2 Synopsis

Trial Registration ID-number NCT01190956	**EudraCT number –** 2009-015721-36 **Japanese Registration number –** 22-0677
Title of Trial An extension trial to NN1250-3585 investigating safety and efficacy of NN1250[a] compared to insulin detemir in subjects with type 1 diabetes mellitus in a basal–bolus treatment regimen This report contains the results after 52 weeks treatment (26 weeks in the main trial [NN1250-3585] and 26 weeks in the present extension trial [NN1250-3725]).	
Investigators There were 54 principal investigators (one principal investigator was appointed for each site). The signatory investigator was: Dr. [redacted]	
Trial Sites A total of 54 sites in 7 countries: Brazil (2 sites), Finland (8 sites), India (10 sites), Italy (5 sites), Japan (15 sites), Macedonia (1 site) and United Kingdom (13 sites), screened and enrolled subject	
Publications None	
Trial Period 07 September 2010 to 16 June 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 detemir (IDet), both in combination with IAsp after 52 weeks of treatment (26 weeks of treatment in trial NN1250-3585 plus 26 weeks of treatment in this extension trial) in terms of the listed safety assessments from which endpoints were calculated: • Adverse events (AEs) • Hypoglycaemic episodes • Clinical evaluations • Laboratory assessments • Insulin dose • Body weight **Secondary Objectives:** The secondary objective was to compare the efficacy between IDeg and IDet, both in combination with IAsp after 52 weeks of treatment in terms of the listed efficacy assessments from which endpoints were calculated: • Glycosylated haemoglobin (HbA_{1c}) at a central laboratory • Fasting plasma glucose (FPG) measured at a central laboratory • 9-point self-measured plasma glucose (SMPG) profile • 4-point SMPG profile	
Methodology This was a 26-week controlled, open-labelled, multinational, multicentre, two-arm, parallel, treat-to-target trial. This trial was an extension of a 6 month, 2:1 randomised, controlled, confirmatory, multinational, multicentre,	

[a] NN1250 was the name previously used for insulin degludec

open-labelled, treat-to-target parallel-group trial (NN1250-3585) comparing two active treatment groups in subjects with type 1 diabetes mellitus: IDeg once daily (OD) + meal-time IAsp with that of IDet OD or twice daily (BID) + meal-time IAsp. In the main trial (NN1250-3585), IDeg was administered OD throughout the trial but the investigator had the option to intensify IDet administration to BID if adequate glycaemic control was not reached after 8 weeks of OD treatment.

The main trial included a screening visit (Visit 1) followed by a randomisation visit (Visit 2) approximately 1 week later (no later than 2 weeks). The subjects were required to attend further visits and phone contacts during the 26 weeks of treatment. A follow-up visit was scheduled at least 7 days after end of treatment with either IDeg or IDet to ensure assessment of any safety issues related to treatment discontinuation and to assess insulin antibodies.

All subjects were offered and encouraged to participate in an extension trial after completion of the 6-month treatment period in Trial NN1250-3585. The purpose of the extension trial was to collect safety data. Subjects who consented to participate in the extension trial restarted by receiving same treatment regimen with either IDeg OD + IAsp or IDet OD/BID + IAsp as previously randomly allocated in Trial NN1250-3585. The subjects previously on IDet OD could be intensified to IDet BID if adequate glycaemic control was not achieved with OD.

The extension trial included a screening visit to assess eligibility on the same day as the follow-up visit in Trial NN1250-3585. In addition, the subjects were required to attend 8 visits and 7 phone contacts during the 26 weeks of treatment, followed by a follow-up visit after discontinuing the trial treatment. Throughout the trial, a strict treat-to-target approach was applied to ensure the enforced titration towards tight glycaemic control. This included site/phone visits with the investigator every second week (+1 week after initiation). At the end-of-treatment visit (Visit 44), subjects were switched to NPH insulin BID + IAsp for measurement of antibodies at the follow-up visit (Visit 45), which took place no less than 1 week post-treatment for all subjects.

