2 Synopsis

Trial Registration ID-number NCT01079234	**IND Number –** 76,496 **EudraCT number –** 2009-012923-27
Title of Trial A 26-week trial investigating the dosing flexibility, efficacy and safety of NN1250[1] in subjects with type 1 diabetes with a 26-week extension.	
Investigator(s) There were 71 principal investigators (1 principal investigator was appointed for each site.) [redacted] MD, was appointed the signatory investigator: [redacted].	
Trial Sites The trial was conducted at 71 sites in 6 countries: Belgium (5 sites), Germany (7 sites), Norway (5 sites), Poland (5 sites), United Kingdom (U.K.) (12 sites) and United States of America (U.S.) (37 sites). These sites enrolled subjects.	
Publications No publications were prepared as of the finalisation of this report.	
Trial Period 03 March 2010 to 12 November 2010	**Development Phase** Phase 3a

Objectives

Primary Objective:

To confirm the efficacy of insulin degludec (IDeg) administered once daily in a flexible dosing schedule in combination with meal-time insulin aspart (IAsp) 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 administered in this flexible regimen in combination with meal-time IAsp with insulin glargine (IGlar) administered once daily according to approved labelling in combination with meal-time IAsp 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 administered once daily in the flexible dosing schedule in combination with meal-time IAsp with the efficacy of IDeg administered once daily with the main evening meal in combination with meal-time IAsp, in terms of change from baseline 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 $HbA_{1c} < 7\%$
  - Fasting plasma glucose (FPG) from a central laboratory
  - 9-point self-measured plasma glucose (SMPG) profile
  - 4-point profiles (SMPG) for dose adjustments
  - Adverse Events (AEs)
  - Body weight
  - Hypoglycaemic episodes
  - Clinical and laboratory assessments
  - Insulin antibodies
  - Basal and bolus insulin doses

Methodology

This was a multinational, multi-centre, open-label, randomised, three-arm, parallel, treat-to-target trial comparing the efficacy and safety of IDeg injected once daily (OD) at intervals of approximately 8 to 40 h between doses (IDeg

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

Flex) versus IGlar injected OD according to local labelling at approximately the same time in subjects with type 1 diabetes mellitus. Secondarily, the efficacy and safety of IDeg Flex was compared to that of IDeg injected OD with the main evening meal. All subjects in the 3 treatment arms also injected IAsp at meal times.

The treatment groups consisted of subjects randomised to:

- IDeg Flex: administered OD according to a flexible dosing schedule with 8 to 40 h intervals between doses:
  - Monday, Wednesday and Friday: injected in the morning (morning was defined as the time period from waking up to first meal of the day)
  - Tuesday, Thursday, Saturday and Sunday: injected in the evening (evening was defined as the time period from start of main evening meal to bedtime)
- IDeg OD: administered OD with the evening meal
- IGlar OD: administered OD according to local labelling

The trial included a screening visit (Visit 1) to assess subject eligibility, followed by a randomisation visit (Visit 2) approximately 1 week later to assign treatment group. At this visit, the subjects were randomised to a treat-to-target basal-bolus insulin regimen in a 1:1:1 fashion (IDeg Flex: IDeg OD: IGlar OD). 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 the intermediate-acting Neutral Protamine Hagedorn (NPH) insulin to wash out the long-acting insulin products before taking antibody measurements at the follow-up visit (Visit 29). The total duration of trial participation by each individual subject was approximately 28 weeks.

During the treatment period, both basal and bolus insulin doses were to be self-titrated by the subjects. The basal insulin dose was to be adjusted 3 times weekly, whereas bolus insulin doses was to be adjusted on a daily basis according to the subject's needs. It was the responsibility of the investigator to instruct, discuss and advise the subjects on self-adjustment of insulin doses based on daily self-measured plasma glucose (SMPG), the recommendations of the Insulin Titration Guideline and the treat-to-target approach.

