2 Synopsis

Trial Registration ID-number NCT01074268	**EudraCT number –** 2009-011672-29 **Japanese Trial number –** 21-2885
Title of Trial A Trial Investigating the Efficacy and Safety of NN1250[1] Compared to Insulin Detemir in Subjects with Type 1 Diabetes Mellitus in a Basal-bolus Treatment Regimen (BEGIN™: BB T1)	
Investigator(s) There were 55 principal investigators from Brazil, Finland, India, Italy, Japan, Macedonia and United Kingdom. The Signatory Investigator was: Dr. [redacted].	
Trial Site(s) The trial was conducted at 55 sites in 7 countries: Brazil (2), Finland (8), India (10), Italy (6), Japan (15), Macedonia (1) and United Kingdom (13).	
Publications None at the time of the clinical trial report	
Trial Period 22 February 2010 - 8 December 2010	**Development Phase** Phase 3a
Objectives **Primary Objective:** To confirm the efficacy of insulin degludec (IDeg) + insulin aspart (IAsp) in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA_{1c}) after 26 weeks of treatment. This is done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment between IDeg + IAsp and insulin detemir (IDet) + 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 IDet + IAsp after 26 weeks of treatment in terms of: • Nocturnal hypoglycaemic episodes (severe and minor) • Hypoglycaemic episodes (severe and minor) • Fasting plasma glucose (FPG) from central laboratory • Within-subject variability in pre-breakfast 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 • Insulin dose • Body weight • Adverse events (AEs) • Hypoglycaemic episodes • Clinical and laboratory assessments • Insulin antibodies • Patient reported outcome (PRO)	
Methodology This trial was a confirmatory 26-week randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of IDeg and IDet both administered once daily in a basal/bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes mellitus. Subjects were randomised in a 2:1	

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

fashion (IDeg: IDet).

Subjects attended a screening visit (Visit 1) followed by a randomisation visit (Visit 2) approximately 1 week later (no later than 2 weeks). The subjects were randomised to a treat-to-target basal/bolus insulin regimen with either IDeg or IDet both in combination with IAsp as mealtime insulin. For initial basal insulin, doses were transferred on a 1:1 basis from previous treatment.

At Visit 3 and throughout the rest of the treatment period, the subject's insulin dose was titrated weekly according to subject's prebreakfast (for basal) and premeal (for bolus) SMPG level and as per insulin titration guidelines. A strict treat-to-target approach was applied to ensure the enforced titration towards tight glycaemic control which included weekly trial site/phone visits with the investigator.

Subjects were to be switched to NPH insulin in combination with IAsp at the last IDeg or IDet treatment visit until the follow-up visit (if these were done on different days). 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. A follow-up visit was scheduled for subjects withdrawing prematurely during the trial.

Total duration for the individual subjects participating in the trial was approximately 28 weeks.

All subjects were offered and encouraged to participate in an extension trial after completion of trial NN1250-3585. The purpose of the extension trial was to collect long-term safety data. The informed consent process for the extension trial was preferably to take place as early as possible during trial NN1250-3585 and at the latest at the follow-up visit (Visit 29).

Number of Subjects Planned and Analysed

The planned number of subjects to be screened (609), randomised (426) and complete the trial (360) was based on the sample size calculation. The 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)
Withdrawn at/after Randomisation	20 (6.6)	15 (9.8)	35 (7.7)
Adverse Event	3 (1.0)	1 (0.7)	4 (0.9)
Ineffective Therapy	0 (0.0)	2 (1.3)	2 (0.4)
Non-Compliance With Protocol	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	283 (93.4)	138 (90.2)	421 (92.3)
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)

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,

$HbA_{1c} \leq 10.0\%$ by central laboratory analysis and body mass index (BMI) ≤ 35.0 kg/m^2, were included in the trial.

Subjects using any 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 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.

