2 Synopsis

Trial registration ID-number NCT01198041	**IND number – 76,496** **EudraCT number – 2009-015755-24**
Title of trial An extension trial to trial NN1250-3583 comparing safety and efficacy of NN1250[1] with insulin glargine, both with insulin aspart as meal-time insulin, in type 1 diabetes	
Investigators There were 73 Principal Investigators. One Principal Investigator was appointed for each site. Dr. [redacted] was appointed Signatory Investigator: [redacted].	
Trial sites The trial was conducted at 73 sites in 6 countries: France (6), Germany (5), Russian Federation (6), South Africa (3), United Kingdom (U.K.) (5) and United States (U.S.) (48). These sites enrolled subjects.	
Publications No publications were prepared as of the finalisation of this report.	
Trial period Main Trial (NN1250-3583): Initiation date : 1 September 2009 Completion date: 8 November 2010 Extension Trial (NN1250-3644): Initiation date: 9 September 2010 Completion date: 15 November 2011	**Development phase** Phase 3a

Objectives

Primary objective:

- The primary objective was to investigate the long-term safety and tolerability of insulin degludec (IDeg) in combination with insulin aspart (IAsp). This was done by comparing IDeg to insulin glargine (IGlar), both in combination with insulin aspart, after 104 weeks of treatment (52 weeks of treatment in NN1250-3583 plus 52 weeks of treatment in this extension trial) in terms of the listed safety assessments from which endpoints were calculated:
  - Adverse events
  - Hypoglycaemic episodes
  - Clinical evaluation
  - Central laboratory assessments
  - Body weight
  - Insulin dose

Secondary objectives:

- The secondary objectives were to compare the efficacy between IDeg and IGlar, both in combination with insulin aspart, after 104 weeks of treatment, in terms of the listed efficacy assessments from which endpoints were calculated:
  - HbA_{1c} (central laboratory)
  - Fasting plasma glucose (FPG) measured at a central laboratory
  - 9-point self-measured plasma glucose (SMPG) profile
  - 4-point self-measured plasma glucose (SMPG) profile
  - Patient Reported Outcome (PRO) Questionnaire

Methodology

This trial (NN1250-3644) was an extension of a 52-week, 3:1 randomised, controlled, open-label, multicentre,

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

multinational, parallel, treat-to-target trial (NN1250-3583) comparing the efficacy and safety of once-daily IDeg with once-daily IGlar (both in a basal-bolus regimen with IAsp as mealtime insulin) in subjects diagnosed with type 1 diabetes.

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

Subjects who consented to participation in this extension trial continued to receive treatment with either IDeg or IGlar as previously randomly allocated in the main trial (NN1250-3583). Subjects attended a screening visit (Visit 43) to assess their eligibility on the same day as the follow-up visit of the main trial NN1250-3583 (Visit 42). There were biweekly contacts (13 visits and 14 telephone contacts) during the 52 weeks of trial treatment in this extension trial. Following the trial drug treatment period, all subjects switched to NPH insulin as basal insulin and continued on IAsp as mealtime insulin during the follow-up period.

A follow-up visit was performed no earlier than 1 week after discontinuation of the trial treatment. A follow-up visit was also offered to subjects who withdrew from the trial prematurely. The total duration of each subject's treatment in the main and extension trials was approximately 104 weeks, and the total duration for individual subjects participating in both the main and extension trials was approximately 109 weeks.

Number of subjects planned and analysed

For the main trial (NN1250-3583), the planned number of subjects to be screened, randomised and to complete the trial was 887, 624 and 528 respectively. For the extension trial (NN1250-3644), the planned number of subjects to be screened and to complete the trial was 396 (75% of the main-trial completers) and 297, respectively.

The actual number of subjects included in the trial are presented 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)
Completed Main Trial	404 (85.6)	137 (87.3)	541 (86.0)
Withdrawn at/after Randomisation and Before extension	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)		2 (0.3)
Non-Compliance	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 Main Trial Not screened for extension	51 (10.8)	18 (11.5)	69 (11.0)
Completed Main Trial screening failure in extension	2 (0.4)	1 (0.6)	3 (0.5)
Included in Extension	351 (74.4)	118 (75.2)	469 (74.6)
Withdrawn during extension	21 (4.4)	5 (3.2)	26 (4.1)
Adverse Event	3 (0.6)	2 (1.3)	5 (0.8)
Ineffective Therapy	1 (0.2)		1 (0.2)
Non-Compliance	1 (0.2)	2 (1.3)	3 (0.5)
Withdrawal Criteria	5 (1.1)		5 (0.8)
Other	11 (2.3)	1 (0.6)	12 (1.9)
Completed Extension	330 (69.9)	113 (72.0)	443 (70.4)

Full Analysis Set	472 (100.0)	157 (100.0)	629 (100.0)
PP Analysis Set	448 (94.9)	147 (93.6)	595 (94.6)
Safety Analysis Set	472 (100.0)	154 (98.1)	626 (99.5)
Extension Trial Set	351 (74.4)	118 (75.2)	469 (74.6)

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 must have completed the 52-week treatment period in the main trial in order to enrol in the extension trial.

