2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT01009580	2008-005768-15

Title of Trial

A 26-week, randomised, open-labelled, two-arm, parallel-group, treat-to-target trial comparing efficacy and safety of NN5401 [1] twice daily (BID) with biphasic insulin aspart (BIAsp) 30 BID, with or without metformin, with or without DPP-4 inhibitor, with or without pioglitazone in subjects with type 2 diabetes in inadequate glycaemic control on once or twice daily premixed or self-mixed insulin regimen with or without OADs

Investigator

There were 51 principal investigators in this trial. Dr. [redacted] was appointed signatory investigator.

Trial Sites

The trial was conducted at 50 sites in 10 countries: Australia (5 sites), Denmark (7 sites), Finland (5 sites), India (9 sites), Malaysia (3 sites), Poland (5 sites), Sweden (6 sites), Taiwan (3 sites), Thailand (3 sites), Turkey (4 sites). In addition, 1 site in Thailand screened but did not randomise any subjects.

Publications

Results from this trial have not been published at the time of this report.

Trial Period	**Development Phase**
05 November 2009 to 23 August 2010	Phase 3a

Objectives

Primary Objective:

To confirm the efficacy of insulin degludec/insulin aspart (IDegAsp) twice daily (BID) ± metformin ± dipeptidyl peptidase-4 (DPP-4) inhibitor ± pioglitazone 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 IDegAsp BID ± metformin ± DPP-4 inhibitor ± pioglitazone and biphasic insulin aspart 30 (BIAsp 30) BID ± metformin ± DPP-4 inhibitor ± pioglitazone 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 IDegAsp BID ± metformin ± DPP-4 inhibitor ± pioglitazone to insulin BIAsp 30 BID ± metformin ± DPP-4 inhibitor ± pioglitazone after 26 week of treatment in terms of:

- Fasting plasma glucose (FPG) from central laboratory
- Hypoglycaemic episodes
- Frequency of responders for HbA_{1c} without hypoglycaemic episodes
- Body weight
- Nocturnal hypoglycaemic episodes

To compare efficacy and safety in terms of:

- 9-point self-measured plasma glucose (SMPG) profile
- SMPG for dose adjustments
- Frequency of responders for HbA_{1c}
- Insulin dose
- Adverse events (AEs)
- Hypoglycaemic episodes

[1] NN5401 is synonymous with insulin degludec/insulin aspart (IDegAsp) and was previously referred to as soluble insulin analogue combination (SIAC).

- Clinical and laboratory assessments
- Patient reported outcome (PRO)

Methodology

This trial was a multinational, multi-centre, open-labelled, 1:1 randomised, stratified, two-arm parallel group, efficacy and safety, treat-to-target trial comparing treatment with IDegAsp BID ± metformin ± DPP-4 inhibitor ± pioglitazone with that of BIAsp 30 BID ± metformin ± DPP-4 inhibitor ± pioglitazone in subjects diagnosed with type 2 diabetes, not optimally controlled on once daily (OD) or BID premixed or self-mixed insulin regimen ± OADs. Total trial duration for the individual subject was approximately 28 weeks.

The subjects attended a screening visit (Visit 1) in order to assess their eligibility. If found eligible, the subjects were randomised 1:1 into 1 of the 2 treatment arms (IDegAsp BID or BIAsp 30 BID) at Visit 2. At Visit 2 previous diabetes treatment, except for metformin, pioglitazone and DPP-4 inhibitor oral antidiabetic drug (OAD) treatments were to be discontinued. Stratification was carried out according to the number of daily injections at screening (1 insulin injection a day or 2 insulin injections a day). In the period between Visit 3 and Visit 28, the subsequent 25 weeks of treatment, the subject's insulin dose was titrated weekly according to the insulin titration guideline provided in the protocol. The weekly contacts between trial site and subjects were a combination of trial site visits and phone contacts.

The glycaemic control at baseline was described by HbA_{1c}, FPG and the 9-point plasma glucose (PG) profile (SMPG). These endpoints were followed throughout the trial accompanied by the SMPG values used for insulin titration.

A follow-up visit (Visit 29) at least 7 days after end of trial treatment was to be performed to ensure assessment of any safety issues related to treatment discontinuation.

