2 Synopsis

Trial Registration ID-number NCT01079234	**IND Number –** 76,496 **EudraCT number –** 2009-012923-27
Title of Trial A 26-week trial investigating the dosing flexibility, efficacy and safety of NN1250[1] in subjects with type 1 diabetes with a 26-week extension. This synopsis presents the results of 52 weeks of treatment (26 weeks in the main trial period and 26 weeks in the extension trial period).	
Investigator(s) There were 71 principal investigators in the main trial period and 68 principal investigators in the extension trial period (1 principal investigator was appointed for each site). [redacted], MD, was appointed the signatory investigator: [redacted]	
Trial Sites The main/extension trial periods were conducted at 71/68 sites in 6 countries: Belgium (5/5 sites), Germany (7/7 sites), Norway (5/5 sites), Poland (5/5 sites), United Kingdom (UK) (12/11 sites), and United States of America (U.S.) (37/35 sites). These were sites that enrolled subjects.	
Publications No publications were prepared as of the finalisation of this report.	
Trial Period 03 March 2010 to 12 November 2010 (main period) 14 September 2010 to 23 May 2011 (extension period)	**Development Phase** Phase 3a

Objectives

Main Trial Period

Primary Objective:

To confirm the efficacy of insulin degludec (IDeg) administered once daily in a flexible dosing schedule in combination with meal-time insulin aspart (IAsp) in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA_{1c}) after 26 weeks of treatment. This was done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment between IDeg administered in this flexible regimen in combination with meal-time IAsp with insulin glargine (IGlar) administered once daily according to approved labelling in combination with meal-time IAsp to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.

Secondary Objectives:

- To compare the efficacy of IDeg administered once daily in the flexible dosing schedule in combination with meal-time IAsp with the efficacy of IDeg administered once daily with the main evening meal in combination with meal-time IAsp, in terms of change from baseline HbA_{1c} after 26 weeks of treatment.
- To compare the efficacy and safety after 26 weeks of treatment between the 3 treatment groups in terms of:
  - Frequency of responders for $HbA_{1c} < 7\%$
  - Fasting plasma glucose (FPG) from a central laboratory
  - 9-point self-measured plasma glucose (SMPG) profile
  - 4-point profiles (SMPG) for dose adjustments
  - Adverse Events (AEs)
  - Body weight
  - Hypoglycaemic episodes
  - Clinical and laboratory assessments
  - Insulin antibodies
  - Basal and bolus insulin doses

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

Extension Trial Period

In addition, the long-term safety and tolerability after 52 weeks of treatment with IDeg (26 weeks in the main trial and 26 weeks in the extension trial) were investigated by comparing the IDeg treatment arm to the IGlar treatment arm, both in combination with IAsp in terms of:

- adverse events
- hypoglycaemic episodes
- clinical and laboratory assessments
- insulin antibodies
- body weight

Although not specified in the protocol objectives, a 52-week analysis was performed on the efficacy endpoints similar to that done at Week 26 (see the Statistical Methods Section below for details of the 52-week efficacy endpoints). These efficacy endpoints were also specified in the trial protocol and its amendments.

Methodology

This entire trial consisted of a 26-week main trial period and a 26-week extension trial period. The total duration of the trial was approximately 56 weeks (including one week for screening, two times 26-week treatment periods and two times 7-12 day follow-up periods).

Main Trial Period

The methodology for the main trial period has been described in detail in the synopsis for the main trial period (dated 27 May 2011). Hence, only key points in the methodology for the main trial period are presented in this document for contextual purposes. The main trial period was a multinational, multi-centre, open-label, randomised, three-arm, parallel, treat-to-target trial comparing the efficacy and safety of 2 different dosing regimens of IDeg and 1 dosing regimen of IGlar, all in combination with mealtime IAsp, in subjects with type 1 diabetes mellitus.

Subjects in the main trial period were randomised to one of 3 treatment arms:

- IDeg Flex arm: administered OD according to an alternating dosing schedule with 8 to 40 h intervals between doses (given in the morning on Mondays, Wednesdays, Fridays and given in the evening on other days of the week).
- IDeg OD arm: administered OD with the evening meal
- IGlar OD arm: administered OD according to local labelling

(See the report for the main trial period [dated 27 May 2011] for details of the trial design for that period.)

Extension Trial Period

The extension trial period was a 26-week, multinational, multi-centre, open-label, randomised, two-arm, parallel, treat-to-target trial investigating the long-term safety and efficacy of IDeg by comparing 2 different treatment regimens of basal insulin (IDeg OD Free Flex and IGlar OD), both in combination with meal time IAsp used as standard bolus insulin therapy.