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, AP50167, YP50742_2.

IDeg was to be injected subcutaneously 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 total duration of treatment in the main and extension trials for each subject was 104 weeks. The total duration of participation in the main and extension trials for each subject was approximately 109 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, 40C423, 40C531, 40C700, 40C777, and 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, YP50474, YP50474_2, and YP51172_2.

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 insulin 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 subcutaneously 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
- PRO questionnaire

Criteria for evaluation – safety

- Adverse events
- Hypoglycaemic episodes
- Clinical evaluation (physical examination, fundoscopy/fundusphotography, 12-lead ECG, vital signs)
- Central laboratory assessments (biochemistry, haematology, lipids, insulin antibodies, urinary albumin-to-creatinine ratio assessed in spot urine, urine by sticks [tests for blood, protein and ketones])
- Body weight
- Insulin dose

Statistical methods

Analysis Sets

The following analysis sets were defined:

- Full Analysis Set (FAS): includes 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: includes 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 (SAS): includes 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".
- Extension Trial Set (ETS): includes subjects who attended Visit 43.

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 SAS. The robustness of the results for the HbA_{1c} endpoint was explored by additional analysis on the PP Analysis Set.

Analyses based on the ETS were to be performed for treatment-emergent adverse events (TEAEs) (specifically, serious adverse event and adverse events leading to withdrawal), the number of severe and minor treatment-emergent hypoglycaemic episodes, insulin antibodies, central laboratory parameters (ALAT/SGPT, ASAT/SGOT) and HbA_{1c}. In addition, the data for demographic and baseline characteristics, trial product exposure, basal insulin dose, SF-36 v2 and lipids were summarised based on the ETS.

Primary Safety Analysis

- A 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 14.1) of the Medical Dictionary for Regulatory Activities (MedDRA) coding. Evaluation of TEAEs was based on descriptive statistics. Adverse events 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 Analysis of Variance (ANOVA) method similar to that used for the analysis of the HbA_{1c} endpoint.

- Antibodies specific for IDeg and IAsp 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 104 weeks of treatment was analysed using an ANOVA method similar to that used for the analysis of the HbA_{1c} endpoint.
- Remaining laboratory parameters, physical examination, ECG, fundoscopy/fundusphotography, vital signs and insulin dose were evaluated using descriptive statistics.

Efficacy Analysis

- Change from baseline in HbA_{1c} after 104 weeks of treatment was analysed using an (ANOVA) method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} as covariates.
- The HbA_{1c} responder endpoints (HbA_{1c} < 7.0%) with or without hypoglycaemic episodes were analysed separately using a logistic regression model using treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} as covariates.
- Change from baseline in FPG after 104 weeks of treatment was analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline FPG as covariates.
- 9-point Profile (SMPG)
  - The analysis of the 9-point SMPG profile was based on a mixed model (as specified in the trial protocol) but with a repeated measurement model having the same mean structure without the random subject effect and with an unstructured residual covariance matrix. 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 104 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.
- 4-point SMPG profile
  - The mean PG values taken before meals or before bedtime after 104 weeks of treatment was analysed using an ANOVA method similar to that used for the analysis of the HbA_{1c} 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 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.

Demography of Trial Population

The baseline and diabetes characteristics (FAS) 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 104 weeks of treatment with IDeg OD + meal time IAsp or IGlar OD + meal time IAsp, the following was concluded:

Secondary Endpoints:

- **HbA_{1c}:** The estimated mean reduction in HbA_{1c} during the trial was -0.30%-points with IDeg and -0.26%-points with IGlar with an estimated mean difference of -0.04%-point $[-0.17;0.09]_{95\%CI}$ (FAS) after 104 weeks of treatment, which was not statistically significant. After 104 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.4 (1.0)% with IDeg and 7.5 (1.1)% with IGlar.
- **Responders for HbA_{1c}:** A total of 34.3% of subjects treated with IDeg achieved HbA_{1c} <7.0% compared to 31.2% for subjects treated with IGlar. The estimated odds of achieving this target was 0.34 with IDeg compared to 0.26 with IGlar; estimated odds ratio (IDeg/IGlar) was 1.31 $[0.79;2.16]_{95\%\ CI}$. The difference between treatment groups was not statistically significant, as the 95% CI for the estimated odds ratio (IDeg/IGlar) contained 1.
- **Responders for HbA_{1c} without hypoglycaemia:** The proportion of subjects achieving HbA_{1c} < 7% without confirmed hypoglycaemic episodes during the last 12 weeks of treatment was 6.6% with IDeg and 5.4% with IGlar. The estimated odds ratio (IDeg/IGlar) of achieving this target was 1.27 $[0.55;2.94]_{95\%\ CI}$. The proportion of subjects achieving HbA_{1c} < 7% without severe hypoglycaemic episodes during the last 12 weeks of treatment was 32.2% with IDeg and 30.2% with IGlar. The estimated odds ratio (IDeg/IGlar) of achieving this target was 1.16 $[0.69;1.93]_{95\%\ CI}$
- **FPG:** FPG decreased during the trial by 1.06 mmol/L in the IDeg group and by 1.20 mmol/L in the IGlar group after 104 weeks of treatment. The estimated mean reduction from baseline in FPG during this trial was similar (IDeg: -1.43 mmol/L and IGlar: -1.14 mmol/L); estimated mean treatment difference after 104 weeks of treatment was -0.29 mmol/L $[-0.97;0.40]_{95\%CI}$. There was no statistically significant difference between treatment groups at the end of the trial.
- **9-point SMPG profiles:** The 9-point mean SMPG value was similar in both treatment groups. After 104 weeks of treatment, the observed mean fluctuation in 9-point SMPG was 1.4 mmol/L in both the IDeg and IGlar groups, estimated treatment ratio (IDeg/IGlar) was 0.98 $[0.88; 1.11]_{95\%\ CI}$.

- **SMPG for dosing**: Mean SMPG before breakfast, lunch, main evening meal and bedtime were reduced in both the IDeg and IGlar groups during the trial. There was no statistically significant difference in the within-subject variability in SMPG between treatment groups at the end of the trial (estimated treatment ratio [IDeg/IGlar]; 0.95 $[0.85;1.04]_{95\%CI}$). The proportion of subjects who met the pre-specified prebreakfast SMPG titration target of < 5 mmol/L after 104 weeks of treatment was 13.6% in the IDeg group and 14.6% in the IGlar group.
- **PRO:** In general, physical and mental scores changed marginally in both treatment groups during the trial. Statistical analyses did not identify any differences between treatments.

Safety Results and Conclusions

After 104 weeks of treatment with IDeg OD + meal time IAsp or IGlar OD + meal time IAsp, the following was concluded:

Primary Endpoints:

- **Adverse events:** The percentage of subjects reporting treatment-emergent AEs (TEAEs) and the rate of TEAEs per 100 patient years of exposure (PYE) were similar in the IDeg group (87.5%; 383 events per 100 PYE) and the IGlar group (89.0%; 374 events per 100 PYE). The majority of AEs were of mild or moderate severity. The majority of subjects recovered from the AEs at the end of trial.
- The rate of AEs probably related to investigational product was the same with IDeg and IGlar (11 events per 100 PYE in both the IDeg and IGlar groups). The rate of AEs possibly related to investigational product was numerically higher with IDeg than with IGlar (15 events per 100 PYE in the IDeg group and 8 events per 100 PYE in the IGlar group, respectively).
- The observed rate of severe AEs was similar between the IDeg and IGlar groups (22 and 26 events per 100 PYE, respectively). The most frequently reported AEs in both treatment groups were nasopharyngitis, upper respiratory tract infection, headache, hypoglycaemia, and sinusitis. The percentage of subjects with injection site reactions was low in both treatment groups (IDeg: 3.0%; IGlar: 5.8%). The rate of injection site reactions was similar in both groups (3 events per 100 PYE [IDeg] and 5 events per 100 PYE [IGlar]).
- **Deaths, serious adverse events and other significant adverse events:** Four deaths occurred in the IDeg group and 3 deaths occurred in the IGlar group. These were myocardial infarction (Subject [redacted], IDeg; main trial); myocardial infarction (Subject [redacted], IDeg; main trial); sudden death (Subject [redacted], IGlar; main trial and Subject [redacted], IDeg; extension trial): ventricular tachychardia (Subject [redacted]; IDeg; extension trial), metastasic gallbladder cancer (Subject [redacted]; IGlar; extension trial) and ventricular arrhythmia (Subject [redacted]; IGlar; extension trial).
- The rate of SAEs was 14 and 17 events per 100 PYE for the IDeg and IGlar groups. The most frequently reported SAE was hypoglycaemia in both treatment groups (rate of 5 events per 100 PYE for IDeg and 4 events per 100 PYE for IGlar). A total of 19 (3.0%) subjects reported AEs as the primary reason leading to withdrawal: 15 (3.2%) subjects in the IDeg treatment group (12 during the main trial, 3 during the extension) and 4 (2.5%) subjects in the IGlar group (2 during the main trial and 2 during the extension).
- **Hypoglycaemic episodes:** The percentage of subjects who experienced confirmed hypoglycaemic episodes during the treatment period was 96% in both IDeg and IGlar treatment groups, while the rate of confirmed hypoglycaemic episodes per 100 PYE was 3750 with IDeg and 3743 with IGlar. No statistically significant difference in the rate of confirmed hypoglycemic episodes between IDeg and IGlar was found; estimated rate ratio (IDeg/IGlar) for confirmed hypoglycaemia: 1.02 $[0.85; 1.24]_{95\% CI}$.
- The percentage of subjects who experienced severe hypoglycaemia during the treatment period was 15.3% with IDeg and 15.6% with IGlar. The rate of severe hypoglycaemia episodes was 17 episodes per 100 PYE with IDeg and 15 episodes per 100 PYE with IGlar. No statistically significant difference was observed between the IDeg and IGlar groups after 104 weeks of treatment. The estimated rate ratio (IDeg/IGlar) for severe hypoglycaemia was 1.27 $[0.70; 2.32]_{95\% CI}$.
- The percentage of subjects who experienced nocturnal confirmed hypoglycaemic episodes during the treatment period was 77.5% with IDeg and 79.2% with IGlar, with rates of 390 and 532 nocturnal confirmed hypoglycaemic episodes per 100 PYE, respectively. IDeg was superior to IGlar in terms of a lower estimated rate of nocturnal confirmed hypoglycaemic episodes as the upper limit of the 95% CI for the estimated rate ratio (IDeg/IGlar) was