All subjects who completed the main trial period were encouraged to participate in an extension trial period following the 1-week follow-up period. The purpose of the extension trial was to collect safety data. In this case, verbal and written information was to be provided to the subjects. Further, an informed consent form was to specifically be signed by the subject and the investigator for the extension trial.

Number of Subjects Planned and Analysed

The planned number of subjects to be screened (695) and to be randomised (486) and to complete the main trial (411) was based on the sample size calculation. The numbers of subjects included in the trial are shown below.

	IDeg OD FF N (%)	IDeg OD N (%)	IGlar OD N (%)	Total N (%)
Screened				549
Screening Failures				56
Withdrawn before Randomisation				0
Randomised	164 (100.0)	165 (100.0)	164 (100.0)	493 (100.0)
Exposed	164 (100.0)	165 (100.0)	161 (98.2)	490 (99.4)
Withdrawn at/after Randomisation	26 (15.9)	26 (15.8)	12 (7.3)	64 (13.0)
Adverse Event	5 (3.0)	4 (2.4)	1 (0.6)	10 (2.0)
Ineffective Therapy	2 (1.2)	1 (0.6)	1 (0.6)	4 (0.8)
Non-Compliance With Protocol	6 (3.7)	2 (1.2)	4 (2.4)	12 (2.4)
Withdrawal Criteria	6 (3.7)	6 (3.6)	2 (1.2)	14 (2.8)
Other	7 (4.3)	13 (7.9)	4 (2.4)	24 (4.9)
Completed	138 (84.1)	139 (84.2)	152 (92.7)	429 (87.0)
Full Analysis Set	164 (100.0)	165 (100.0)	164 (100.0)	493 (100.0)
PP Analysis Set	141 (86.0)	152 (92.1)	156 (95.1)	449 (91.1)
Safety Analysis Set	164 (100.0)	165 (100.0)	161 (98.2)	490 (99.4)

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

Diagnosis and Main Criteria for Inclusion

Patients were eligible for inclusion in the trial if they were men or women aged ≥ 18 years with type 1 diabetes mellitus (clinically diagnosed and treated on basal-bolus regimen) for ≥ 12 months with an HbA_{1c} of ≤ 10.0% by central laboratory analysis and a body mass index (BMI) of ≤ 35.0 kg/m^2 and were currently treated with any basal insulin (e.g., IGlar, IDet, NPH insulin) using 1 or 2 daily injections and no less than 3 injections with bolus insulin (e.g. IAsp, insulin lispro [ILis], insulin glulisine [IGlu], human insulin [HI]) as meal-time bolus insulin therapy and had the ability to self-manage insulin therapy as assessed by confirmation (verbal confirmation at screening visit) of a changed bolus insulin dose the preceding 2 months prior to screening.

Patients were excluded from the trial if they had used any antidiabetic glucose lowering drug other than insulin within the last 3 months, initiated or significantly changed any systemic treatment that in the investigator's opinion could interfere with glucose metabolism, previously participated in this trial, had a 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 1 diabetes that in the investigator's opinion could interfere with the results of the trial.

Test Product, Dose and Mode of Administration, Batch Number

IDeg 100 U/mL, FlexPen®, 3 mL was administered once daily with alternating morning or evening dosing (IDeg Flex) or with the evening meal (IDeg OD). IDeg was to be injected subcutaneously either in the thigh, upper arm (deltoid area) or abdomen as preferred by the subject. The subjects were to be instructed by the investigator to self-adjust their basal insulin doses according to the Insulin Titration Guideline on the basis of their SMPG values. For subjects in either the IDeg Flex or IDeg OD arms, the basal insulin dose was to be adjusted on Mondays, Wednesdays and Fridays on the basis of the mean prebreakfast SMPG values of the preceding 2 to 3 days. No maximum insulin dose was specified.
Batch No. XP52863 (used in all countries) and Batch No. YP50743 (used in UK).