All subjects who completed the main trial period (Visits 1–28) were invited to participate in the extension trial period following the 1-week follow up period (Visit 29). There were only 2 treatment arms in the extension period (IDeg OD Free Flex and IGlar OD, both with mealtime IAsp as bolus insulin therapy):

- IDeg OD Free Flex arm: IDeg was administered OD at any time of the day, with a minimum time interval of 8 hours and a maximum time interval of 40 hours between injections. The subjects who had been randomised to the IDeg Flex or IDeg OD arms during the main trial period were allocated to this arm during the extension trial period.
- IGlar OD arm: IGlar was administered OD according to local labelling. The subjects who had been randomised to the IGlar OD arm during the main trial period continued in this arm during the extension trial period.

Apart from the treatment arms for the IDeg groups, the trial designs for the main and extension trial periods were generally similar.

Verbal and written information was to be provided to the subjects prior to the extension period. Further, an informed consent form specific to the extension period was to be signed by the subjects and the investigators. No screening of subjects was required in order for them to enter the extension period.

The subjects were required to attend a total of 8 visits and 7 phone contacts during the 26 weeks of treatment in the extension period (Visits 30–44). At Visit 44, subjects switched basal insulin treatment to the intermediate-acting Neutral Protamine Hagedorn (NPH) insulin to wash out the long-acting insulin products before taking antibody measurements at the follow-up visit (Visit 45) 7–12 days after Visit 44. The planned duration of trial participation by each individual subject in the extension trial period was approximately 28 weeks. All subjects who had prematurely withdrawn from the extension trial period were also scheduled for a follow-up visit (Visit 45) after their last visit.

Both basal and bolus insulin doses were to be self-titrated by the subjects. The basal insulin dose was to be adjusted up to 3 times weekly, whereas bolus insulin doses were to be adjusted on a daily basis according to the subject's needs. During the extension trial period, subjects were recommended to record 4-point SMPG values between Visits 30 and 44 in the extension trial period in the same way that it had been done during the main trial period; however, only pre-breakfast (1-point) SMPG values were required to be reported everyday, whereas 4-point profile SMPGs (before breakfast, lunch, main evening meal, and bedtime) only needed to be recorded in the diary and transcribed to the eCRF for the 3 consecutive days before each visit and phone contact. It was the responsibility of the investigator to instruct, discuss and advise the subjects on self-adjustment of insulin doses based on daily SMPG, the recommendations of the Insulin Titration Guideline and the treat-to-target approach.

Number of Subjects Planned and Analysed

Main and Extension Trial Periods

The planned number of subjects to be screened (695) and randomised (486) and to complete the main trial (411) was based on the sample size calculation. No screening was performed for the extension trial period. The subjects in the 2 IDeg treatment arms in the main trial period (IDeg Flex and IDeg OD) were pooled into the IDeg OD Free Flex arm (denoted by IDeg OD F) in this report.

The numbers of subjects included in the trial are shown in the table below.

	IDeg OD F N (%)	IGlar OD N (%)	Total N (%)
Screened			549
Screening Failures			56
Withdrawn before Randomisation			0
Randomised	329 (100.0)	164 (100.0)	493 (100.0)
Exposed	329 (100.0)	161 (98.2)	490 (99.4)
Completed Main Trial	277 (84.2)	152 (92.7)	429 (87.0)
Withdrawn at/after Randomisation and before extension	**52 (15.8)**	**12 (7.3)**	**64 (13.0)**
Adverse Event	9 (2.7)	1 (0.6)	10 (2.0)
Ineffective Therapy	3 (0.9)	1 (0.6)	4 (0.8)
Non-Compliance With Protocol	8 (2.4)	4 (2.4)	12 (2.4)
Withdrawal Criteria	12 (3.6)	2 (1.2)	14 (2.8)
Other	20 (6.1)	4 (2.4)	24 (4.9)
*Completed Main Trial Not screened For extension	38 (11.6)	19 (11.6)	57 (11.6)
Included in Extension	239 (72.6)	133 (81.1)	372 (75.5)
Withdrawn during extension	**16 (4.9)**	**11 (6.7)**	**27 (5.5)**
Adverse Event	0 (0.0)	1 (0.6)	1 (0.2)
Ineffective Therapy	2 (0.6)	0 (0.0)	2 (0.4)
Non-Compliance With Protocol	5 (1.5)	2 (1.2)	7 (1.4)
Withdrawal Criteria	2 (0.6)	4 (2.4)	6 (1.2)
Other	7 (2.1)	4 (2.4)	11 (2.2)
Completed Extension	223 (67.8)	122 (74.4)	345 (70.0)
Full Analysis Set	329 (100.0)	164 (100.0)	493 (100.0)
PP Analysis Set	293 (89.1)	156 (95.1)	449 (91.1)
Safety Analysis Set	329 (100.0)	161 (98.2)	490 (99.4)
Extension Trial Set	239 (72.6)	133 (81.1)	372 (75.5)