<1; estimated rate ratio (IDeg/IGlar): 0.75[0.59;0.95]$_{95\%CI}$.

- **Insulin dose:** The dose levels for IDeg remained stable throughout the treatment period while for IGlar a more pronounced increase was observed in the first 5 weeks and a slight, gradual increase during the remaining treatment period. The mean total daily (basal and bolus) insulin dose after 104 weeks was 64 U (0.78 U/kg) in the IDeg group and 68 U (0.85 U/kg) in the IGlar group. The mean total daily basal insulin dose after 104 weeks was 31 U (0.37 U/kg) in the IDeg group and 33 U (0.40 U/kg) in the IGlar group. The mean total daily bolus insulin dose after 104 weeks was 34 U (0.41 U/kg) in the IDeg group and 36 U (0.45 U/kg) in the IGlar group. The dose ratio (IDeg/IGlar) of total daily insulin dose in units at the end of the trial was 0.94 and in units/kg was 0.92.
- **Vital signs, ECG, fundoscopy**, **physical examination** : No clinically relevant differences from baseline to end of treatment or between treatment groups were observed in regard to vital signs, ECG and physical examination. Changes to 'abnormal, clinically significant' fundoscopy/fundusphotography findings were reported for 6 subjects in the IDeg group.
- **Laboratory values:** Mean haematology, biochemistry, lipids, and urine laboratory values remained stable during the trial, and there were no apparent differences across the treatment groups in mean values or mean change in values during the trial, except for a statistically significantly greater increase in HDL cholesterol from baseline in the IGlar group compared with the IDeg group.
- **Insulin antibodies:** The mean level of cross-reacting antibodies at baseline was low in both treatment groups and stayed low throughout the treatment period. The mean levels of IDeg-, IGlar- and IAsp-specific antibodies were low at baseline and remained low throughout the trial period.
- **Body weight:** No statistically significant difference between the IDeg and IGlar groups was identified with respect to change in body weight; the estimated treatment difference (IDeg-IGlar) was 0.12 kg [-0.73;0.98]$_{95\%CI}$. The observed mean weight gain was similar in the IDeg and IGlar groups (2.1 kg and 2.0 kg, respectively) at the end of the trial.

Conclusions

This confirmatory, randomised, controlled, extension trial investigated the long-term safety and efficacy of treatment with IDeg versus IGlar both administered once daily in a basal-bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes mellitus after 104 weeks of treatment. The data support the following conclusions:

- In this trial, no safety issues are identified with IDeg + IAsp during 104 weeks of treatment.
- There is no apparent difference between IDeg + IAsp and IGlar + IAsp with respect to AEs and standard safety parameters.
- Subjects treated with IDeg + IAsp experience a lower rate of nocturnal confirmed hypoglycaemic episodes compared to subjects treated with IGlar + IAsp.
- The rates of severe and confirmed hypoglycaemic episodes are similar with IDeg + IAsp and IGlar + IAsp.
- Antibody development is sparse for both treatment regimens.
- The average total daily insulin dose is numerically lower in subjects treated with IDeg + IAsp compared to subjects treated with IGlar + IAsp.
- Modest body weight increases are observed for both treatment regimens.
- Treatment with IDeg + IAsp effectively improves long-term glycaemic control as measured by HbA_{1c}.

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 13-Dec-2011.