2 Synopsis

Trial Registration ID-number NCT00982228	**IND Number –** 76,496 **EudraCT number –** 2008-005774-13
Title of Trial A 52-week randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of NN1250[1] and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin in subjects with type 1 diabetes	
Investigator(s) There were 79 principal investigators. One principal investigator was appointed for each site. Dr. [redacted] was appointed signatory investigator.	
Trial Site(s) The trial was conducted at 79 sites in 6 countries: France (6), Germany (5), Russia (7), South Africa (3), United Kingdom (U.K.) (6), United States (U.S.) (52). These sites enrolled subjects.	
Publications Results from this trial have not been published at the time of this report.	
Trial Period 01 September 2009 - 08 November 2010	**Development Phase** Phase 3a
Objectives **Primary Objective:** • To confirm the efficacy of insulin degludec (IDeg) once daily (OD) + insulin aspart (IAsp) in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA_{1c}) after 52 weeks of treatment. This was done by comparing the difference in change from baseline in HbA_{1c} after 52 weeks of treatment between IDeg OD + IAsp and IGlar (insulin glargine) OD + IAsp 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 + IAsp to IGlar + IAsp after 52 weeks of treatment in terms of: – Nocturnal hypoglycaemic episodes – Hypoglycaemic episodes – Fasting Plasma Glucose (FPG) measured at a central laboratory – Within-subject variability in prebreakfast self-measured plasma glucose (SMPG) • To compare efficacy and safety in terms of: – Frequency of responders for HbA_{1c} – 9 point profile (SMPG) – 4 point profile (SMPG) for dose adjustments – Glucose profile as measured by continuous glucose monitoring (CGM) in a sub-population – Insulin dose – Body weight – Adverse events (AEs) – Hypoglycaemic episodes – Clinical and laboratory assessments – Insulin antibodies – Patient reported outcome (PRO)	

[1] NN1250 was the name previously used for insulin degludec (IDeg).

Methodology

This was a confirmatory, 52-week randomised, controlled, open-labelled, multicentre, multinational, parallel, treat to target trial comparing efficacy and safety of IDeg with IGlar, both administered subcutaneously (s.c.) OD in a basal-bolus regimen with IAsp as mealtime insulin, in subjects with type 1 diabetes mellitus. There was a 1-week period after the 52-week treatment period for safety follow-up.

The trial included a screening visit (Visit 1) to assess eligibility, followed by a randomisation visit (Visit 2) to assign treatment groups. Subjects were randomised (3:1) to IDeg OD + IAsp or IGlar OD + IAsp. If prior basal insulin was used OD, doses were transferred 1:1 for initial doses of both IDeg and IGlar. If prior basal insulin was taken more than OD, the dose was transferred 1:1 for subjects randomised to IDeg and recommended to be reduced by 20-30% for subjects randomised to IGlar.

The treatment groups consisted of subjects randomised to:

- IDeg OD + IAsp: IDeg administered OD with main evening meal and IAsp administered as mealtime insulin just before each main meal (breakfast, lunch and dinner). Additional IAsp could be administered with a fourth meal.
- IGlar OD + IAsp: IGlar administered OD according to approved labelling and mealtime IAsp as described above

The subjects were required to attend a total of 17 visits and 22 phone contacts during the 52 weeks of treatment. At Visit 41 (Week 52) subjects switched basal insulin (IDeg/IGlar) to insulin neutral protamine Hagedorn (NPH) before antibody measurements at follow-up visit (Visit 42/Week 53). During the first 26 weeks of treatment, weekly site/phone visits were scheduled to allow a strict treat-to-target approach, followed by biweekly visits from Week 26 to Week 52. Total duration of individual subject participation in the trial was approximately 55 weeks.

At selected trial sites (25), subjects underwent assessment of their 24 hour interstitial glucose (IG)* profile with a CGM device for 3 consecutive days at baseline (72 hours before Visit 2), and at Visits 28 and 41 (Weeks 26 and 52, respectively). The assessment was included in the subject information and informed consent form.

All subjects were offered to participate in an extension trial (separate protocol and informed consent) after the one week follow-up period. The purpose of the extension trial was to collect safety data.