Number of Subjects Planned and Analysed

The planned number of subjects to be screened (643), randomised (450) and complete the trial (382) was based on the sample size calculation to meet the primary objective with at least 85% power. The actual numbers of subjects included in the trial are shown below.

	IDegAsp BID N (%)	BIAsp 30 BID N (%)	Total N (%)
Screened			661
Screening Failures			214
Withdrawn before Randomisation			0
Randomised	224 (100.0)	223 (100.0)	447 (100.0)
Exposed	224 (100.0)	222 (99.6)	446 (99.8)
Withdrawn at/after Randomisation	27 (12.1)	35 (15.7)	62 (13.9)
Adverse Event	4 (1.8)	4 (1.8)	8 (1.8)
Ineffective Therapy	0 (0.0)	1 (0.4)	1 (0.2)
Non-Compliance With Protocol	2 (0.9)	3 (1.3)	5 (1.1)
Withdrawal Criteria	4 (1.8)	6 (2.7)	10 (2.2)
Other	17 (7.6)	21 (9.4)	38 (8.5)
Completed	197 (87.9)	188 (84.3)	385 (86.1)
Full Analysis Set	224 (100.0)	222 (99.6)	446 (99.8)
PP Analysis Set	200 (89.3)	193 (86.5)	393 (87.9)
Safety Analysis Set	224 (100.0)	222 (99.6)	446 (99.8)

N: Number of subjects

%: Proportion of randomised subjects

Diagnosis and Main Criteria for Inclusion

Male or female subjects aged ≥ 18 years, with type 2 diabetes mellitus (diagnosed clinically) ≥ 6 months, HbA_{1c} 7.0-10.0% (both inclusive) by central laboratory analysis, body mass index (BMI) ≤ 40.0 kg/m^2 and on premixed human or analogue insulin or self-mixed insulin regimen, containing 20-40% fast/rapid-acting component, OD or BID, with or without OADs (metformin, sulphonylurea [SU], glinides, alpha-glucosidase inhibitor, DPP-4 inhibitor and pioglitazone), for at least 3 months before Visit 1 were included in the trial.

Subjects treated with other insulin regimens than those listed in inclusion criterion within 3 months prior to Visit 1, treatment with rosiglitazone or GLP-1 receptor agonists within 3 months prior to Visit 1, anticipated change in concomitant medication known to interfere with glucose metabolism, off-label use of any concomitant medication including OADs, anticipated significant lifestyle changes during the trial, shift work , as well as highly variable eating habits, cardiovascular disease within the last 6 months prior to Visit 1 or uncontrolled treated/untreated severe hypertension, or with any clinically significant disease or disorders were excluded from the trial.

Test Product, Dose and Mode of Administration, Batch Number

IDegAsp 100 U/mL, 3 mL Flexpen®. During the treatment period, the trial insulin was administered BID with breakfast and the main evening meal. IDegAsp was to be administered subcutaneously in the abdomen, upper arm (deltoid region) or thigh. At Week 26, the subjects were to discontinue all trial products and switched to a suitable marketed treatment at the discretion of the investigator.

Batch No.: XP50558 and XP51553

Duration of Treatment

The treatment period was 26 weeks. Total trial duration for the individual subject was approximately 28 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

BIAsp 30 (NovoMix® 30/NovoLog® Mix 70/30) 100 U/mL, 3 mL FlexPen®. During the treatment period, the trial insulin was administered BID with breakfast and the main evening meal. BIAsp 30 was to be administered subcutaneously in the thigh or in the abdominal wall. If convenient, the gluteal or deltoid region could be used. At Week 26, the subjects were to discontinue all trial products and switched to a suitable marketed treatment at the discretion of the investigator.