Test Product, Dose and Mode of Administration, Batch Number

Treatment with IDeg 100 U/mL, 3 mL FlexPen®, in combination with IAsp as mealtime insulin. IDeg was to be administered as basal insulin, injected subcutaneously once daily 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 provided with the protocol. Batch Number: XP52274 and XP52063

Duration of Treatment

The treatment period was approximately 26 weeks. Total duration for the individual subjects participating in the trial was approximately 28 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

Treatment with IDet (Levemir®) 100 U/mL, 3 mL FlexPen®, in combination with IAsp as mealtime insulin. IDet was to be administered as basal insulin and treatment was to be initiated once daily in the evening (from start of main evening meal to bedtime). IDet was to be injected subcutaneously and the injection area was to be according to approved labelling. The dose of IDet was to be based on the insulin titration guideline. In case of inadequate glycaemic control after 8 weeks of once daily treatment and optimisation of dosing, the investigator could consider adding a second dose of IDet according to the insulin titration guideline provided with the protocol. Batch Number: XP52645 and XP51639

IAsp (NovoRapid®/NovoLog®) 100 U/mL, 3 mL FlexPen® was to be administered as bolus insulin, injected subcutaneously in the abdomen as mealtime insulin and dosed according to the insulin titration guideline. Batch Number: XP52681, XP50716 and XP51084

NPH insulin (Insulatard®/Prothaphane®/Novolin N™/ Novolin®N) 100 IU/mL, 3 mL FlexPen® was to be administered twice a day. NPH insulin was to be used in combination with IAsp from the last IDeg or IDet treatment visit until the follow-up visit for antibody measurements. Batch Number: XP52489 and XP52034

Criteria for Evaluation – Efficacy

The following efficacy variables were to be assessed:

- HbA_{1c}
- FPG
- SMPG
  - 4-point Profiles (SMPG)
  - 9-point profile (SMPG) with additional 4-point Profiles (SMPG)
- PRO questionnaires

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes[#]
- Insulin dose
- Physical examination
- Vital signs
- Fundoscopy/fundusphotography
- Electrocardiogram (ECG)
- Laboratory safety variables
- Body weight

[#]: Hypoglycaemic episodes were categorised according to the American Diabetes Association (ADA) classification.

In addition 'minor episodes' with a PG < 3.1 mmol/L were recorded. The pool of severe and minor episodes is referred to as 'confirmed hypoglycaemia'.

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 26 weeks of treatment was analysed using an Analysis of Variance (ANOVA) method with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} as covariates. 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 I error. The consequence of this fixed testing procedure was that superiority could only be confirmed for endpoints where all previous hypotheses had been confirmed. The order of the endpoints defines the testing sequence:

1. Number of treatment emergent nocturnal (00:01-05:59 a.m.) confirmed (severe or minor [PG < 3.1 mmol/L]) hypoglycaemic episodes
   - The number of nocturnal treatment emergent 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, region as fixed factors and age as covariate.
2. Number of treatment emergent confirmed hypoglycaemic episodes
   - The number of treatment emergent 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, region as fixed factors and age as covariate.
3. Change from baseline in FPG after 26 weeks of treatment (analysed at central laboratory)
   - Change from baseline in FPG after 26 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 pre-breakfast SMPG after 26 weeks of treatment
   - 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

could be calculated from the corresponding residual variance.

Secondary Supportive Efficacy Analyses:

- 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 primary analysis.
- 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 logarithmically transformed fluctuations (mmol/L) in the 9-point profile (SMPG), prandial PG increment and nocturnal PG endpoints after 26 weeks of treatment were analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.
- SMPG Values Used for Dose Adjustment
  - The mean of before meal/before breakfast PG values after 26 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 change in PRO score from baseline was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.

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. AEs 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 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 ADA classification into the following five 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 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.
- 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, 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 after 26 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, funduscopy/fundusphotography, vital signs and insulin dose were evaluated based on descriptive statistics.

Demography of Trial Population

In general, the trial population was well matched with only marginal differences between the treatment groups. There

were 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 most commonly used treatment regimen at screening was basal-bolus insulin treatment corresponding to 'basal OD + bolus TID or more' (65.3%).

	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
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, N = Number of Subjects, SD = Standard Deviation

Efficacy Results and Conclusions

After 26 weeks of treatment with IDeg + IAsp or IDet + IAsp, the following was concluded:

Primary Endpoint

- **HbA_{1c}:** IDeg effectively improved glycaemic control, since non-inferiority to IDet in terms of lowering HbA_{1c} was confirmed; estimated mean treatment difference (IDeg – IDet) –0.09%-point $[-0.23; 0.05]_{95\% CI}$. The estimated mean change in HbA_{1c} was –0.71%-points with IDeg and –0.61%-points with IDet. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.3 (1.0)%-points with IDeg and 7.3 (0.9)%-points with IDet.