*Interstitial glucose is glucose extracted from the interstitial fluid.

Number of Subjects Planned and Analysed

The planned number of subjects to be screened (887), randomised (624) and to complete the trial (528) was based on sample size calculation. The actual number of subjects included in the trial is shown below.

	IDeg OD N (%)	IGlar OD N (%)	Total N (%)
Screened			722
Screening Failures			93
Withdrawn before Randomisation			0
Randomised	472 (100.0)	157 (100.0)	629 (100.0)
Exposed	472 (100.0)	154 (98.1)	626 (99.5)
Withdrawals	68 (14.4)	20 (12.7)	88 (14.0)
Adverse Event	12 (2.5)	2 (1.3)	14 (2.2)
Ineffective Therapy	2 (0.4)	0 (0.0)	2 (0.3)
Non-Compliance with Protocol	11 (2.3)	2 (1.3)	13 (2.1)
Withdrawal Criteria	15 (3.2)	3 (1.9)	18 (2.9)
Other	28 (5.9)	13 (8.3)	41 (6.5)
Completed	404 (85.6)	137 (87.3)	541 (86.0)
Full Analysis Set (FAS)	472 (100.0)	157 (100.0)	629 (100.0)
Per Protocol (PP) Analysis Set	448 (94.9)	147 (93.6)	595 (94.6)
Safety Analysis Set	472 (100.0)	154 (98.1)	626 (99.5)

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

Diagnosis and Main Criteria for Inclusion

Male or female subjects ≥ 18 years with type 1 diabetes mellitus (diagnosed clinically) ≥ 12 months, current treatment with any basal-bolus insulin regimen for at least 12 months prior to Visit 1 (screening), HbA_{1c} ≤ 10.0% by central laboratory analysis, body mass index (BMI) ≤ 35.0 kg/m^2.

Subjects were excluded from the trial for meeting any of the following criteria: use of antidiabetic glucose-lowering drug other than insulin within the last 3 months prior to Visit 1, anticipated change in concomitant medication known to interfere significantly with glucose metabolism, cardiovascular disease (defined as stroke, decompensated heart failure New York Heart Association class III or IV, myocardial infarction, unstable angina pectoris, or coronary arterial bypass graft or angioplasty) within the last 6 months prior to Visit 1, uncontrolled treated/untreated severe hypertension (systolic blood pressure [BP] ≥ 180 millimetre [mm] Hg and/or diastolic BP ≥ 100 mmHg), or any significant disease or disorder.

Test Product, Dose and Mode of Administration, Batch number

IDeg 100 U/mL, 3 mL FlexPen® was administered OD with main evening meal and dosed according to titration guidelines. Batch numbers: XP50766, XP52063, XP52274, YP50742

IDeg was to be injected s.c. either in the thigh, upper arm (deltoid area) or abdomen as preferred by the subject. Injection site was to be changed within the injection area to prevent lipohypertrophy.

Duration of Treatment

The duration of treatment was 52 weeks and total duration of the trial for each subject was approximately 55 weeks including screening and follow-up visit.

Reference Therapy, Dose and Mode of Administration, Batch Number

IGlar (Lantus®) 100 U/mL, 3 mL SoloStar® was administered OD according to local labelling and dosed according to titration guidelines. Batch numbers: 0F090A, 40C296, 40C309, 40C320, 40C326, 40C359, 40C423, 40C423, 40C531, 40C700, 40C777, 40U268

IAsp (NovoRapid®/NovoLog®) 100 U/mL, 3 mL FlexPen® was administered as mealtime insulin just before each main meal (breakfast, lunch and dinner). Additional IAsp could be administered with a fourth meal. Dose was titrated according to titration guidelines. Batch numbers: XP50716, XP50729, XP51084, YP51172

NPH insulin (Insulatard®/Prothaphane®/Novolin N™) 100 IU/mL, 3 mL FlexPen® was administered twice daily, morning and evening in the follow-up period only. The NPH dose corresponded to total daily basal dose at end of the treatment period reduced by 20% and divided by two. Batch numbers: XP51117, YP51141

All insulin products were to be injected s.c. either in the thigh, upper arm (deltoid area) or abdomen as preferred by the subject. The injection site was to be changed within the injection area to prevent lipohypertrophy.

