CTR synopsis

Trial registration ID-number NCT01513590	**UTN – U1111-1120-5633** **EudraCT number – 2011-001712-61**
TITLE OF TRIAL A trial comparing efficacy and safety of insulin degludec/insulin aspart and BIAsp 30 in insulin naïve subjects with type 2 diabetes	
INVESTIGATORS One principal investigator was appointed at each of the 47 trial sites in the trial. The following investigator was designated signatory investigator for the trial, and was responsible for reviewing and approving the Clinical Trial Report: Dr. [redacted]	
TRIAL SITE(S) The following 47 sites in 10 countries enrolled subjects: Algeria (4 sites), Bulgaria (7 sites), Croatia (5 sites), Czech Republic (4 sites), Germany (5 sites), Poland (5 sites), Romania (5 sites), Slovakia (3 sites), Turkey (2 sites), and Ukraine (7 sites).	
PUBLICATIONS No publications were prepared at the time of finalisation of this report.	
TRIAL PERIOD First Patient First Visit: 16 January 2012 Last Patient Last Visit: 19 November 2012	**DEVELOPMENT PHASE** Phase 3b

OBJECTIVES

Primary objective:

- To confirm the efficacy of insulin degludec/insulin aspart (IDegAsp) twice daily (BID) added to metformin in controlling glycaemia with respect to change from baseline in 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 IDegAsp and biphasic insulin aspart 30 (BIAsp 30) both BID added to metformin, 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 added to metformin against BIAsp 30 BID added to metformin after 26 weeks of treatment in terms of:
  - Fasting plasma glucose (FPG) from central laboratory
  - Nocturnal hypoglycaemic episodes (severe and minor) i.e., nocturnal confirmed hypoglycaemic episodes
  - Hypoglycaemic episodes (severe and minor) i.e., confirmed hypoglycaemic episode
  - Body weight
  - Frequency of responders for HbA_{1c} (<7.0 %) without severe or minor hypoglycaemic episodes

- To confirm efficacy and safety of IDegAsp BID added to metformin against BIAsp 30 BID added to metformin after 26 weeks of treatment in terms of:
  - 9-point profile self-measured plasma glucose (SMPG)
  - 2-point profile (SMPG) for dose adjustments
  - Frequency of responders for HbA_{1c} targets
  - Adverse events (AEs)
  - Hypoglycaemic episodes
  - Clinical and laboratory assessments
  - Insulin dose

METHODOLOGY

This trial was a 26 week, multinational, randomised, controlled, open-label, two-arm, parallel-group, treat-to-target trial comparing the efficacy and safety of IDegAsp and BIAsp 30 both BID added to metformin, in subjects with type 2

diabetes inadequately controlled on metformin monotherapy or metformin in any combination with one additional OAD. Subjects were randomised 1:1 into one of two parallel treatment arms (IDegAsp BID or BIAsp 30 BID, both in combination with metformin). The trial included a screening visit (Visit 1), a randomisation visit (Visit 2), followed by a 26-week treatment period consisting of 13 site visits (including a follow-up visit [Visit 29] 7 days after the end of treatment) and 14 phone contacts.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

The planned number of subjects to be randomised was 394. The actual numbers of subjects included in the trial are shown below.

Subject disposition and analysis sets

	IDegAsp BID N (%)	BIAsp 30 BID N (%)	Total N (%)
Screened			525
Screening Failures			131
Withdrawn before Randomisation			0
Randomised	197 (100.0)	197 (100.0)	394 (100.0)
Exposed	196 (99.5)	195 (99.0)	391 (99.2)
Withdrawn at/after Randomisation	10 (5.1)	13 (6.6)	23 (5.8)
Adverse Event	2 (1.0)	3 (1.5)	5 (1.3)
Withdrawal Criteria	3 (1.5)	0 (0.0)	3 (0.8)
Other	5 (2.5)	10 (5.1)	15 (3.8)
Completed	187 (94.9)	184 (93.4)	371 (94.2)
Full Analysis Set	197 (100.0)	197 (100.0)	394 (100.0)
PP Analysis Set	191 (97.0)	184 (93.4)	375 (95.2)
Safety Analysis Set	196 (99.5)	195 (99.0)	391 (99.2)

N: Number of subjects
%: Proportion of randomised subjects
PP: per protocol

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Criteria for inclusion included: male or female subjects ≥18 years of age with type 2 diabetes mellitus (diagnosed clinically) for ≥24 weeks, HbA_{1c} 7.0-10.0% (both inclusive), body mass index (BMI) ≤ 40.0 kg/m^2 and subjects currently treated with metformin monotherapy or metformin in any combination with one of the following OADs (insulin secretagogue [sulphonylurea or glinide], dipeptidyl peptidase IV [DPP-IV] inhibitor, α-glucosidase inhibitors for at least 12 weeks prior to randomisation [Visit 2] with the minimum doses stated in the protocol. Subjects were insulin naïve with the exception of prior short-term insulin treatment up to 14 days (insulin treatment during hospitalisation or during gestation diabetes was permitted for more than 14 days).