Secondary Efficacy Endpoints

Confirmatory Efficacy 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:** The estimated mean change in FPG was greater with IDeg (–2.40 mmol/L) than with IDet (–0.75 mmol/L) with a mean treatment difference (IDeg – IDet) of –1.66 mmol/L $[-2.37; -0.95]_{95\% CI.}$ FPG decreased during the trial to mean (SD) levels of 7.3 (3.4) mmol/L with IDeg and 8.9 (4.1) mmol/L with IDet.
- **Within-subject variability:** The estimated within-subject variation (CV%) in self-measured FPG was similar

with IDeg (36.1%) and IDet (35.5%). The estimated treatment ratio (IDeg/IDet) was 1.02 $[0.91; 1.12]_{95\% CI}$.

Supportive Efficacy Endpoints

- **Responder for HbA_{1c}:** The observed proportion of subjects achieving HbA_{1c} <7% was 41.1% with IDeg and 37.3% with IDet. The estimated odds of achieving this target were numerically higher (27%) with IDeg compared to IDet; the estimated odds ratio (IDeg/IDet) of 1.27 $[0.77; 2.09]_{95\% CI}$. The observed proportion of subjects achieving HbA_{1c} ≤6.5% was 24.2% with IDeg and 21.6% with IDet. There was no statistically significant difference between IDeg and IDet; the estimated odds ratio (IDeg/IDet) of 1.15 $[0.68; 1.96]_{95\% CI}$.
- **Responder for HbA_{1c} without hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemic episodes was 6.2% with IDeg and 6.9% with IDet. The observed proportion of subjects achieving HbA_{1c} <7% without severe hypoglycaemic episodes was 39.7% with IDeg and 36.6% with IDet. A numerically lower proportion of subjects achieved the target ≤6.5% without confirmed or severe hypoglycaemia compared to the target <7% in both IDeg and IDet. There were no statistically significant differences 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.
- **9-point SMPG Profiles:** After 26 weeks of treatment, the 9-point profiles were in general similar with IDeg and IDet. The only difference observed was a steeper decrease in PG concentration during the night (from bedtime to 4:00 a.m.) with IDet. The mean PG value was higher with IDeg than with IDet at 4:00 a.m. The reduction in the period between bedtime and 4:00 a.m. was smaller with IDeg (0.7 mmol/L) than IDet (1.6 mmol/L) and the reduction in the period between 4:00 a.m. and breakfast was greater with IDeg (1.3 mmol/L) and IDet (0.3 mmol/L).
- **SMPG for dosing:** Approximately 24% of subjects in both treatment groups achieved the prebreakfast SMPG target <5 mmol/L at the end of trial. Time to achieve before 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 prebreakfast SMPG was 6.6 mmol/L with IDeg and 6.7 mmol/L with IDet after 26 weeks of treatment.
- **PRO:** The results related to PRO appeared similar between the two treatment groups with only marginal changes over time. The score in the 'Social Functioning' domain of the SF-36 v 2 questionnaire decreased with IDeg compared with IDet. Apart from this, there was no statistically significant difference between the groups.

Safety Results and Conclusions

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

Secondary Endpoints

Confirmatory Safety Endpoint

- **Nocturnal confirmed hypoglycaemia:** Superiority of IDeg to IDet was demonstrated in terms of a lower rate of nocturnal confirmed hypoglycaemic episodes; estimated rate ratio (IDeg/IDet) 0.66 $[0.49; 0.88]_{95\% CI}$, reflecting a 34% lower rate with IDeg than with IDet. The observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was 414 episodes for IDeg and 593 episodes for IDet.
- **Confirmed hypoglycaemia:** The observed rate of confirmed hypoglycaemic episodes per 100 PYE was 4583 episodes for IDeg and 4569 episodes for IDet. The estimated rate of confirmed hypoglycaemia was similar with IDeg and IDet; estimated rate ratio (IDeg/IDet) was 0.98 $[0.80; 1.20]_{95\% CI.}$ Superiority of IDeg compared to IDet could not be demonstrated and consequently the hierarchical testing procedure was stopped. Therefore, superiority could not be formally confirmed for the remaining confirmatory endpoints.