Duration of Treatment

The total duration for each individual subject participating in the trial was approximately 28 weeks, including the 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 according to the approved labelling and administered subcutaneously injections in the thigh, upper arm or stomach as preferred by the subjects. The IGlar dose was to be adjusted on Mondays, Wednesdays and Fridays on the basis of the mean prebreakfast SMPG values of the preceding 2 to 3 days. No maximum insulin dose was specified. (Batch Nos. 40C408 [U.S.] and 40C531 [all countries except the U.S.]).
IAsp, 100 U/mL, FlexPen®, 3 mL. IAsp was to be injected at meal times subcutaneously either in the abdominal region, thigh, upper arm (deltoid area) or the gluteal region as preferred by the subject. (Batch No. XP52945).
Adjustment of daily meal-time doses of IAsp as follows:

- Pre-breakfast IAsp dose was to be titrated according to the preceding day's pre-lunch SMPG.
- Pre-lunch IAsp dose was to be titrated according to the preceding day's pre-dinner SMPG.
- Pre-dinner IAsp dose was to be titrated according to the preceding day's bedtime SMPG.

Human isophane insulin, Neutral Protamine Hagedorn insulin, 100 IU/mL, FlexPen®, 3 mL (Batch No. YP50037).
NPH insulin was to be injected twice-daily during the follow-up period (from Weeks 26 to 27). To determine the dose of NPH insulin to be taken during the follow-up period, the total daily basal dose at the end of the treatment period was to be reduced by 20% and divided by 2 to be administered morning and evening.

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - 4-point profile (SMPG)
  - Combined 9-point & 4-point profiles (SMPG) before selected trial site visits
- Hypoglycaemic episode - Interview questionnaire

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes
- Basal and bolus insulin doses (and adjustment)
- Physical examination
- Vital signs
- Eye Examination
- Electrocardiogram (ECG)
- Laboratory safety variables
- Body weight

Statistical Methods

The following analysis sets were defined:

- Full analysis set (FAS): 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 IDeg or IGlar 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 IDeg or IGlar. 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 treatments was to be 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 two levels: 1. twice daily basal injections, 2. once daily basal injection. The region was a factor with 2 levels: Europe (Germany, Poland, Belgium, Norway and U.K.) and North America (U.S.). 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 analysis.
- The responder endpoints were analysed separately based on a logistic regression model using the same factors and covariates as those used for the primary analysis.
- Change from baseline in FPG after 26 weeks (analysed at a central laboratory) was analysed using an ANOVA model similar to that used for the primary analysis.
- 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 covariate and subject as random effect. From the model, the mean profile by treatment and relevant treatment differences was estimated and explored. Mean and fluctuation in the 9-point SMPG profile, prandial PG increment and nocturnal PG endpoints were analysed separately using an ANOVA model similar to that used for the primary endpoint. Fluctuation in the 9-point profile (SMPG) was logarithmically transformed before being analysed.
- The mean prebreakfast PG values after 26 weeks were analysed using an ANOVA model similar to that used for the primary endpoint. 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.

Safety Analyses

- A treatment-emergent adverse event (TEAE) was defined as an event that had an 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 13.1) of the Medical Dictionary for Regulatory Activities (MedDRA) coding. Evaluation of TEAEs was based on descriptive statistics. Adverse events were also presented as the rate of 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 h and 05:59 h (both included) was considered nocturnal. Hypoglycaemic episodes were classified according to the ADA classification into the following five categories based on blood glucose (BG) measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia. Further, 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 in which a hypoglycaemic episode was 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. Hypoglycaemic episodes were also presented as the rate of events per 100 PYE.
- Antibodies specific for IDeg, IAsp and IGlar, as well as antibodies cross-reacting to human insulin were presented 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.
- Other laboratory parameters, physical examination, ECG, fundoscopy or fundusphotography and vital signs were evaluated using descriptive statistics.