*"Completed Main Trial Not screened for extension": refer to subjects who completed the main trial period but did not enter the extension period.
"Screening" refers to the main trial period. No screening was performed for the extension trial period.
IDeg OD F: IDeg OD Free Flex treatment arm.
The subjects in the 2 IDeg treatment arms in the main trial period (IDeg Flex and IDeg OD) were pooled into the IDeg OD Free Flex arm in this table and in this report.

Diagnosis and Main Criteria for Inclusion

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

Patients were excluded from the trial if they had used any antidiabetic glucose lowering drug other than insulin within the last 3 months, initiated or significantly changed any systemic treatment that in the investigator's opinion could interfere with glucose metabolism, previously participated in this trial, had a known or suspected allergy to any of the trial products or related products, and any clinically significant disease or disorder, except for conditions associated with type 1 diabetes that in the investigator's opinion could interfere with the results of the trial.

Test Product, Dose and Mode of Administration, Batch Number

During the extension period, IDeg 100 U/mL, FlexPen®, 3 mL was administered in a dosing regimen that allowed the subjects in the IDeg OD Free Flex arm to inject IDeg at any time of the day, with a minimum time interval of 8 hours and a maximum of 40 hours between IDeg doses. During the main trial period, IDeg 100 U/mL, FlexPen®, 3 mL was administered once daily with alternating morning or evening dosing (IDeg Flex) or with the evening meal (IDeg OD).

IDeg was to be injected subcutaneously either in the thigh, upper arm (deltoid area) or abdomen as preferred by the subject. The subjects were to be instructed by the investigator to self-adjust their basal insulin doses according to the Insulin Titration Guideline on the basis of their SMPG values. The IDeg dose was to be adjusted on Mondays, Wednesdays and Fridays on the basis of the mean prebreakfast SMPG values of the preceding 2 to 3 days. No maximum insulin dose was specified.
Batch No. XP52863 (all countries) and Batch No. YP50743 (US, UK, PL, DE, BE).

Duration of Treatment
The total duration for each individual subject participating in the main and extension trial period was approximately 56 weeks, including the the screening and follow-up visits.

Reference Therapy, Dose and Mode of Administration, Batch Number
IGlar (Lantus®) 100 U/mL, SoloStar™, 3 mL.
During the main and extension trial periods, IGlar was to be injected once daily according to the approved labelling and administered subcutaneously in the thigh, upper arm or stomach as preferred by the subjects. The IGlar dose was to be adjusted on Mondays, Wednesdays and Fridays on the basis of the mean prebreakfast SMPG values of the preceding 2 to 3 days. No maximum insulin dose was specified.
(Batch Nos. 40C408 [U.S.] and 40C531 [all countries except the U.S.]).

IAsp, 100 U/mL, FlexPen®, 3 mL.
During the main and extension trial periods, IAsp was to be injected at meal times subcutaneously either in the abdominal region, thigh, upper arm (deltoid area) or the gluteal region as preferred by the subject. Adjustment of daily meal-time doses of IAsp as follows:

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

(Batch No. XP52945; all countries).

Human isophane insulin, Neutral Protamine Hagedorn insulin, 100 IU/mL, FlexPen®, 3 mL.
NPH insulin was to be injected twice-daily during the follow-up periods of the main and extension trial periods. To determine the dose of NPH insulin to be taken during the follow-up periods, the total daily basal dose at the end of the treatment period was to be reduced by 20% and divided by 2 to be administered in the morning and evening.
(Batch No. YP50037; stated as YP50037_1 in the US).

Criteria for Evaluation – Efficacy

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

Criteria for Evaluation – Safety

- AEs
- Hypoglycaemic episodes
- Basal and bolus insulin doses (and adjustment)
- Physical examination
- Vital signs

- Eye Examination
- Electrocardiogram (ECG)
- Laboratory safety variables
- Body weight

Statistical Methods

Data from the entire trial period (52-week data) were reported in 2 treatment arms (IDeg OD Free Flex and IGlar OD) in this report.