Batch No.: XP51303 and YP50153

Criteria for Evaluation – Efficacy

- HbA_{1c}
- FPG
- SMPG
  - 2-point SMPG Profile (pre-breakfast and pre-main evening meal)
  - 9 point profile with additional 2 point profile (SMPG)
- PRO questionnaires

Criteria for Evaluation – Safety

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

[#]Hypoglycaemic episodes were categorised according to the ADA classification. In addition "minor episodes" with a PG < 3.1 mmol/L (56 mg/dL) 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 1 error. The consequence of this fixed testing procedure is that superiority can only be confirmed for endpoints where all previous hypotheses have been confirmed. The following order of the endpoints defines the testing sequence:

1. 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.
2. Number of treatment emergent confirmed (severe or minor (PG < 3.1 mmol/L)) hypoglycaemic episodes
   - The number of treatment emergent confirmed hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate.
3. Responder without hypoglycaemic episodes (HbA_{1c} <7.0% at end of trial and no confirmed hypoglycaemic episodes during the last 12 weeks of treatment plus 7 days after the last dose of treatment in subjects exposed for at least 12 weeks)
   - Responder without hypoglycaemic episodes is a dichotomous endpoint (responder/non-responder) that is defined based on whether a subject has met the American Diabetes Association (ADA) HbA_{1c} target at end of trial (HbA_{1c} <7% at end of trial) without confirmed hypoglycaemic episodes during the last 12 weeks of treatment plus 7 days after last dose of treatment. Responder analysis was based on a logistic regression model using the same factors and covariates as for the primary analysis.
4. Change from baseline in body weight after 26 weeks of treatment
   - 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.

5. Number of treatment emergent nocturnal confirmed hypoglycaemic episodes
   - The number of treatment emergent confirmed nocturnal (00:01-05:59 a m.) hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate.

Secondary Supportive Efficacy Analyses

- The HbA_{1c} responder endpoints (HbA_{1c} < 7% or ≤6.5% at end of trial) were analysed separately based on a logistic regression model using 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 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 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 main evening 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 logarithmically transformed SMPG values available before breakfast and before main evening meal 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.
- The change in patient reported outcome 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. Adverse Events were coded using version (version 13.0) of the Medical Dictionary for Regulatory Activities (MedDRA) coding. Evaluation of TEAEs was based on descriptive statistics. AEs and hypoglycaemic episodes are also presented as the rate of the events per 100 patient years of exposure (PYE).
- A hypoglycaemic episode was defined as treatment emergent using the same definition as for TEAE above. A hypoglycaemic episode with time of onset between 00:01 and 05:59 a m. (both included) was considered nocturnal. Hypoglycaemic episodes were classified according to the ADA classification into the following five categories based on 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 nocturnal confirmed hypoglycaemia was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period

for which a hypoglycaemic episode is considered treatment emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. Confirmed and nocturnal confirmed hypoglycaemic episodes were analysed separately.

- Change from baseline in lipid endpoints was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.
- 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 two groups were comparable in baseline characteristics, with only marginal differences between the treatment groups. The population consisted of male and female subjects with type 2 diabetes mellitus, with a mean age of 58.7 years and a mean duration of diabetes of 13.0 years (ranging from 0.6 to 41.4 years), with a mean HbA_{1c} of 8.4% and a mean BMI of 29.3 kg/m^2. There were more men than women in each of the two treatment groups. The trial subjects were white (52.5%), Asian Indian (27.1%), or Asian non-Indian (20.0%). Only two subjects were of other races.

	IDegAsp BID	BIAsp 30 BID	Total
Number of Subjects	224	222	446
Age (years)			
N	224	222	446
Mean (SD)	58.7 (9.9)	58.8 (9.8)	58.7 (9.8)
Median	59.7	59.5	59.5
Min ; Max	32.7 ; 88.8	20.4 ; 79.4	20.4 ; 88.8
Height (m)			
N	224	222	446
Mean (SD)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)
Median	1.6	1.6	1.6
Min ; Max	1.4 ; 1.9	1.4 ; 1.9	1.4 ; 1.9
Body Weight (kg)			
N	224	222	446
Mean (SD)	81.5 (18.1)	78.9 (17.6)	80.2 (17.9)
Median	79.0	76.0	77.9
Min ; Max	44.9 ; 140.1	38.7 ; 127.3	38.7 ; 140.1
BMI (kg/m^2)			
N	224	222	446
Mean (SD)	29.6 (4.6)	29.0 (4.9)	29.3 (4.8)
Median	29.5	28.8	29.0
Min ; Max	18.0 ; 40.0	17.2 ; 39.6	17.2 ; 40.0
Duration of Diabetes (year)			
N	224	222	446
Mean (SD)	12.8 (6.8)	13.1 (7.4)	13.0 (7.1)
Median	11.4	11.7	11.5
Min ; Max	0.7 ; 39.4	0.6 ; 41.4	0.6 ; 41.4
HbA1c (%)			
N	224	222	446
Mean (SD)	8.3 (0.8)	8.4 (0.9)	8.4 (0.8)
Median	8.3	8.4	8.3
Min ; Max	6.6 ; 10.5	5.3 ; 10.7	5.3 ; 10.7
FPG (mmol/L)			
N	224	220	444
Mean (SD)	8.9 (2.9)	8.6 (2.6)	8.7 (2.8)
Median	8.7	8.3	8.5
Min ; Max	3.3 ; 23.0	3.1 ; 19.3	3.1 ; 23.0