Subjects were excluded from the trial if they were treated with antidiabetic regimens other than those listed above, treatment with thiazolidinediones or glucagon-like peptide-1 (GLP-1) receptor agonists within 12 weeks prior to Visit 1, anticipated change in concomitant medication known to interfere significantly with glucose metabolism or any clinically significant disease or disorder, except for conditions associated with type 2 diabetes mellitus, which in the investigator's opinion could have interfered with the results of the trial. Subjects with recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic event during the last 1 year), hypoglycaemic unawareness as judged by the investigator, or hospitalisation for diabetic ketoacidosis during the previous 24 weeks were excluded from the trial.

INVESTIGATIONAL MEDICINAL PRODUCT AND/ORINVESTIGATIONAL MEDICAL DEVICE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Insulin degludec/insulin aspart (IDegAsp) 100 U/mL, 3 mL pre-filled investigational pen (PDS290). During the treatment period, the trial insulin was to be administered by subcutaneous injection BID with the breakfast meal and main evening meal. For IDegAsp the prioritised order of injection areas was the abdomen, upper arm (deltoid area) or thigh. At randomisation (Visit 2), subjects initiated treatment with IDegAsp BID with a dose of 6 U given with breakfast and 6 U given with the main evening meal. Batch numbers: AP50532, AP51609, and BP50086.

DURATION OF TREATMENT

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

REFERENCE THERAPY AND/OR NON-INVESTIGATIONAL MEDICAL DEVICE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Biphasic insulin aspart 30 (BIAsp 30) (NovoMix® 30/NovoLog® Mix 70/30), 100 U/mL, 3 mL pre-filled pen (FlexPen®). During the treatment period, the trial insulin was to be administered BID with the breakfast meal and main evening meal. BIAsp 30 was to be administered by subcutaneous injection preferably in the thigh or in the abdomen according to local labelling. If convenient, the gluteal or deltoid region could be used. At randomisation (Visit 2), subjects initiated treatment with BIAsp 30 BID with a dose of 6 U given with breakfast and 6 U given with the main evening meal. Batch numbers: AP51647 and BP50239.

CRITERIA FOR EVALUATION – EFFICACY

- HbA_{1c}
- FPG
- SMPG
  - 2-point profile
  - 9-point profile with additional 2-point profile

CRITERIA FOR EVALUATION – SAFETY

- Adverse events
- Hypoglycaemic episodes
- Insulin dose
- Physical examination
- Body weight
- Vital signs
- Eye examination
- Electrocardiogram (ECG)
- Laboratory safety variables

STATISTICAL METHODS

Power calculation

The sample size was determined using a t-statistic under the assumption of a one-sided test size 2.5% and a zero mean treatment difference (i.e. D=0%). Based on experience from previous phase 3 trials in subjects with type 2 diabetes mellitus treated with insulin an estimate for the SD of 1.3% for HbA_{1c} was used in the sample size calculation. The minimum sample size required to meet the primary objective with at least 80% power was 334 subjects, with an assumed SD of 1.3%. As this was a non-inferiority trial, sample size was determined such that the anticipated power was at least 80% in the evaluation of the PP analysis set. In previous phase 3 trials in type 2 diabetes mellitus treated with insulin 5-25% of the randomised subjects were excluded from the PP analysis set. The number of excluded subjects was dependent on the trial design. In this trial, an estimate of 15% was used and sample size was ceiled in the FAS to have integer sample size for each group that adheres exactly to the group allocation weights (1:1). Hence, the total number of randomised subjects was at least 394 subjects in order to have at least 80% power in the evaluation of the PP analysis set

Analysis sets

The following analysis sets were defined:

- Full analysis set (FAS): includes all randomised subjects. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomised".
- Per protocol (PP) analysis set: includes subjects in the FAS who fulfil the following criteria: have not violated any inclusion criteria, have not fulfilled any exclusion criteria, have a non-missing HbA_{1c} at screening or randomisation, have at least one non-missing HbA_{1c} after 12 weeks of exposure, have at least 12 weeks of exposure. Subjects in the PP set contribute to the evaluation 'as treated'.
- Safety analysis set: includes all subjects receiving at least one dose of the IDegAsp or BIAsp 30. Subjects in the safety set will 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 treatments 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. The antidiabetic therapy at screening was a factor with the three levels: 1) metformin monotherapy; 2) combination therapy with metformin and SU; 3) combination therapy with metformin and a non-SU OAD. Region was a factor with two levels: 1) Africa; 2) Europe. Non inferiority was considered confirmed if the upper bound of the two sided 95% confidence interval (CI) for the treatment difference (IDegAsp−BIAsp 30) for the mean change in HbA_{1c} was ≤0.4%. Superiority was considered confirmed if the upper bound of the two sided 95% CI was <0%.