Demography of Trial Population

The demographics and baseline characteristics in the 3 treatment groups were similar, with one exception: 62.2% of the subjects in the IDeg Flex group were men, compared with 57% in the IDeg OD group and 53.7% in the IGlar OD group. The majority of subjects were White (97.6%). The majority of subjects were of Non-Hispanic or Non-Latino ethnicity (96.6%). The baseline demographics and diabetes characteristics are shown in the table below. The different pre-trial regimens were equally represented in the 3 treatment groups. The majority (70.6%) of all subjects were treated with basal-bolus regimens involving once-daily basal insulin plus three or more bolus insulin injections, while 28.8% were treated with basal-bolus regimens involving twice-daily basal insulin plus three or more bolus insulin injections. The most commonly used basal insulin products were IGlar (63.7% of all subjects) and IDet (27.2% of all subjects).

	IDeg OD FF	IDeg OD	IGlar OD	Total
Number of Subjects	164	165	164	493
Age (years)				
N	164	165	164	493
Mean (SD)	42.6 (13.4)	44.5 (13.1)	44.1 (12.6)	43.7 (13.1)
Median	41.4	43.6	44.9	43.5
Min ; Max	19.3 ; 82.4	20.1 ; 76.2	20.5 ; 71.6	19.3 ; 82.4
Body Weight (kg)				
N	164	165	164	493
Mean (SD)	81.7 (15.5)	79.5 (15.5)	80.4 (15.6)	80.6 (15.5)
Median	80.8	79.4	81.0	80.6
Min ; Max	46.9 ; 123.7	42.3 ; 130.8	47.0 ; 120.6	42.3 ; 130.8

BMI (kg/m^2)				
N	164	165	164	493
Mean (SD)	27.0 (3.8)	26.4 (4.0)	26.8 (4.0)	26.7 (3.9)
Median	27.4	26.1	26.5	26.5
Min ; Max	18.6 ; 35.0	16.9 ; 35.1	18.4 ; 34.9	16.9 ; 35.1
Duration of Diabetes (years)				
N	164	165	164	493
Mean (SD)	17.3 (12.2)	20.0 (12.5)	18.2 (11.9)	18.5 (12.2)
Median	14.7	18.1	15.6	16.0
Min ; Max	1.1 ; 52.7	1.1 ; 51.7	1.3 ; 49.1	1.1 ; 52.7
HbA1c (%)				
N	164	165	164	493
Mean (SD)	7.7 (1.0)	7.7 (0.9)	7.7 (0.9)	7.7 (0.9)
Median	7.7	7.7	7.7	7.7
Min ; Max	5.2 ; 10.0	5.2 ; 10.2[a]	5.4 ; 9.7	5.2 ; 10.2
FPG (mmol/L)				
N	161	164	162	487
Mean (SD)	9.6 (4.1)	10.0 (4.0)	9.7 (4.2)	9.8 (4.1)
Median	9.4	10.0	9.2	9.5
Min ; Max	0.9 ; 20.4	2.4 ; 23.9	2.4 ; 28.1	0.9 ; 28.1

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation, FPG = Fasting Plasma Glucose; % = proportion of subjects

[a]The maximum values for HbA_{1c} and BMI in the IDeg OD group were above the limit allowed in the inclusion criteria, due to an increase in HbA_{1c} in one subject ([redacted] from 9.9% at visit 1 to 10.2% at visit 2, and due to an increase in BMI in one subject ([redacted] from 34.6 kg/m^2 to 35.3 kg/m^2, respectively. These subjects met the selection criteria on the basis of their respective HbA_{1c} and BMI values at Visit 1.

Efficacy Results

After 26 weeks of treatment with IDeg Flex, IDeg OD or IGlar OD, all injected in a basal-bolus regimen with IAsp, the following was concluded:

Primary Endpoint

- **HbA_{1c}**: IDeg Flex was non-inferior to IGlar OD in terms of lowering HbA_{1c}, with an estimated treatment difference (IDeg Flex – IGlar OD) of 0.17% points $[0.04;0.30]_{95\%CI}$. The estimated mean change in HbA_{1c} was –0.40% points with IDeg Flex and –0.57% points with IGlar OD. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.3 (0.9)% with IDeg Flex and 7.1 (0.8)% with IGlar OD.

