg Flex, 45 U (0.52 U/kg) for IDeg OD and 44 U (0.52 U/kg) for IGlar OD. The dose ratio of mean daily insulin dose (U) was 1.04 for IDeg Flex/IGlar OD, 1.04 for IDeg Flex/IDeg OD and 1.00 for IDeg OD/IGlar OD.

Overall Conclusions

This confirmatory, randomised, controlled 26-week trial in subjects with type 2 diabetes mellitus demonstrates the efficacy and safety of IDeg injected once daily, with varying dosing intervals (IDeg Flex) versus IGlar injected once daily according to local labelling (same time every day) or IDeg once daily in the evening (IDeg OD). Subjects were

previously treated with oral antidiabetic therapy, basal insulin or a combination of these.

The data support the following conclusions for IDeg used in a once-daily flexible regimen vs. IGlar OD administered at the same time every day:

- IDeg effectively improves long-term glycaemic control as measured by HbA_{1c} (noninferior to IGlar)
- IDeg reduces FPG more than IGlar, while IGlar is associated with a lower day-to-day variation in self-measured FPG
- Glucose levels are equally stable during the day on different treatment regimens as measured by fluctuations in self-measured plasma glucose
- The rate of confirmed hypoglycaemia does not differ between treatments; the flexible dosing regimen does not increase the risk of confirmed hypoglycaemia
- There are no statistically significant differences between treatments for the remaining efficacy endpoints, with the exception of minor differences observed with continuous glucose monitoring
- The average daily insulin dose is similar with IDeg and IGlar
- No safety issues are identified with IDeg; there are no apparent differences between IDeg and IGlar with respect to AEs, standard safety parameters or body weight. Antibody development is modest and injection site reactions are generally mild and infrequent (occur in less than 5% of subjects).

The data support the following conclusions for IDeg used in a once-daily flexible regimen vs. IDeg once-daily injected at the main evening meal:

- IDeg Flex effectively improves long-term glycaemic control as measured by HbA_{1c} (noninferior to IDeg OD)
- There are no statistically significant differences between treatments for the remaining efficacy endpoints, with the exception of minor differences observed with continuous glucose monitoring
- There are no apparent differences between IDeg Flex and IDeg OD with respect to hypoglycaemia, AEs, standard safety parameters or body weight.

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 06-Oct-2010