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

Efficacy Results and Conclusions

After 26 weeks of treatment with IDegAsp BID or BIAsp 30 BID, the following can be concluded:

Primary Endpoint

- **HbA_{1c}**: IDegAsp effectively improved glycaemic control and non-inferiority to BIAsp 30 in terms of lowering HbA_{1c} was confirmed; estimated treatment difference (IDegAsp-BIAsp 30) of -0.03% points, $[-0.18; 0.13]_{95\% CI}$. The estimated mean change in HbA_{1c} was -1.31% points with IDegAsp and -1.29% points with BIAsp 30. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 7.1 (0.9)% with IDegAsp and 7.1 (0.9)% with BIAsp 30.

Secondary Efficacy Endpoints

Confirmatory Endpoints

- **FPG:** Superiority of IDegAsp to BIAsp 30 was confirmed in terms of lowering FPG; estimated treatment difference (IDegAsp-BIAsp 30) -1.14 mmol/L, $[-1.53; -0.76]_{95\% CI}$. The estimated mean change in FPG was -2.80 mmol/L with IDegAsp and -1.65 mmol/L with BIAsp 30. After 26 weeks of treatment, the observed mean (SD) FPG was 5.8 (1.9) mmol/L with IDegAsp and 6.8 (2.4) mmol/L with BIAsp 30.
- **Confirmed hypoglycaemia** – please see safety results and conclusions.
- **HbA_{1c} < 7.0% without confirmed hypoglycaemia:** The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemic episodes was 21.8% with IDegAsp and 14.9% with BIAsp 30. The odds of achieving this target were numerically higher (60%) with IDegAsp compared to BIAsp 30; estimated odds ratio (IDegAsp/BIAsp 30) 1.60 $[0.94; 2.72]_{95\% CI}$). Superiority could not be confirmed and consequently, the hierarchical testing procedure was stopped. Therefore, superiority could not be confirmed for the remaining confirmatory secondary endpoints (change in body weight and number of nocturnal confirmed hypoglycaemia).
- **Change in body weight** – please see safety results and conclusions.
- **Nocturnal confirmed hypoglycaemia** – please see safety results and conclusions.

Supportive Endpoints

- **Responder for HbA_{1c}**: The observed proportion of subjects who achieved HbA_{1c} <7% was 50.4% with IDegAsp and 48.6% with BIAsp 30. No statistically significant difference was detected in the odds of achieving this target with the two treatments, (estimated odds ratio (IDegAsp/BIAsp 30) 1.06 $[0.70; 1.60]_{95\% CI}$). The proportion achieving HbA_{1c} ≤6.5% was 29.5% with IDegAsp and 28.4% with BIAsp 30. There was no statistically significant difference in the odds of achieving this target with the two treatments, (estimated odds ratio (IDegAsp/BIAsp 30) 1.00 $[0.65; 1.56]_{95\% CI}$).
- **Responder for HbA_{1c} without severe hypoglycaemia**: The observed proportion of subjects who achieved HbA_{1c} <7% without severe hypoglycaemia was 55.4% with IDegAsp and 50.0% with BIAsp 30. The odds of achieving this target were numerically higher (not significant) with IDegAsp compared to BIAsp 30 (estimated odds ratio (IDegAsp/BIAsp 30) 1.22 $[0.79; 1.90]_{95\% CI}$).
- **9-point SMPG profiles:** The mean SMPG values before breakfast was lower for IDegAsp compared to BIAsp 30 (estimated difference: -0.51 mmol/L $[-0.88; -0.14]_{95\% CI}$). This was also true for SMPG taken 90 minutes after breakfast (estimated difference: -0.98 mmol/L $[-1.58; -0.39]_{95\% CI}$), and before breakfast the following day (estimated difference: -0.85 mmol/L $[-1.21; -0.48]_{95\% CI}$). There was no difference in the fluctuation in SMPG between IDegAsp and BIAsp 30. IDegAsp produced a greater decrease in SMPG overnight (as measured by nocturnal increment from bedtime to breakfast) compared to BIAsp30; estimated treatment difference -0.95 mmol/L $[-1.46; -0.44]_{95\%CI}$.