Number of Subjects Planned and Analysed

The planned number of subjects to be screened, randomised and complete the main trial was 609, 426 and 360, respectively based on the sample size calculation. The planned number of subjects to be screened (324) and complete (291) the extension trial was based on the number of subjects continuing from the main trial. The actual numbers of subjects included in the trial are shown below:

	IDeg OD N (%)	IDet N (%)	Total N (%)
Screened			512
Screening Failures			56
Withdrawn before Randomisation			0
Randomised	303 (100.0)	153 (100.0)	456 (100.0)
Exposed	301 (99.3)	152 (99.3)	453 (99.3)
Completed Main Trial	283 (93.4)	138 (90.2)	421 (92.3)
Withdrawn at/after Randomisation and Before extension	20 (6.6)	15 (9.8)	35 (7.7)
Adverse Event	3 (1.0)	1 (0.7)	4 (0.9)
Ineffective Therapy		2 (1.3)	2 (0.4)
Non-Compliance	3 (1.0)	4 (2.6)	7 (1.5)
Withdrawal Criteria	6 (2.0)	3 (2.0)	9 (2.0)
Other	8 (2.6)	5 (3.3)	13 (2.9)
Completed Main Trial Not screened for extension	35 (11.6)	16 (10.5)	51 (11.2)
Completed Main Trial screening failure in extension	0 (0.0)	0 (0.0)	0 (0.0)

Included in Extension	248 (81.8)	122 (79.7)	370 (81.1)
Withdrawn during extension	6 (2.0)	7 (4.6)	13 (2.9)
Adverse Event	1 (0.3)	1 (0.7)	2 (0.4)
Ineffective Therapy	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance		2 (1.3)	2 (0.4)
Withdrawal Criteria	2 (0.7)	2 (1.3)	4 (0.9)
Other	3 (1.0)	2 (1.3)	5 (1.1)
Completed Extension	242 (79.9)	115 (75.2)	357 (78.3)
Full Analysis Set	302 (99.7)	153 (100.0)	455 (99.8)
PP Analysis Set	291 (96.0)	144 (94.1)	435 (95.4)
Safety Analysis Set	301 (99.3)	152 (99.3)	453 (99.3)
Extension Trial Set	248 (81.8)	122 (79.7)	370 (81.1)

N: Number of subjects
%: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Male or female subjects aged ≥ 18 years (≥ 20 years for Japan) 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, HbA_{1c} ≤ 10.0% by central laboratory analysis and body mass index (BMI) ≤ 35.0 kg/m^2, were included in the main trial. Subjects who completed the 6 month treatment period (Visit 28) in the main trial (NN1250-3585) were included in the extension trial (NN1250-3725).

Subjects with use of any other antidiabetic glucose-lowering drug 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 within the last 6 months prior to Visit 1, recurrent severe hypoglycaemia or hypoglycaemic unawareness or hospitalisation for diabetic ketoacidosis during the previous 6 months and previous participation in this trial were excluded from the main and extension trial.

Test Product, Dose and Mode of Administration, Batch Number

IDeg 100 U/mL, 3 mL FlexPen® was administered subcutaneously OD in the evening (from start of main evening meal to bedtime), either in the thigh, upper arm (deltoid area) or abdomen as preferred by the subject. The dose of IDeg was to be based on the Insulin Titration Guideline. Batch number: YP50742.

Duration of Treatment

The treatment period was approximately 52 weeks (26 weeks in main trial NN1250-3585 and 26 weeks in extension trial NN1250-3725). Total duration for the individual subject's participating in the trial was approximately 28 weeks in the main trial and 27 weeks in the extension trial.

Reference Therapy, Dose and Mode of Administration, Batch Number

IDet (Levemir®) 100 U/mL, 3 mL FlexPen® was administered subcutaneously OD in the evening (from start of main evening meal to bedtime) or BID in the morning (before breakfast) and evening. The injection area was according to approved labelling. The dose of IDet was to be based on the insulin titration guideline. Batch numbers: YP50703 and YP51061.