The following analysis sets were defined:

- Full analysis set (FAS): included all randomised subjects. The statistical evaluation of the FAS was to follow the intention-to-treat (ITT) principle and subjects were to contribute to the evaluation "as randomised".
- Per protocol (PP) analysis set: included subjects without any major protocol violations that may have affected the primary endpoint. Moreover, subjects must have been exposed to the IDeg or IGlar for more than 12 weeks and must have had a valid assessment necessary for deriving the primary endpoint. Subjects in the PP set were to contribute to the evaluation "as treated".
- Safety analysis set: included all subjects receiving at least one dose of IDeg or IGlar. Subjects in the safety set were to contribute to the evaluation "as treated".
- Extension Trial Set: included subjects who attended Visit 30.

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 change in HbA_{1c} endpoint was explored by additional analysis on the PP analysis set. Analyses were repeated for serious treatment emergent AEs, number of severe and minor treatment emergent hypoglycaemic episodes, antibodies, central laboratory parameters (ALAT/SGPT, ASAT/SGOT) and HbA_{1c} using the Extension Trial Set (ETS) to assess the stability of key results.

Primary Efficacy Analysis

Main Trial Period

The primary endpoint was change from baseline in HbA_{1c} (%) after 26 weeks of treatment. This had previously been analysed and reported in the clinical trial report for the main trial period (dated 27 May 2011); please refer to that report for details of the statistical analysis of this endpoint and supportive secondary endpoints reported in the main trial period.

Supportive Secondary Efficacy Analyses

Extension Trial Period

In this report for the extension trial period, the difference in change from baseline in HbA_{1c} after 52 of treatment with IDeg or IGlar was analysed using the same Analysis of Variance (ANOVA) method that had been used in the main trial period, i.e., with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA_{1c} as covariates. The antidiabetic therapy at screening was a factor with the following two levels: 1. twice-daily basal injections, 2. once-daily basal injection. The region was a factor with 2 levels: Europe (Germany, Poland, Belgium, Norway and United Kingdom) and North America (United States of America).

- The responder endpoints were analysed separately based on a logistic regression model using the same factors and covariates as those used for the analysis of change in HbA_{1c}.
- Change from baseline in FPG after 52 weeks (analysed at a central laboratory) was analysed using an ANOVA model similar to that used for the analysis of change in HbA_{1c}.
- A mixed-effect model was fitted to the 9-point profile (SMPG) data. The model included treatment, time, interaction between treatment and time, antidiabetic therapy at screening, sex and region as fixed factors, age and baseline values as covariate and subject as random effect. From the model, the mean profile by treatment and relevant treatment differences was estimated and explored. Mean and fluctuation in the 9-point SMPG profile, prandial PG increment and nocturnal PG endpoints were analysed separately using an ANOVA model similar to that used for the endpoint for change in HbA_{1c}. Fluctuation in the 9-point profile (SMPG) was logarithmically

transformed before being analysed.

- The mean prebreakfast PG values after 52 weeks were analysed using an ANOVA model similar to that used for the endpoint for change in HbA_{1c}. The time from randomisation until the date a subject met the titration target for the first time was analysed in a Cox proportional hazards model including treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as covariate. The logarithmically transformed SMPG values available before breakfast were analysed as repeated measures in a linear mixed model with treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as covariate and subject as random factor. The model assumed independent within- and between-subject errors with variances depending on treatment. Within-subject variability as measured by CV% for a treatment was calculated from the corresponding residual variance.

Safety Analyses

- A treatment-emergent adverse event (TEAE) was defined as an event that had an onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. Adverse events were coded using the most recent version (version 13.1) of the Medical Dictionary for Regulatory Activities (MedDRA) coding. Evaluation of TEAEs was based on descriptive statistics. Adverse events were also presented as the rate of events per 100 patient years of exposure (PYE).
- A hypoglycaemic episode was defined as treatment emergent using the same definition as for TEAE above. A hypoglycaemic episode with time of onset between 00:01 h and 05:59 h (both included) was considered nocturnal. Hypoglycaemic episodes were classified according to the ADA classification into the following five categories based on blood glucose (BG) measurements and symptoms: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia. Further, confirmed hypoglycaemic episodes were defined as episodes of severe hypoglycaemia and minor hypoglycaemic episodes with a confirmed PG value of less than 3.1 mmol/L (56 mg/dL). The number of treatment-emergent confirmed and nocturnal hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as covariate. Confirmed and nocturnal hypoglycaemic episodes were analysed separately. Hypoglycaemic episodes were also presented as the rate of events per 100 PYE.
- Antibodies specific for IDeg and IAsp, as well as antibodies cross-reacting to human insulin were presented using descriptive statistics.
- 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 change in HbA_{1c}.
- Other laboratory parameters, physical examination, ECG, fundoscopy or fundusphotography and vital signs were evaluated using descriptive statistics.