- **SMPG for dosing:** With IDegAsp, subjects achieved the titration targets faster than with BIAsp 30. For subjects, who had yet not achieved the before breakfast and before main evening meal titration targets at a given visit, the chance of achieving both targets at the next visit when treated with IDegAsp was 2.01 $[1.48 ; 2.73]_{95\% CI}$ times higher than for subjects in the BIAsp 30 group.
- **Within-subject variability in fasting SMPG:** The estimated treatment ratios for within-subject variation (CV%) (IDegAsp/BIAsp 30) in before breakfast and before main evening meal SMPG were 0.95 $[0.86; 1.05]_{95\% CI}$ and 0.96 $[0.87; 1.06]_{95\% CI}$, respectively, meaning that no statistically significant treatment differences were detected for the day-to-day variation in glucose levels.
- **PRO:** There were no statistical significant differences between IDegAsp and BIAsp 30 in any of the PRO scores, including the total TRIM-D score and any of the subcategories.

Safety Results and Conclusions

After 26 weeks of treatment with IDegAsp BID or BIAsp 30 BID the following can be concluded:

Secondary Endpoints

Confirmatory Safety Endpoints

- **Confirmed hypoglycaemia:** Superiority of IDegAsp to BIAsp 30 was confirmed in terms of a lower rate of confirmed hypoglycaemic episodes; estimated rate ratio (IDegAsp/BIAsp 30) was 0.68 $[0.52; 0.89]_{95\% CI}$, or 32% lower with IDegAsp compared to BIAsp30. The observed rate of confirmed hypoglycaemic episodes per 100 PYE was 972 episodes for IDegAsp and 1396 episodes for BIAsp 30.
- **Change in body weight:** The estimated increase in mean body weight was 2.21 kg with IDegAsp and 2.83 kg with BIAsp 30 with a mean treatment difference (IDegAsp-BIAsp 30) of -0.62 kg, $[-1.15; -0.10]_{95\% CI}$. Superiority of IDegAsp could not be confirmed as the hierarchical testing procedure was stopped prior to this analysis. Mean (SD) body weight at baseline and at the end of the trial was 81.6 (18.2) kg and 83.2 (18.7) kg in the IDegAsp group and 79.0 (17.5) kg and 81.1 (18.5) kg in the BIAsp 30 group, respectively.
- **Nocturnal confirmed hypoglycaemic episodes:** The observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was 74 episodes with IDegAsp and 253 episodes with BIAsp 30. The rate of nocturnal hypoglycaemic episodes was lower (73%) with IDegAsp compared to BIAsp 30; estimated rate ratio (IDegAsp/BIAsp 30) 0.27 $[0.18; 0.41]_{95\% CI}$. Superiority of IDegAsp could not be formally demonstrated as the hierarchical testing procedure was stopped prior to this analysis.