IAsp (NovoRapid®/NovoLog®) 100 U/mL, 3 mL FlexPen® was administered subcutaneously in the abdomen as mealtime insulin and dosed according to the insulin titration guideline. Batch numbers: YP50888, YP51012 and XP52291.

NPH insulin (Insulatard®/Prothaphane®/Novolin N™/Novolin®N) 100 IU/mL, 3 mL FlexPen® was administered subcutaneously BID. To determine the dose of NPH insulin to be taken during the follow-up period, the total daily basal dose at end of the treatment period was to be reduced by 20% and divided by 2 to be administered morning and evening. Batch number: YP51141.

Criteria for Evaluation – Efficacy

- HbA_{1c}

- FPG
- SMPG
  - 4-point SMPG profile
  - 9-point SMPG profile with additional 4-point profile

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes.
- Physical examination
- Fundoscopy/Fundusphotography (Eye Examination)
- 12-lead Electrocardiogram (ECG)
- Vital signs
- Laboratory safety parameters
- Insulin dose
- Body Weight

Statistical Methods

Analysis Sets

The following analysis sets were defined:

- Full analysis set (FAS): including all randomised subjects in the main trial. In exceptional cases subjects from the FAS could be eliminated. In such cases the elimination was to be justified and documented. The statistical evaluation of the FAS follows the intention-to-treat 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 were to 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".

In addition, an ETS was defined that only included subjects that had been exposed to at least one dose of the investigational drug or the comparator in the extension trial.

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.

Primary Safety Analysis

- A Treatment Emergent Adverse Event (TEAE) was defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. AEs were coded using the most recent version (version 14.0) of the Medical Dictionary for Regulatory Activities (MedDRA) coding. Evaluation of TEAEs was based on descriptive statistics. AEs were 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 American Diabetes Association (ADA) classification into the following 5 categories based on PG 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 plasma glucose (PG) value of 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. Nocturnal confirmed hypoglycaemic episodes were analysed separately. Nocturnal severe hypoglycaemic episodes were not analysed due to few number of episodes.

- Antibodies specific for IDeg, IDet and IAsp as well as cross-reacting antibodies to human insulin and the correlation to insulin dose and HbA_{1c} were investigated using descriptive statistics and graphs.
- Change from baseline in body weight 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 body weight as covariates.
- Remaining laboratory parameters, physical examination, ECG, funduscopy/fundusphotography, vital signs and insulin dose were evaluated based on descriptive statistics.

Secondary Supportive Efficacy Analyses

- Change from baseline in HbA_{1c} after 52 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% or ≤6.5% at end of trial) with or without hypoglycaemic episodes were analysed separately based on a logistic regression model using the same factors and covariates as for the analysis of change in HbA_{1c}.
- Change from baseline in FPG after 52 weeks of treatment was analysed using an ANOVA method similar to that used for the analysis of change in HbA_{1c}.
- 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.
- 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 covariate and subject as random effect. From this model, mean profile by treatment and relevant treatment differences were estimated and explored.
  - Mean and fluctuation in the 9-point profile (SMPG), prandial PG increment and nocturnal PG endpoints were to be 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. Fluctuation in the 9-point profile (SMPG) was to be logarithm transformed before analysed.
- 4-point Profile SMPG Values Used for Dose Adjustment
  - The mean of before breakfast PG values was to be analysed using an ANOVA method with treatment, antidiabetic therapy at screening, sex and country/region as fixed factors, and age and the corresponding mean PG at baseline as covariates.
  - 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.

Demography of Trial Population

In general, the trial population was well matched with only marginal differences between the treatment groups. There was a lower percentage of males in the IDeg group (49.7%) compared to the IDet group (56.2%). The largest racial group was White (44.6%), whereas the second-largest group was Asian non-Indian (41.1%). The largest 'country of residence' was Japan (40.9%). The basal-bolus insulin treatment corresponding to 'basal OD + bolus thrice daily (TID) or more' was the most commonly used treatment regimen (65.3% of subjects).