Demography of Trial Population

Main and Extension Trial Periods

The subjects randomised to the 2 IDeg treatment arms during the main trial period (IDeg Flex and IDeg OD) were pooled into the IDeg OD Free Flex arm (denoted by IDeg OD F) in this report. Demographic data and baseline characteristics were only recorded at the start of the main trial period and are presented here.

The demographics and baseline characteristics in the treatment groups were generally similar. The population consisted of men and women with type 1 diabetes mellitus, with a mean age of 43.7 years (ranging from 19.3 to 82.4 years), a mean duration of diabetes of 18.5 years (ranging from 1.1 to 52.7 years), a mean HbA_{1c} of 7.7% (ranging from 5.2% to 10.2%) and a mean BMI of 26.7 kg/m^2 (ranging from 16.9 to 35.1 kg/m^2). The majority of subjects were White (97.6%). The second largest race group was the Black or African-American group (1.8%). The majority of subjects were of Non-Hispanic or Non-Latino ethnicity (96.6%). The baseline demographics and diabetes characteristics are shown in the table below. The different pre-trial regimens were equally represented in the 2 treatment groups. The majority (70.6%) of the subjects were treated with basal-bolus regimens involving once-daily basal insulin plus 3 or more bolus insulin injections and 28.8% were treated with twice-daily basal insulin plus 3 or more bolus insulin injections. The most commonly used basal insulin products were IGlar (63.7% of all subjects) and IDet (27.2% of all subjects).

	IDeg OD F	IGlar OD	Total
Number of Subjects	329	164	493
Age (years)			
N	329	164	493
Mean (SD)	43.6 (13.3)	44.1 (12.6)	43.7 (13.1)
Median	42.2	44.9	43.5
Min ; Max	19.3 ; 82.4	20.5 ; 71.6	19.3 ; 82.4
Body Weight (kg)			
N	329	164	493
Mean (SD)	80.6 (15.5)	80.4 (15.6)	80.6 (15.5)
Median	79.9	81.0	80.6
Min ; Max	42.3 ; 130.8	47.0 ; 120.6	42.3 ; 130.8
BMI (kg/m^2)			
N	329	164	493
Mean (SD)	26.7 (3.9)	26.8 (4.0)	26.7 (3.9)
Median	26.5	26.5	26.5
Min ; Max	16.9 ; 35.1	18.4 ; 34.9	16.9 ; 35.1
Duration of Diabetes (years)			
N	329	164	493
Mean (SD)	18.7 (12.4)	18.2 (11.9)	18.5 (12.2)
Median	16.7	15.6	16.0
Min ; Max	1.1 ; 52.7	1.3 ; 49.1	1.1 ; 52.7
HbA1c (%)			
N	329	164	493
Mean (SD)	7.7 (1.0)	7.7 (0.9)	7.7 (0.9)
Median	7.7	7.7	7.7
Min ; Max	5.2 ; 10.2	5.4 ; 9.7	5.2 ; 10.2
FPG (mmol/L)			
N	325	162	487
Mean (SD)	9.8 (4.0)	9.7 (4.2)	9.8 (4.1)
Median	9.7	9.2	9.5
Min ; Max	0.9 ; 23.9	2.4 ; 28.1	0.9 ; 28.1

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation
[a]The maximum values for HbA_{1c} and BMI in the IDeg OD F group were above the limit allowed in the inclusion criteria, due to an increase in HbA_{1c} in one subject ([redacted] from 9.9% at visit 1 to 10.2% at visit 2, and due to an increase in BMI in one [redacted]t ([redacted] from 34.6 kg/m^2 to 35.1 kg/m^2, respectively. These subjects met the selection c[redacted] on the basis of their respective HbA_{1c} and BMI values at Visit 1.
IDeg OD F: IDeg OD Free Flex treatment arm. The subjects in the 2 IDeg treatment arms in the main trial period (IDeg Flex and IDeg OD) were pooled into the IDeg OD Free Flex arm in this table and in this report.
Baseline and diabetes characteristics were only recorded at the start of the main trial period and are presented here.