Supportive Safety Endpoints

- **Hypoglycaemic episodes:** The observed rate of severe hypoglycaemic episodes per 100 PYE was 31 episodes for IDeg and 39 episodes for IDet. The estimated rate of severe hypoglycaemia was similar with IDeg and IDet; estimated rate ratio (IDeg/IDet) was 0.92 $[0.46; 1.81]_{95\% CI.}$ The observed rate of nocturnal severe hypoglycaemic episodes with IDeg and IDet was 9 and 8 episodes per 100 PYE, respectively.
- **Body weight:** IDeg was associated with slightly more weight gain than IDet after 26 weeks of treatment; the estimated treatment difference (IDeg – IDet) was 1.08 kg $[0.58; 1.57]_{95\% CI}$. The mean (SD) body weight at baseline and at the end of the trial was 66.6 (14.9) kg and 68.0 (15.5) kg with IDeg and 66.8 (13.4) kg and 67.1

(13.8) kg with IDet, respectively.

- **Adverse events:** There was no clinically relevant difference between the treatment groups in the reporting of AEs. A similar percentage of subjects reported AEs with IDeg and IDet (72.8% and 73.7%, respectively). The rate of all AEs was numerically higher with IDeg than IDet (545 and 484 events per 100 PYE, respectively), while the rate of severe AEs was similar for IDeg and IDet (31 and 44 events per 100 PYE, respectively). The most frequently reported AEs in both treatment groups were nasopharyngitis, headache and hypoglycaemia. The rate of AEs possibly or probably related to investigational product was similar with IDeg and IDet (71 and 64 events per 100 PYE, respectively). The most frequently reported AE considered possibly or probably related to investigational product was hypoglycaemia. The percentage of subjects with injection site disorders was low in both treatment groups (4.0% and 2.0%, with IDeg and IDet, respectively).
- **Deaths, serious adverse events and other significant adverse events:** No deaths were reported in this trial. The event rate per 100 PYE of SAEs was similar with IDeg (23) and IDet (18) as were the rate of SAEs considered possibly or probably related to investigational product (11 and 14 events per 100 PYE, respectively). The most frequent SAEs were hypoglycaemia in both treatment groups. A total of 4 subjects withdrew from the trial due to AEs in the IDeg (3) and the IDet (1) groups.
- **Insulin antibodies:** The mean level of cross-reacting antibodies was low at baseline and declined slightly during the treatment period in the IDeg group. In the IDet group, mean levels were low at baseline and increased slightly throughout the treatment period. The mean levels of IDeg, IDet and IAsp specific antibodies were low at baseline and remained low throughout the treatment periods.
- **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.
- **Insulin dose:** After 26 weeks of treatment, the mean daily basal insulin dose was numerically lower in the IDeg group (25 U) compared with the IDet group (29 U). After 26 weeks of treatment, the mean total daily bolus insulin dose was numerically lower in the IDeg group (36 U) compared with the IDet group (41 U). After 26 weeks of treatment, the mean total (basal and bolus) daily insulin dose appeared numerically lower for the IDeg group (61 U) as compared to the IDet groups (69 U). The ratio of IDeg/IDet mean daily insulin dose (in U) after 26 weeks of treatment was 0.88 for basal insulin dose and total (basal and bolus) insulin dose and 0.87 for bolus insulin dose.

Overall Conclusions

This confirmatory, randomised, controlled, 26-week trial demonstrates the efficacy and safety of IDeg versus IDet, 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 IDet was confirmed).
- IDeg reduces FPG more than IDet, whereas the day-to-day variation in self-measured prebreakfast plasma glucose is similar with IDeg and IDet.
- IDeg is superior to IDet in terms of a lower rate of nocturnal confirmed hypoglycaemic episodes. The rate of confirmed hypoglycaemic episodes is similar between treatments.
- The average total daily insulin dose is numerically lower with IDeg+IAsp than with IDet+IAsp.
- In this trial, no safety issues are identified with IDeg with respect to AEs and standard safety parameters. Body weight increases slightly more in the IDeg treatment group compared to the IDet group. Antibody development is modest and only a few injection site reactions are reported with IDeg.

In conclusion, these findings confirm the efficacy and safety of once-daily 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 25 January 2011.