	IDeg OD	IDet	Total
Number of Subjects	302	153	455

Age (years)			
N	302	153	455
Mean (SD)	41.1 (14.9)	41.7 (14.4)	41.3 (14.7)
Median	39.5	39.9	39.6
Min ; Max	18.1 ; 79.6	18.1 ; 80.9	18.1 ; 80.9
Height (m)			
N	302	153	455
Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Median	1.7	1.7	1.7
Min ; Max	1.4 ; 1.9	1.5 ; 1.9	1.4 ; 1.9
Body Weight (kg)			
N	302	153	455
Mean (SD)	66.5 (14.9)	66.7 (13.4)	66.6 (14.4)
Median	64.0	65.5	64.9
Min ; Max	36.3 ; 121.8	39.0 ; 100.1	36.3 ; 121.8
BMI (kg/m^2)			
N	302	153	455
Mean (SD)	24.0 (3.5)	23.7 (3.4)	23.9 (3.5)
Median	23.6	23.6	23.6
Min ; Max	16.7 ; 34.5	16.2 ; 32.6	16.2 ; 34.5
Duration of Diabetes (years)			
N	302	153	455
Mean (SD)	13.7 (10.6)	14.4 (9.7)	13.9 (10.3)
Median	10.4	10.8	10.7
Min ; Max	1.1 ; 51.7	1.0 ; 39.0	1.0 ; 51.7
HbA1c (%)			
N	302	153	455
Mean (SD)	8.0 (1.0)	8.0 (0.9)	8.0 (0.9)
Median	8.0	7.9	7.9
Min ; Max	4.9 ; 10.1	5.8 ; 10.2	4.9 ; 10.2
FPG (mmol/L)			
N	301	148	449
Mean (SD)	9.9 (4.0)	9.5 (4.0)	9.8 (4.0)
Median	9.3	9.3	9.3
Min ; Max	2.1 ; 25.4	2.4 ; 24.7	2.1 ; 25.4

BMI = Body Mass Index, FPG= Fasting Plasma Glucose, HbA1c= glycosylated haemoglobin, N = Number of Subjects, SD = Standard Deviation

Efficacy Results

After 52 weeks of treatment with IDeg + IAsp or IDet + IAsp, the following was concluded:

Secondary Endpoints

- **HbA_{1c}**: IDeg effectively improved long−term glycaemic control, as measured by HbA_{1c}.The estimated mean reduction in HbA_{1c} at week 52 was similar with IDeg (0.48 %-points) and IDet (0.47 %-points), and the estimated mean difference was -0.01 %-points [-0.17; 0.14] $_{95\%CI}$. After 52 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.5 (1.1) % with IDeg and 7.5 (0.9) % with IDet.
- **Responders for HbA_{1c}:** The proportion of subjects who achieved the ADA-specified HbA_{1c} target of <7.0% at end-of-trial was 31.5% with IDeg and 32.0% with IDet. The proportion of subjects who attained the stricter IDF-specified target of ≤6.5% was 15.9% of subjects treated with IDeg and 12.4% of subject treated with IDet. No statistically significant difference was observed between the two treatment groups for subjects who achieved the target of HbA_{1c} <7% (the estimated odds ratio (IDeg/IDet) of 1.01 $[0.61, 1.65]_{95\%CI}$). Likewise, no statistically significant difference was observed between IDeg and IDet group for subjects who achieved the target of HbA_{1c} ≤6.5% with an estimated odds ratio (IDeg/IDet) of 1.43 [0.75, 2.74] $_{95\%CI}$.
- **Responders for HbA_{1c} without hypoglycaemia**: The estimated odds of achieving HbA_{1c} <7% target without confirmed and severe hypoglycaemic episodes were 6.5% and 30.5% with IDeg and 11.7% and 31.0% with IDet,

respectively. No statistically significant differences were observed between IDeg and IDet with respect to the proportion of subjects who achieved the target of <7% without confirmed or severe hypoglycaemia or the target of ≤6.5% without confirmed or severe hypoglycaemia.