Efficacy Results and Conclusions

Data from the entire trial treatment period (52-week data) were reported in 2 treatment arms (IDeg OD Free Flex and IGlar OD) in this report. Therefore, data for the IDeg Flex and IDeg OD arms collected during the first 26 weeks (main trial period) were pooled into the IDeg OD Free Flex arm in this report.

After 52 weeks of treatment with IDeg or IGlar, all injected in a basal-bolus regimen with IAsp, the following was concluded:

Primary Efficacy Endpoint

- **HbA_{1c}:** The primary endpoint was change from baseline in HbA_{1c} (%) after 26 weeks of treatment. This had previously been analysed and reported in the clinical trial report for the main trial period (dated 27 May 2011); please refer to that report for details of this endpoint and supportive secondary endpoints reported in the main trial

period.

Secondary Efficacy Endpoints

- **HbA_{1c}**: IDeg OD Free Flex was not statistically significantly different from IGlar OD in terms of lowering HbA_{1c}; the estimated treatment difference (IDeg OD Free Flex – IGlar OD) was 0.07% points $[-0.05;0.19]_{95\%CI}$. The estimated mean change in HbA_{1c} was −0.13% points with IDeg OD Free Flex and −0.20% points with IGlar OD.

  After 52 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.6 (1.0)% with IDeg OD Free Flex and 7.5 (0.9)% with IGlar OD. The mean HbA_{1c} decreased during the first 26 weeks of treatment in both groups (main trial period). Although the mean HbA_{1c} values increased slightly in both groups during the 26-week extension trial period, they remained below baseline levels until the end of the trial.

- **Responders for HbA_{1c} <7:** The observed proportion of subjects who achieved HbA_{1c} <7% was 27.7% and 25.6% with IDeg OD Free Flex and IGlar OD, respectively. The estimated odds of achieving this target were 0.19 with IDeg OD Free Flex and 0.20 with IGlar OD, with no statistically significant difference between IDeg OD Free Flex and IGlar OD as the estimated odds ratio (IDeg OD Free Flex/IGlar OD) was 0.94 $[0.55;1.59]_{95\%CI}$.

- **Responders for HbA_{1c} (<7%) without severe hypoglycaemia**: The observed proportion of subjects exposed for at least 12 weeks who achieved HbA_{1c} <7% without severe hypoglycaemia during the last 12 weeks of treatment was 28.7% and 23.7% with IDeg OD Free Flex and IGlar OD, respectively. The estimated odds of achieving this target were 0.21 with IDeg OD Free Flex and 0.19 with IGlar OD, with no statistically significant difference between treatments; the estimated treatment odds ratio (IDeg OD Free Flex/IGlar OD) was 1.06 $[0.62;1.84]_{95\%CI}$.

- **Responders for HbA_{1c} (<7.0%) without confirmed hypoglycaemia**: The observed proportion of subjects exposed for at least 12 weeks who achieved HbA_{1c} <7% without confirmed hypoglycaemic episodes during the last 12 weeks of treatment was 3.4% and 1.9% with IDeg OD Free Flex and IGlar OD, respectively. The estimated odds of achieving this target were 0.02 with IDeg OD Free Flex and 0.01 with IGlar OD, with no statistically significant difference between treatments; the estimated treatment odds ratio (IDeg OD Free Flex/IGlar OD) was 1.50 $[0.39;5.70]_{95\%CI}$.

- **FPG**: FPG decreased to a statistically significantly lower mean value in the IDeg OD Free Flex treatment group, compared with the IGlar OD treatment group. After 52 weeks of treatment, the observed mean (SD) FPG was 8.0 (3.9) mmol/L with IDeg OD Free Flex and 9.1 (4.0) mmol/L with IGlar OD. The estimated treatment difference (IDeg OD Free Flex – IGlar OD) was −1.07 $[-1.82;-0.32]_{95\%CI}$.

- **9-point SMPG Profiles:** After 52 weeks of treatment, the SMPG profiles were similar in both groups at all timepoints except at 90 minutes after the main evening meal, which was statistically significantly lower in the IDeg OD Free Flex group compared with the IGlar OD group; the estimated treatment difference (IDeg OD Free Flex – IGlar OD) was −0.82 $[-1.53;-0.12]_{95\%CI}$.

  The observed fluctuation in 9-point profile after 52 weeks was 1.6 mmol/L with both IDeg OD Free Flex and IGlar OD, with no treatment difference; the estimated treatment ratio (IDeg OD Free Flex/IGlar OD) was 1.00 $[0.90;1.11]_{95\%CI}$.