Supportive Safety Endpoints

- **Hypoglycaemic episodes:**
  - The percentage of subjects who experienced severe hypoglycaemia during the treatment period with IDegAsp and BIAsp 30 was 3.1% and 7.2%, respectively, while the rate of severe hypoglycaemia with IDegAsp and BIAsp 30 was 9 and 25 episodes per 100 PYE, respectively.
  - The percentage of subjects who experienced nocturnal severe hypoglycaemia with IDegAsp and BIAsp 30 was 0.4% and 3.6%, respectively, and the rate of nocturnal severe hypoglycaemia with IDegAsp and BIAsp 30 was 1 and 9 episodes per 100 PYE, respectively
  - The rate of hypoglycaemic episodes according to the ADA classification with IDegAsp and BIAsp 30 was 3671 and 3508 episodes per 100 PYE, respectively, and the rate of nocturnal hypoglycaemia according to the ADA classification with IDegAsp and BIAsp 30 was 293 and 487 episodes per 100 PYE, respectively.
- **Adverse events:** A total of 147 (65.6%) subjects reported 465 adverse events in the IDegAsp group while 140 (63.1%) subjects reported 426 adverse events in the BIAsp 30 group. The event rate per 100 PYE of all adverse events were similar in the two treatment groups: 455 for IDegAsp and 431 for BIAsp 30. The event rate per

100 PYE of severe adverse events was numerically lower with IDegAsp (15) than with BIAsp 30 (33). The event rate per 100 PYE of adverse events possibly or probably related to trial product was numerically lower with IDegAsp than with BIAsp 30: 41 for IDegAsp and 53 for IDegAsp. The most frequent adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infection, and headache. The percentage of subjects with injection site reactions was low in both treatment groups (IDegAsp: 0.4%; BIAsp 30: 0.9%, 2 events in each group).

- **Deaths, serious adverse events and other significant adverse events:** 2 deaths were reported in this trial: interstitial lung disease in the IDegAsp group and head injury in the BIAsp 30 group. A total of 19 (8.5%) subjects reported 21 serious adverse events in the IDegAsp group while 36 (16.2%) subjects reported 41 serious adverse events in the BIAsp 30 group. The event rate per 100 PYE of serious adverse events was numerically lower with IDegAsp (21) than with BIAsp 30 (42). The most frequently reported SAEs in the overall trial population were hypoglycaemia and hypoglycaemic unconsciousness. A similar percentage of subjects withdrew from the trial due to AEs in the IDegAsp (1.8%) and the BIAsp 30 (1.8%) groups.
- **Vital signs, ECG, fundoscopy, physical examination and laboratory values:** No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed for vital signs, ECG, fundoscopy/fundusphotography, physical examination and laboratory values.
- **Insulin dose:** The mean total daily insulin dose after 26 weeks was numerically lower in the IDegAsp group: 90 U (1.08 U/kg) for IDegAsp and 98 U (1.20 U/kg) for BIAsp 30, producing a ratio of IDegAsp to BIAsp 30 of 0.90. Morning and evening doses after 26 weeks were 38 and 52 U for IDegAsp and 44 and 54 U for BIAsp 30, respectively.

Overall Conclusions

The results of this confirmatory, randomised, controlled, 26-week trial demonstrate the efficacy and safety of IDegAsp versus BIAsp 30, both administered twice daily with or without metformin, DPP-4 inhibitors and pioglitazone in subjects with type 2 diabetes mellitus.

- IDegAsp effectively improves long-term glycaemic control as measured by HbA_{1c} (non-inferior to BIAsp 30) and the data confirm superiority to BIAsp 30 with respect to lowering FPG.
- With IDegAsp, the average self-measured plasma glucose is lower and the time to achieve plasma glucose targets is shorter compared to BIAsp 30.
- Superiority of IDegAsp compared to BIAsp 30 can not be demonstrated for subjects achieving the treatment target (HbA_{1c} < 7%) without confirmed hypoglycaemia
- IDegAsp is associated with a lower rate of confirmed hypoglycaemia compared to BIAsp 30, and analyses confirm superiority. In addition, subjects treated with IDegAsp experience a lower rate of nocturnal confirmed hypoglycaemic episodes.
- With IDegAsp, body weight increases less than with BIAsp 30.
- Subjects treated with IDegAsp achieve the titration targets faster than with BIAsp 30.
- In this trial, no safety issues are identified with IDegAsp; there is no apparent difference between IDegAsp and BIAsp 30 with respect to AEs and standard safety parameters.

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 23-Sep-2010.