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - 4 point SMPG profile
  - 9 point SMPG profile with additional 4 point profile
- CGM
- PRO questionnaire

Criteria for Evaluation – Safety

- Adverse events
- Hypoglycaemic episodes
- Insulin dose
- Physical examination
- Vital signs

- Eye examination (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 affect 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 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 52 weeks of treatment was analysed using an Analysis of Variance (ANOVA) method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline 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%. 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, a number of confirmatory secondary endpoints were 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. The order of the endpoints defines the testing sequence:

1. Number of treatment emergent nocturnal confirmed (severe or minor (PG < 3.1 mmol/L)) hypoglycaemic episodes
   - The number of treatment emergent nocturnal (00:01-05:59 a.m.) confirmed 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 is considered treatment emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate.
2. Number of treatment emergent confirmed hypoglycaemic episodes
   - The number of treatment emergent confirmed hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period 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.
3. Change from baseline in FPG after 52 weeks of treatment (analysed at central laboratory)
   - Change from baseline in FPG after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.
4. Within-subject variability in prebreakfast SMPG
   - 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 assumes independent within- and between-subject errors with variances depending on treatment. Within-subject variability as measured by coefficient of

variation (CV%) for a treatment can be calculated from the corresponding residual variance.

Secondary Supportive Efficacy Analyses

- The HbA_{1c} responder endpoints (HbA_{1c} < 7%)
  - A dichotomous endpoint (responder/non-responder) was defined based on whether a subject had met the American Diabetes Association HbA_{1c} target (HbA_{1c} <7%). Additional dichotomous endpoints were defined based on whether these treatment targets at end of trial were achieved without severe or confirmed hypoglycaemic episodes in the last 12 weeks of treatment for subjects that had been exposed for at least 12 weeks.
  - The responder endpoints were to be analysed separately based on a logistic regression model using the same factors and covariates as for the primary analysis.
- 9-point Profile (SMPG)
  - A repeated measure 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 the 9-point SMPG profile at baseline as covariates. 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 52 weeks of treatment were analysed separately using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and relevant baseline value as covariate.
- SMPG Values Used for Dose Adjustment
  - The mean of before meal/before breakfast PG values after 52 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 following endpoints were derived based on continuous glucose measurements:
  - Mean and variation in IG profile, night time characteristics of IG profile, meal characteristics of IG profile as well as number of episodes of low (<2.5 mmol/L, <3.0 mmol/L, <3.5 mmol/L and <4.0 mmol/L) and high (>8.0 mmol/L,> 9.0 mmol/L and >12.0 mmol/L) IG readings and the total time spent at low and high IG readings. 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 profile (entire or nocturnal part) as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. All other endpoints were analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and relevant baseline value as covariates.
- The change in patient reported outcome score from baseline was analysed separately using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and the relevant baseline value as covariates.

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 13.1) 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 blood 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 PG value 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 hypoglycaemic episodes were analysed separately.

- Change from baseline in lipid endpoints was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.
- Antibodies specific for: IDeg, IAsp and IGlar as well as antibodies cross-reacting to human insulin were summarised using descriptive statistics and their correlation to total insulin dose and HbA_{1c} were investigated using scatter plots.
- Change from baseline in body weight after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.
- Remaining laboratory parameters, physical examination, ECG, fundoscopy/fundusphotography, vital signs and insulin dose were evaluated based on descriptive statistics.

Demography of Trial Population

The baseline and diabetes characteristics are shown in the table below:

	IDeg OD	IGlar OD	Total
Number of Subjects	472	157	629
Age (years)			
N	472	157	629
Mean (SD)	42.8 (13.7)	43.7 (13.3)	43.0 (13.6)
Median	43.4	44.0	43.6
Min ; Max	18.4 ; 76.2	19.4 ; 78.2	18.4 ; 78.2
Body Weight (kg)			
N	472	157	629
Mean (SD)	78.9 (14.3)	78.3 (16.2)	78.8 (14.8)
Median	78.5	77.4	78.3
Min ; Max	46.5 ; 120.2	43.0 ; 123.2	43.0 ; 123.2
BMI (kg/m^2)			
N	472	157	629
Mean (SD)	26.3 (3.7)	26.4 (4.2)	26.3 (3.8)
Median	26.1	26.2	26.1
Min ; Max	14.7 ; 34.8	16.6 ; 35.0	14.7 ; 35.0
Duration of Diabetes (years)			
N	472	157	629
Mean (SD)	19.1 (12.2)	18.2 (11.4)	18.9 (12.0)
Median	17.2	15.6	16.6
Min ; Max	1.0 ; 63.2	1.4 ; 54.3	1.0 ; 63.2
HbA_{1c} (%)			
N	472	157	629
Mean (SD)	7.7 (0.9)	7.7 (1.0)	7.7 (1.0)
Median	7.6	7.7	7.6
Min ; Max	5.3 ; 9.9	5.5 ; 9.7	5.3 ; 9.9
FPG (mmol/L)			
N	465	155	620
Mean (SD)	9.1 (4.0)	9.7 (4.4)	9.3 (4.1)
Median	8.7	9.5	8.9
Min ; Max	1.4 ; 22.0	2.2 ; 21.8	1.4 ; 22.0

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

The demographics and baseline characteristics in the two treatment groups were similar with only marginal differences between the treatment groups. Males comprised 58.5% of the trial population. The majority of the subjects that reported their race were White (93%) and of non-Hispanic/Latino origin. The pre-trial anti diabetic treatment regimens were evenly distributed in the two treatment groups and basal-bolus insulin treatment corresponding to “basal OD + bolus thrice a day (TID)” was the most commonly used (70.4%) antidiabetic

treatment regimens at screening.

Efficacy Results and Conclusions

After 52 weeks of treatment with IDeg OD + IAsp or IGlar OD + IAsp, the following can be concluded:

Primary Endpoint (HbA_{1c})

- **HbA_{1c}**: IDeg effectively improved glycaemic control (non-inferiority to IGlar in terms of lowering HbA_{1c} was confirmed); estimated mean treatment difference (IDeg – IGlar) is -0.01 %-points [-0.14; 0.11] $_{95\%CI}$. The estimated mean change in HbA_{1c} was -0.36 %-points with IDeg and -0.34 %-points with IGlar. After 52 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.3 (1.0)% with IDeg and 7.3 (1.1)% with IGlar.

Secondary Endpoints:

Confirmatory Endpoints

- **Nocturnal confirmed hypoglycaemia:** see conclusion in Safety Results and Conclusions section below.
- **Confirmed hypoglycaemia:** see conclusion in Safety Results and Conclusions section below.
- **FPG**: FPG decreased during the trial to similar mean (SD) levels; 7.8 (3.8) mmol/L with IDeg and 8.3 (4.2) mmol/L with IGlar. The estimated mean change in FPG was -1.53 mmol/L with IDeg and -1.20 mmol/L with IGlar and the estimated mean treatment difference (IDeg – IGlar) was -0.33 mmol/L [-1.03; 0.36]$_{95\% CI}$.
- **Within-subject variability (CV%) in prebreakfast SMPG**: The estimated treatment ratio (IDeg/IGlar) for within-subject variability (CV%) in self-measured prebreakfast PG was 0.96 [0.86; 1.05]$_{95\% CI}$ meaning that there was no statistically significant difference in the day-to-day variability in prebreakfast PG.