  The prandial increments for the main evening meal and across all meals were statistically significantly lower in the IDeg OD Free Flex group compared with the IGlar OD group; the estimated treatment differences (IDeg OD Free Flex – IGlar OD) were −1.28 $[-2.11;-0.45]_{95\%CI}$ (main evening meal) and −0.51 $[-0.99;-0.02]_{95\%CI}$ (all meals).

  The statistical analyses of the estimated treatment differences did not identify any statistically significant differences for breakfast or lunch. The statistical analysis of the estimated treatment difference (IDeg OD Free

Flex – IGlar OD) did not identify any statistically significant treatment difference in the change in nocturnal SMPG measurements.

- **Prebreakfast SMPG for Dose Adjustment**: There was no statistically significant difference between the mean SMPG values in the IDeg OD Free Flex and IGlar OD groups for all mealtimes after 52 weeks as the estimated treatment differences (IDeg OD Free Flex –IGlar OD) contained 0.

  After 52 weeks of treatment, the estimated day-to-day prebreakfast variation (CV%) in SMPG was 39.8% in the IDeg OD Free Flex group and 43.6% in the IGlar OD group. There was no statistically significant difference in the within-subject variation in SMPG (CV%) in prebreakfast SMPG in the IDeg OD Free Flex and IGlar OD groups; the estimated treatment ratio (IDeg OD Free Flex/IGlar OD) was 0.91 $[0.82;1.01]_{95\%CI}$.

  The median time to achieving the prebreakfast titration target for the first time was 6.0 weeks in both the IDeg OD Free Flex and IGlar OD groups.

Safety Results and Conclusions

Data from the entire trial treatment period (52-week data) were reported in 2 treatment arms (IDeg OD Free Flex and IGlar OD) in this report. Therefore, data for the IDeg Flex and IDeg OD arms collected during the first 26 weeks (main trial period) were pooled into the IDeg OD Free Flex arm in this report.

After 52 weeks of treatment with IDeg or IGlar, all injected in a basal-bolus regimen with IAsp, the following were concluded:

- **Adverse events:** A similar percentage of subjects reported AEs in the IDeg OD Free Flex and IGlar OD groups (81.5% and 83.2%, respectively). The event rate for all AEs was 447 events per 100 PYE in the IDeg OD Free Flex group and 481 events per 100 PYE in the IGlar OD group. The majority of subjects in both groups recovered from these AEs (76.3% of subjects in the IDeg OD Free Flex group and 80.7% in the IGlar OD group).

  Severe AEs were reported at a rate of 32 events per 100 PYE and 42 events per 100 PYE in the IDeg OD Free Flex and IGlar OD groups, respectively. The rates of AEs considered possibly or probably related to investigational product by the Investigator were 42 events per 100 PYE in the IDeg OD Free Flex group and 43 events per 100 PYE in the IGlar OD group.

  The most frequently reported AEs across both treatment groups were nasopharyngitis, headache, hypoglycaemia, upper respiratory tract infection, oropharyngeal pain and sinusitis. The percentage of subjects with injection-site reactions was low in both treatment groups (12 [3.6%] subjects reported 17 events in the IDeg OD Free Flex group and 4 [2.5%)] subjects reported 6 events in the IGlar OD group).

- **Deaths, serious adverse events and other significant adverse events:** One death (suicide [redacted]) occurred during the main trial period (Subject [redacted] in the IDeg Flex group). (Because of the pooling of the IDeg Flex and IDeg OD arms in this report, this subject is listed in the IDeg OD Free Flex arm in the data tables for this report).

  A total of 50 SAEs were reported by 37 subjects during the trial. The rates of SAEs were low in both treatment groups (13 and 10 events per 100 PYE in the IDeg OD Free Flex and IGlar OD groups, respectively). The most frequently reported SAEs were related to hypoglycaemia in both groups.

  A total of 11 subjects were withdrawn from this trial due to AEs (9 in the IDeg OD Free Flex group and 2 in the IGlar OD group). The most frequently reported AEs leading to withdrawal were hypoglycaemia (5 events).

- **Hypoglycaemic episodes:** The rates of confirmed hypoglycaemic episodes were 6811 and 6341 episodes per 100 PYE in the IDeg OD Free Flex and IGlar OD groups, respectively. There was no statistically significant difference between the IDeg OD Free Flex and IGlar OD groups with respect to the rate of confirmed hypoglycaemic episodes after 52 weeks of treatment as the 95% CI contained 1. The estimated rate ratio (IDeg OD Free Flex/IGlar OD) for confirmed hypoglycaemia was 1.09 $[0.91;1.29]_{95\%CI}$.