- **FPG**: The mean reduction in FPG during this trial was larger with IDeg (2.51 mmol/L) than IDet (1.40 mmol/L) with an estimated mean difference (IDeg-IDet) of -1.11 mmol/L$[-1.83; -0.40]_{95\%CI}$. FPG decreased during the trial to mean (SD) levels of 7.7 mmol/L with IDeg and 8.7 mmol/L with IDet.
- **9-point SMPG profiles**: The mean SMPG value was lower with IDeg before the main evening meals (estimated difference [IDeg – IDet]: -0.98 mmol/L $[-1.66; -0.29]_{95\% CI}$) and higher with IDeg during early morning (at 04:00) (estimated difference [IDeg – IDet]: 0.92 mmol/L $[0.22; 1.63]_{95\% CI}$) than IDet after 52 weeks of treatment. The blood glucose values at the remaining timepoints of the 9-point SMPG profiles were similar for IDeg and IDet. There was no statistically significant difference for fluctuation in 9-point SMPG profiles. The reduction in the period between bedtime and breakfast was comparable between the two groups. The reduction in the period between bedtime and 04:00 was smaller with IDeg (0.8 mmol/L) than IDet (1.8 mmol/L) and the reduction in the period between 04:00 and breakfast was greater with IDeg (1.3 mmol/L) than IDet (0.2 mmol/L).
- **SMPG for dosing:** After 52 weeks of treatment, approximately 20% of the subjects in both the treatment groups achieved the pre-breakfast SMPG target of < 5 mmol/L. The estimated day-to-day variation in prebreakfast SMPG as measured by the CV% was higher in IDeg (37.4%) than IDet (33.5%) after 52 weeks of treatment, as the lower limit of the 95% CI for the estimated treatment ratio (IDeg/IDet) was > 1.0 (1.0010). Time to achieve pre-breakfast target appeared similar between the groups. The median time to achieve the target for the first time was 4 weeks with IDeg and 5 weeks with IDet. The observed mean pre-breakfast SMPG was 7.0 mmol/L with IDeg and 7.2 mmol/L with IDet after 52 weeks of treatment.

Safety Results

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

Primary Endpoints

- **Hypoglycaemic episodes:** The observed rate of confirmed and nocturnal confirmed hypoglycaemic episodes per 100 PYE was 3778 and 338 for IDeg and 3926 and 481 for IDet, respectively. The estimated rate for confirmed hypoglycaemia was similar between IDeg and IDet; estimated rate ratio (IDeg/IDet) was 0.95 $[0.78; 1.17]_{95\% CI}$, whereas the estimated rate of nocturnal confirmed hypoglycaemia was 33% lower with IDeg than with IDet; estimated rate ratio (IDeg/IDet) was 0.67 $[0.51; 0.88]_{95\% CI}$. The observed rates of severe and nocturnal severe hypoglycaemia per 100 PYE were 23 and 7 for IDeg and 28 and 5 for IDet. There was no statistically significant difference in the rate of severe hypoglycaemic episodes between IDeg and IDet after 52 weeks of treatment. The estimated rate ratio (IDeg/IDet) for severe hypoglycaemia was 0.86 $[0.46; 1.62]_{95\% CI}$.
- **Adverse events:** There was no clinically relevant difference between the treatment groups in the reporting of AEs. A similar percentage of subjects reported AEs in the IDeg and IDet groups (82.4% and 77.6%, respectively). The rate of all AEs was numerically higher in the IDeg group than in the IDet group (459 and 420 events per 100 PYE, respectively). Few of the AEs in either treatment group were severe, and the rate of severe AEs was 23 and 35 events per 100 PYE in the IDeg and IDet treatment groups, respectively. The rate of AEs considered possibly or probably related to investigational product (IDeg or IDet) was similar in the IDeg and the IDet groups (50 and 47 events per 100 PYE, respectively). The most frequently reported AEs in both treatment groups were nasopharyngitis, headache, upper respiratory tract infection and hypoglycaemia. The rate of injection site reactions was similar in the IDeg group and the IDet group (5 and 3 events per 100 PYE, respectively). The majority of subjects in both treatment groups recovered from the AEs at the end-of-trial.
- **Deaths, serious adverse events and other significant adverse events:** No death was reported in this trial. A total of 36 (12.0%) and 11 (7.2%) subjects in the IDeg and IDet groups, respectively, reported 77 SAEs; 54 events in the IDeg group and 23 events in the IDet group. The rate of SAEs was similar in the IDeg and IDet groups (20 and 17 events per 100 PYE, respectively). The most frequently reported SAEs were hypoglycaemia (by 4.0% and 3.3% in the IDeg and IDet group, respectively) and hypoglycaemic unconsciousness in both treatment groups (by 3.0% and 3.3% in the IDeg and IDet group, respectively). A total of 6 subjects (4 in the IDeg group and 2 in the IDet group) reported 9 AEs leading to withdrawal.
- **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 or laboratory values.