Supportive Efficacy Endpoints

- **Responders for HbA_{1c} <7%:** The observed proportion of subjects achieving HbA_{1c} <7% was 39.8% with IDeg and 42.7% with IGlar. The estimated odds of achieving this target was numerically lower (18%) with IDeg compared to IGlar, (odds ratio (IDeg/IGlar) 0.82 [0.51; 1.33]$_{95\% CI}$).
- **Responders for HbA_{1c} <7% without confirmed hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemic episodes was 7.3% with IDeg and 5.4% with IGlar. The estimated odds of achieving this target were numerically higher (40%) with IDeg compared to IGlar (odds ratio (IDeg/IGlar) 1.40 [0.61; 3.20]$_{95\% CI}$).
- **Responders for HbA_{1c} <7% without severe hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without severe hypoglycaemic episodes was 38.4% with IDeg and 42.3% with IGlar. The estimated odds of achieving this target were numerically lower (25%) with IDeg compared to IGlar (odds ratio (IDeg/IGlar) 0.75 [0.46; 1.22]$_{95\% CI}$).
- **9-point SMPG profiles:** There was no statistically significant difference in the fluctuation in 9-point profile between treatments with IDeg and IGlar. The estimated treatment ratio (IDeg/IGlar) for fluctuation in 9-point profile was 0.94 [0.84; 1.05]$_{95\% CI}$. There were no statistically significant differences in the mean of the 9-point SMPG profile, in prandial PG increments and changes in nocturnal SMPG measurements between the two treatments.
- **SMPG for dosing**: Approximately 15% of subjects in both treatment groups achieved the prebreakfast SMPG target <5 mmol/L. The median time to achieve the target for the first time was 5 weeks with IDeg and 10 weeks with IGlar. Subjects who had not yet achieved the titration target at a given visit had a 1.37 times higher chance of achieving target at the next visit with IDeg than with IGlar; estimated hazard ratio (IDeg/IGlar) 1.37 [1.12; 1.67]$_{95\% CI}$. The mean prebreakfast SMPG was lower with IDeg than IGlar; estimated treatment difference (IDeg – IGlar) was -0.55 mmol/L [-1.03; -0.08]$_{95\% CI}$.
- **CGM related endpoints in sub-population**: There was no statistically significant difference in mean nocturnal IG profile with IDeg and IGlar; estimated treatment difference (IDeg – IGlar) was -1.21 mmol/L [-2.47; 0.05]$_{95\% CI}$. There were no clinically relevant statistically significant differences for the remaining CGM related endpoints.
- **PRO:** The results related to PRO appeared similar between the two treatment groups, with only marginal changes over time. The improvement in perceived diabetes management was greater with IDeg than IGlar; estimated treatment difference (IDeg – IGlar) was 3.6 [0.5; 6.6]$_{95\% CI}$. The improvement in perceived efficacy was greater

for IDeg; estimated treatment difference (IDeg – IGlar) was 3.3 $[0.4; 6.3]_{95\% CI}$.

Safety Results and Conclusions

After 52 weeks of treatment with IDeg OD + IAsp or IGlar OD + IAsp the following can be concluded:

Secondary Endpoints

Confirmatory Safety Endpoints

- **Nocturnal confirmed hypoglycaemia:** Superiority of IDeg to IGlar was demonstrated in terms of a lower rate of nocturnal confirmed hypoglycaemic episodes; estimated rate ratio (IDeg/IGlar) 0.75 $[0.59; 0.96]_{95\% CI}$. The estimated rate of nocturnal confirmed hypoglycaemia (number of episodes per 100 PYE) was 25% lower with IDeg than with IGlar. The observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was 441 episodes with IDeg and 586 episodes with IGlar.
- **Confirmatory hypoglycaemia:** The observed rate of confirmed hypoglycaemic episodes per 100 PYE was 4254 episodes with IDeg and 4018 episodes with IGlar. The estimated rate ratio (IDeg/IGlar) of confirmed hypoglycaemic episodes was 1.07 $[0.89; 1.28]_{95\% CI}$. Superiority of IDeg compared to IGlar could not be demonstrated and the hierarchical testing procedure was stopped.