Secondary Efficacy Endpoints

- **HbA_{1c}:** IDeg Flex was non-inferior to IDeg OD in terms of lowering HbA_{1c}, with an estimated treatment difference (IDeg Flex – IDeg OD) of 0.01% points $[-0.13; 0.14]_{95\%CI}$. The estimated mean change in HbA_{1c} was –0.40% points with IDeg Flex and –0.41% points with IDeg OD. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.3 (0.9)% with IDeg Flex and 7.3 (0.9)% with IDeg OD.
- **Responders for HbA_{1c} <7%:** The observed proportion of subjects who achieved HbA_{1c} <7% was 37.2%, 37.0% and 40.9% with IDeg Flex, IDeg OD and IGlar OD, respectively. The estimated odds of achieving this target were 0.38 with IDeg Flex, 0.38 with IDeg OD and 0.55 with IGlar OD, with no statistically significant difference between IDeg Flex and IGlar OD, and between IDeg Flex and IDeg OD as the estimated odds ratio (IDeg Flex/IGlar OD) was 0.69 $[0.40;1.21]_{95\%CI}$ and (IDeg Flex/IDeg OD) was 1.01 $[0.58;1.77]_{95\%CI}$.
- **Responders for HbA_{1c} (<7%) without severe hypoglycaemia**: The observed proportion of subjects exposed for at least 12 weeks who achieved HbA_{1c} <7% without severe hypoglycaemia during the last 12 weeks of treatment was 37.8%, 36.6% and 38.5% with IDeg Flex, IDeg OD and IGlar OD, respectively. The estimated odds of achieving this target were 0.41 with IDeg Flex, 0.42 with IDeg OD and 0.54 with IGlar OD, with no statistically significant difference between treatments; the estimated treatment odds ratio (IDeg Flex/IGlar OD) was 0.76 $[0.43;1.33]_{95\%CI}$ and (IDeg Flex/IDeg OD) was 0.97 $[0.55;1.71]_{95\%CI}$.

- **Responders for HbA_{1c} (<7.0%) without confirmed hypoglycaemia**: The observed proportion of subjects exposed for at least 12 weeks who achieved HbA_{1c} <7% without confirmed hypoglycaemic episodes during the last 12 weeks of treatment was 2.8%, 5.2% and 3.2% with IDeg Flex, IDeg OD and IGlar OD, respectively. The estimated odds of achieving this target were 0.02 with IDeg Flex, 0.03 with IDeg OD and 0.02 with IGlar OD, with no statistically significant difference between treatments; the estimated treatment odds ratio (IDeg Flex/IGlar OD) was 0.72 $[0.18;2.84]_{95\%CI}$ and (IDeg Flex/IDeg OD) was 0.47 $[0.13;1.64]_{95\%CI}$.
- **FPG:** FPG decreased to a similar level in the IDeg Flex and IGlar OD treatment groups. After 26 weeks of treatment, the observed mean (SD) FPG was 8.3 (4.0) mmol/L with IDeg Flex, 7.4 (3.5) mmol/L with IDeg OD and 8.4 (3.6) mmol/L with IGlar OD. The estimated treatment difference (IDeg Flex − IGlar OD) was −0.05 mmol/L $[-0.85;0.76]_{95\%CI}$ and (IDeg Flex − IDeg OD) was 0.95 mmol/L $[0.15;1.75]_{95\%CI}$.
- **9-point SMPG Profiles**: The observed fluctuation in 9-point profile after 26 weeks was 1.7, 1.7 and 1.6 mmol/L with IDeg Flex, IDeg OD and IGlar OD, respectively, with no treatment difference; the estimated treatment ratio (IDeg Flex/IGlar OD) was 1.06 $[0.94;1.20]_{95\%\ CI}$ and (IDeg Flex/IDeg OD) was 0.98 $[0.87;1.11]_{95\%\ CI}$. There were no marked changes in prandial SMPG increments with any of the 3 treatment groups for any meals.
- **Prebreakfast SMPG for Dose Adjustment**: The estimated day-to-day variation (CV%) in prebreakfast SMPG was 40.11%, 42.20% and 41.97% with IDeg Flex, IDeg OD and IGlar OD, respectively. The estimated treatment ratio (IDeg Flex/IGar OD) was 0.96 $[0.84;1.07]_{95\%CI}$ and (IDeg Flex/IDeg OD) was 0.95 $[0.84;1.07]_{95\%CI}$, with no statistically significant difference between IDeg Flex and IGlar OD, and between IDeg Flex and IDeg OD.