- **Insulin antibodies:** The mean level of cross-reacting insulin antibodies was low at baseline and declined slightly during the treatment period in the IDeg group. In the IDet group, mean level of cross-reacting insulin antibody was low at baseline and a modest increase was detected from baseline to Week 54. At both Weeks 26 and 53, the change from baseline was smaller with IDeg than IDet.
- **Body weight:** The statistical analysis of body weight indicated that weight gain was higher with IDeg than IDet as the lower limit of the 95% CI of the estimated treatment difference (IDeg – IDet) was >0 (the estimated treatment difference: 1.07 kg $[0.47; 1.67]_{95\% CI}$). The mean (SD) body weight at baseline and at the end of the trial was 66.6 (14.9) kg and 68.4 (15.5) kg in the IDeg group and 66.8 (13.4) kg and 67.5 (13.9) kg in the IDet group, respectively.
- **Insulin dose**: After 52 weeks of treatment, the mean daily basal insulin dose was numerically lower in the IDeg group (26 U) compared with the IDet group (31 U). After 52 weeks of treatment, the mean total daily bolus insulin dose was numerically lower in the IDeg group (37 U) compared with the IDet group (42 U). After 52 weeks of treatment, the mean total daily insulin dose was numerically lower for the IDeg group (62 U) as compared to the IDet groups (72 U). The ratio of IDeg/IDet mean daily insulin dose (in U) after 52 weeks of treatment was 0.83 for basal insulin dose, 0.88 for bolus insulin dose and 0.86 for total (basal and bolus) insulin dose.

Conclusions

This randomised, controlled, 52-week trial investigated the long-term safety and efficacy of IDeg versus IDet, in a basal–bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes mellitus. The data support the following conclusions:

- In this trial, no safety issues are identified with IDeg + IAsp after 52 weeks of treatment.
- There is no apparent difference between IDeg + IAsp and IDet + IAsp with respect to AEs and standard safety parameters with the exception of body weight, which increases more with the IDeg + IAsp regimen compared to the IDet + IAsp regimen.
- The rate of severe and confirmed hypoglycaemic episodes is similar with IDeg + IAsp and IDet + IAsp.
- Subjects treated with IDeg + IAsp experience a lower rate of nocturnal confirmed hypoglycaemic episodes compared to subjects treated with IDet + IAsp.
- Antibody development is sparse for both treatment regimens, and only a few injection site reactions are reported with IDeg.
- The average total daily insulin dose is numerically lower in subjects treated with IDeg + IAsp compared to subjects treated with IDet + IAsp.
- Treatment with IDeg + IAsp effectively improves long-term glycaemic control (as measured by HbA_{1c}) and reduces FPG more than IDet + IAsp..

In conclusion, these findings confirm the long-term safety and efficacy of OD treatment with IDeg in combination with IAsp as mealtime insulin in subjects with type 1 diabetes mellitus.

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 08–July–2011.