  A numerically lower rate of severe hypoglycaemia was observed in the IDeg OD Free Flex group than in the IGlar OD group (24 and 38 episodes per 100 PYE, respectively). The estimated rate ratio (IDeg OD Free Flex/IGlar OD) for severe hypoglycaemia was 0.74 [0.38;1.42]95%CI.

  The rate of nocturnal confirmed hypoglycaemic episodes was 640 and 848 episodes per 100 PYE in the IDeg OD Free Flex and IGlar OD groups, respectively. The rate of nocturnal confirmed hypoglycaemic episodes was statistically significantly lower in the IDeg OD Free Flex group compared with the IGlar OD group after 52 weeks of treatment, as the upper limit of the 95% CI was less than 1. The estimated rate ratio (IDeg OD Free Flex/IGlar OD) for nocturnal hypoglycaemia was 0.75 $[0.58;0.97]_{95\%CI}$.

- **Insulin dose:** The mean bolus and basal insulin doses appeared to be similar in both treatment groups at baseline. The mean total daily (basal and bolus) insulin doses at baseline were 59 U (0.73 U/kg) in the IDeg OD Free Flex group and 61 U (0.75 U/kg) in the IGlar OD group, and remained relatively constant throughout the trial in the IDeg OD Free Flex group (to 61 U [0.73 U/kg] at Week 52) but increased in the IGlar OD group to 68 U [0.81 U/kg] at Week 52.

  This difference was driven mainly by the slight decrease in mean daily bolus insulin dose at the end of the trial in the IDeg OD Free Flex group (from 31 U [0.39 U/kg] to 29 U [0.35 U/kg]) and the increase in the IGlar OD group (from 32 U [0.40 U/kg] to 35 U [0.42 U/kg]). The unit insulin dose ratios indicated that the IDeg OD Free Flex group administered numerically less (by 11%) total daily insulin and numerically less (by 19%) daily bolus insulin (for doses measured in units) than the IGlar OD group.

- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values**: 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. Mean haematology, biochemistry, lipids, and urine laboratory values remained stable during the trial, and there was no apparent difference across the treatment groups in mean values or mean change in values during the trial.

  There was no clinically relevant difference between treatment groups in the reporting of abnormal fundoscopy findings. Four pregnancies were reported in this trial: 2 during the main trial period and 2 during the extension trial period.

- **Insulin antibodies:** The mean level of cross-reacting antibodies at baseline was low in both treatment groups and stayed low throughout the treatment period.

- **Body weight:** There was no statistically significant difference in weight gain; the estimated treatment difference (IDeg OD Free Flex−IGlar OD) was −0.51 kg $[-1.24;0.22]_{95\%CI}$. The observed mean weight gain appeared to be similar in the IDeg OD Free Flex and IGlar OD groups (1.3 kg and 1.9 kg, respectively) at the end of the trial. Mean body weight (SD) at baseline was 80.5 (15.5) kg and 80.9 (15.4) kg in the IDeg OD Free Flex group and IGlar OD group, respectively. Mean body weight (SD) at the end of the trial was 81.9 (16.2) kg and 82.8 (16.2) kg in the IDeg OD Free Flex group and IGlar OD group, respectively.

Conclusions

This confirmatory, randomised, controlled, 52-week trial investigated the long-term safety and efficacy of treatment with IDeg once daily (OD) in the evening or at varying dosing intervals vs. IGlar OD, all as part of a basal-bolus regimen with IAsp as mealtime insulin in subjects with type 1 diabetes. During the 26-week extension period, all subjects treated with IDeg could administer it at any time of the day at intervals of 8 to 40 hours. The data support the following conclusions:

- In this trial, no safety issues are identified with IDeg after 52 weeks of treatment.
- There are no clinically relevant differences between IDeg and IGlar with respect to the AE pattern and standard safety parameters, and antibody levels remain low in the present trial.
- Subjects treated with IDeg experience a lower rate of nocturnal confirmed hypoglycaemia compared to IGlar, while the rate of confirmed hypoglycaemia is similar.
- IDeg reduces FPG more than does IGlar, while glucose levels are equally stable during the day as measured by fluctuations in self-measured plasma glucose.
- Long-term glycaemic control, as measured by HbA_{1c}, improves with IDeg and IGlar during the first 26 weeks of treatment, and deteriorates slightly in both groups during the last part of the trial.

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996).

The results presented reflect data available in the clinical database as of 22-Jun-2011.