Safety Results

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:** The rate of confirmed hypoglycaemic episodes per 100 PYE was 8238, 8825 and 7973 episodes in the IDeg Flex, IDeg OD and IGlar OD groups, respectively. There were no statistically significant differences in confirmed hypoglycaemic episodes between IDeg Flex and IGlar OD, and between IDeg Flex and IDeg OD as the estimated rate ratios (IDeg Flex/IGlar OD and IDeg Flex/IDeg OD) were 1.03 $[0.85;1.26]_{95\%\ CI}$ and 0.92 $[0.76;1.12]_{95\%\ CI}$, respectively.

  The rate of severe hypoglycaemia per 100 PYE was 34, 37 and 47 episodes in the IDeg Flex, IDeg OD and IGlar OD groups, respectively. There were no statistically significant differences in the occurrence of severe hypoglycaemia between IDeg Flex and IGlar OD, and between IDeg Flex and IDeg OD as the estimated rate ratios (IDeg Flex/IGlar OD and IDeg Flex/IDeg OD) were 0.89 $[0.40;1.99]_{95\%\ CI}$ and 1.09 $[0.48;2.48]_{95\%\ CI}$, respectively.

  The rate of nocturnal confirmed hypoglycaemic episodes in the IDeg Flex group was lower than in the IDeg OD and IGlar OD groups (623 vs. 961 and 996 episodes per 100 PYE, respectively). A statistically significantly lower rate of nocturnal confirmed hypoglycaemic episodes was observed for IDeg Flex compared to IGlar OD, and for IDeg Flex compared to IDeg OD. The estimated rate ratio (IDeg Flex/IGlar OD) was 0.60 $[0.44;0.82]_{95\%\ CI}$, and the estimated rate ratio (IDeg Flex/IDeg OD) was 0.63 $[0.46;0.86]_{95\%\ CI}$.