Supportive Safety Endpoints

- **Adverse events:** A similar percentage of subjects reported adverse events in the IDeg and IGlar groups (84.1% and 83.1%, respectively). The observed rate of all adverse events was similar for the IDeg and IGlar groups (438 and 432 events per 100 PYE, respectively) as were the observed rates of severe adverse events (25 and 24 events per 100 PYE, respectively). The observed rate of adverse events possibly or probably related to investigational product was numerically higher with IDeg than IGlar (37 and 24 events per 100 PYE, respectively). The most frequently reported adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infection and headache. The most frequently reported adverse events possibly or probably related to investigational product were hypoglycaemia and hypoglycaemic unconsciousness in both treatment groups. The percentage of subjects with injection site reactions was low in both treatment groups (2.8% [17 events] and 5.2% [11 events] in the IDeg and IGlar groups, respectively).
- **Deaths, serious adverse events and other significant adverse events:** Three (3) deaths were reported in this trial: 2 (both myocardial infarctions) in the IDeg group and 1 (sudden death) in the IGlar group. A total of 49 (10.4%) subjects reported 59 serious adverse events in the IDeg group while 17 (11%) subjects reported 23 serious adverse events in the IGlar group. The event rate per 100 PYE of serious adverse events was similar with IDeg (14) and IGlar (16). The most frequent serious adverse events were hypoglycaemia in both treatment groups. A similar percentage of subjects withdrew from the trial due to AEs in the IDeg (2.5%) and the IGlar (1.3%) groups.
- **Severe hypoglycaemia:** The observed rate of severe hypoglycaemic episodes was 21 and 16 hypoglycaemic episodes, per 100 PYE for IDeg and IGlar, respectively. There was no statistically significant difference between treatment groups in the rate of severe hypoglycaemic episodes; estimated rate ratio (IDeg/IGlar) was 1.38 $[0.72; 2.64]_{95\% CI}$. The observed rate of nocturnal severe hypoglycaemic episodes was low (5 episodes per 100 PYE [23 episodes] and 2 episodes per 100 PYE [3 episodes] for IDeg and IGlar, respectively).
- **Insulin antibodies:** The mean level of insulin antibodies cross-reacting to human insulin was low at baseline and remained low in both treatment groups after 52 weeks of treatment. The mean levels of insulin degludec, insulin glargine and insulin aspart specific antibodies were low at baseline and remained low at end of treatment.
- **Vital signs, ECG, fundoscopy, physical examination and laboratory values:** No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed for vital signs, ECG, fundoscopy/fundusphotography, physical examination and laboratory values.
- **Body weight:** There was no statistically significant difference in weight gain between the treatment groups; estimated treatment difference was 0.18 kg $[-0.54; 0.91]_{95\% CI}$. The mean (SD) body weight at baseline and at end of trial was 78.9 (14.3) kg and 80.7 (15.1) kg in the IDeg group and 78.2 (16.1) kg and 79.8 kg (17.2) kg in the IGlar group, respectively.
- **Insulin dose:** The mean daily basal insulin dose at end of trial was numerically lower for IDeg than IGlar: 29 U

(0.35 U/kg) for IDeg and 31 U (0.39 U/kg) for IGlar. The mean total daily bolus insulin (IAsp) dose at end of trial was numerically lower in the IDeg group than in the IGlar group: 32 U (0.40 U/kg) in IDeg group and 35 U (0.44 U/kg) in IGlar group. The mean total daily (basal and bolus) insulin dose at end of trial was numerically lower in the IDeg group compared with the IGlar group: 61 U (0.75 U/kg) for IDeg and 66 U (0.82 U/kg) for IGlar. The ratio of IDeg/IGlar mean daily insulin dose (U) after 52 weeks of treatment was 0.93 for basal insulin, bolus insulin and total (basal and bolus) insulin, meaning that mean doses were numerically lower (7%) in the IDeg group compared with the IGlar group.

Overall Conclusions

This confirmatory, randomised, controlled, 52-week trial demonstrates the efficacy and safety of IDeg versus IGlar, both administered once daily in a basal-bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes mellitus. The data support the following conclusions:

- IDeg effectively improves long-term glycaemic control as measured by HbA_{1c} (non-inferiority to IGlar confirmed).
- FPG decrease is similar in both treatment groups. The time to achieve the prebreakfast plasma glucose target is shorter with IDeg compared to IGlar. The day-to-day variation in self-measured prebreakfast plasma glucose is similar with IDeg and IGlar.
- IDeg is superior to IGlar in terms of a lower rate of nocturnal confirmed hypoglycaemic episodes. The rate of confirmed hypoglycaemic episodes is similar between treatments.
- No safety issues are identified with IDeg with respect to AEs and standard safety parameters in this trial.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (refer to applicable edition).

The results presented reflect data available in the clinical database as of 08-Dec-2010.