- **Body weight:** There was no statistically significant difference in weight gain; the estimated treatment difference (IDeg Flex−IGlar OD) was −0.44 kg $[-1.14;0.27]_{95\%CI}$ and (IDeg Flex − IDeg OD) was 0.33 kg $[-0.38;1.03]_{95\%CI}$. Mean body weight (SD) at baseline and at the end of the trial was 81.6 (15.5) kg and 82.9 (15.8) kg in the IDeg Flex group, 79.4 (15.5) kg and 80.3 (16.0) kg in the IDeg OD group and 80.9 (15.4) kg and 82.5 (16.3) kg in the IGlar OD group.
- **Adverse events:** A similar percentage of subjects reported AEs in the IDeg Flex, IDeg OD and IGlar OD groups (68%, 76% and 72%, respectively). The rate of AEs per 100 PYEs was 443 events in the IDeg Flex group, 550 events in the IDeg OD group and 527 events in the IGlar OD group. The rate of severe AEs per 100 PYE was 36 events in the IDeg Flex group, 47 events in the IDeg OD group and 47 events in the IGlar OD group. The rate of AEs possibly or probably related to investigational product per 100 PYE was 72 events in the IDeg Flex group, 60 events in the IDeg OD group and 57 events in the IGlar OD group. The most frequently reported AEs in all treatment groups were nasopharyngitis, headache, hypoglycaemia, upper respiratory tract infection, oropharyngeal pain and wrong drug administration. The percentage of subjects with injection-site reactions was low in all 3 treatment groups (4.9% [11 events], 1.8% [3 events] and 2.5% [4 events] in the IDeg Flex, IDeg OD and IGlar OD groups, respectively).
- **Deaths, serious adverse events and other significant adverse events:** One death was reported in this trial: a subject in the IDeg OD group [redacted] (hypoglycaemic coma) and expired [redacted]. Suicide [redacted]. The rates of SAEs were low in all treatment groups (17, 12 and 10 events per 100 PYE, in the IDeg Flex [12 events total], IDeg OD [9 events total] and IGlar OD [8 events total] groups, respectively). The most frequently reported SAEs were related to hypoglycaemia in all groups. A total of 10 subjects were withdrawn from this trial due to AEs (5 in the IDeg Flex group, 4 in the IDeg OD group and 1 in the IGlar OD group). The most frequently reported AE leading to withdrawal was hypoglycaemia, which was reported for 3 subjects.
- **Insulin antibodies:** The mean level of cross-reacting antibodies at baseline was low in all treatment groups. Modest increases in the mean levels were observed from baseline to Week 27.
- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values**: No clinically relevant differences from baseline to end of treatment or across the 3 treatment groups were observed in regard to vital signs, ECG, fundoscopy/fundusphotography, physical examination and laboratory values. Two pregnancies were reported during the trial.

- **Insulin dose:** The mean bolus and basal insulin doses appeared to be similar across the 3 treatment groups at baseline. The mean total daily insulin dose increased slightly at the end of the trial in the IDeg Flex and IDeg OD groups (to 65 [0.77 U/kg]) and 58 U [0.70U/kg]) , respectively) and increased to a greater extent in the IGlar OD group (to 70 U [0.84 U/kg]). This difference was driven mainly by the slight decrease in mean daily bolus insulin dose at the end of the trial in the IDeg Flex and IDeg OD groups (to 30 [0.35 U/kg] and 27 U [0.33 U/kg], respectively) and the increase in the IGlar OD group (to 35 U [0.42 U/kg]). The unit insulin dose ratios indicated that the IDeg Flex group administered numerically less (by 6%) total daily insulin and numerically less (by 15%) daily bolus insulin than the IGlar OD group. The dose ratios indicated that the IDeg Flex group administered numerically more (by 11%) total and bolus insulin than the IDeg OD group.

Conclusions

This confirmatory, randomised, controlled 26-week trial 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 (at the same time every day) or IDeg once daily in the evening (IDeg OD) all injected in a basal-bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes mellitus.

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

- IDeg effectively improves long-term glycaemic control as measured by HbA_{1c} (non-inferior to IGlar).
- FPG decreases to a similar level in both treatment groups.
- Glucose levels are equally stable during the day as measured by fluctuations in self-measured plasma glucose.
- Subjects treated with IDeg experience a lower rate of nocturnal confirmed hypoglycaemia, while the rate of confirmed hypoglycaemia is similar.
- There are no major differences between treatments for the remaining glucose-related endpoints.
- The average total daily insulin dose is numerically lower in subjects treated with the IDeg basal-bolus regimen than with the IGlar regimen.
- No safety issues are identified with IDeg; there is no apparent difference between IDeg and IGlar with respect to adverse events or standard safety parameters, and antibody levels remain low in the present trial.

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

- IDeg Flex effectively improves long-term glycaemic control as measured by HbA_{1c}.
- Subjects treated with IDeg Flex experience a lower rate of nocturnal confirmed hypoglycaemia, while the rate of confirmed hypoglycaemia is similar.
- There is no apparent difference between IDeg Flex and IDeg OD with respect to adverse events, standard safety parameters or body weight in the present 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 15-Dec-2010.