Secondary confirmatory analyses

Provided that noninferiority 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 order of the endpoints defines the testing sequence:

- Change from baseline in FPG after 26 weeks of treatment (analysed at central laboratory). This endpoint was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.
- Number of treatment emergent nocturnal severe or minor hypoglycaemic episodes (i.e., confirmed hypoglycaemic episodes: severe [subject unable to treat him/herself] or minor [PG <3.1 mmol/L episodes] with onset from 00:01 to 05:59 a.m. [both inclusive]). This endpoint 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.
- Number of treatment emergent severe or minor (i.e., confirmed) hypoglycaemic episodes severe [subject unable to treat him/herself] or minor [PG <3.1 mmol/L]). This endpoint was analysed using a negative binomial regression model similar to that used for the analysis of nocturnal severe or minor hypoglycaemic episodes.
- Change from baseline in body weight after 26 weeks of treatment. This endpoint was analysed using an ANOVA method similar to that used for the analysis of the primary endpoint.
- HbA_{1c} <7.0% at end of trial without confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after the last randomised treatment including only subjects exposed for at least 12 weeks. Responder without confirmed hypoglycaemic episodes was a dichotomous endpoint (responder/non responder). The analysis of this endpoint was based on a logistic regression model using the same factors and covariates as the primary analysis.

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 and baseline value as covariates 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 met 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 logarithm-transformed SMPG values available before breakfast and before the main evening meal, were analysed separately as repeated measures in a linear mixed model with treatment, antidiabetic therapy at screening, sex and region as fixed factors, baseline SMPG and age as covariates and subject as random factor. The model was to assume independent within- and between-subject errors with variances depending on treatment. Within-subject variability as measured by CV% for a treatment can be calculated from the corresponding residual variance

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 the most recent version (Version 15.1) of the Medical Dictionary for Regulatory Activities (MedDRA). Evaluation of TEAEs was based on descriptive statistics. AEs and hypoglycaemic episodes 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. Confirmed hypoglycaemic episodes were defined as episodes of severe hypoglycaemia (subject unable to treat him/herself) or minor hypoglycaemic episodes with a confirmed PG value <3.1 mmol/L (<56 mg/dL). The analyses of nocturnal confirmed and confirmed hypoglycaemic episodes were confirmatory analyses and are presented above. Hypoglycaemic episodes were classified according to the ADA classification into the following five categories: severe, documented symptomatic, asymptomatic, probable symptomatic and relative hypoglycaemia.
- Change from baseline in lipid endpoints was analysed separately using an ANOVA method similar to that used for the analysis of the primary endpoint.
- The analysis of change from baseline in body weight after 26 weeks of treatment was a confirmatory analysis and is presented above.
- Remaining laboratory parameters, physical examination, ECG, fundoscopy/fundus photography, vital signs and insulin dose were evaluated based on descriptive statistics.

DEMOGRAPHY OF TRIAL POPULATION

The population consisted of male and female subjects with type 2 diabetes mellitus, with a mean age of 58.9 years (ranging from 22.0 to 86.0 years), mean duration of diabetes of 9.5 years (ranging from 0.5 to 47.7 years), mean HbA_{1c} of 8.4% and a mean BMI of 31.2 kg/m^2. The majority of subjects (99.7%) reported their race as 'White'. In general, the trial population was well matched with few differences between the treatment groups. Subjects were randomised based on measurements performed at Visit 1 (screening visit) and baseline values were recorded approximately 1 week later, at Visit 2. Since some subjects had an increase in HbA_{1c} from Visit 1 to Visit 2, the minimum and maximum values for HbA_{1c} shown in table below are not as per limits allowed in the inclusion criteria.

Table 1. Baseline and disease characteristics

	IDegAsp BID	BIAsp 30 BID	Total
Number of Subjects	197	197	394
Age (years)			
N	197	197	394
Mean (SD)	59.0 (9.5)	58.8 (8.4)	58.9 (8.9)
Median	60.0	59.0	60.0
Min ; Max	22.0 ; 86.0	37.0 ; 76.0	22.0 ; 86.0
Body Weight (kg)			
N	197	197	394
Mean (SD)	88.0 (15.0)	88.5 (14.9)	88.2 (14.9)
Median	87.8	88.6	88.0
Min ; Max	55.0 ; 140.0	51.6 ; 137.2	51.6 ; 140.0
BMI (kg/m^2)			
N	197	197	394
Mean (SD)	31.2 (4.3)	31.1 (4.2)	31.2 (4.2)
Median	31.2	30.7	31.0
Min ; Max	22.0 ; 39.9	19.0 ; 39.7	19.0 ; 39.9
Duration of Diabetes (years)			
N	197	197	394
Mean (SD)	9.6 (6.1)	9.4 (5.7)	9.5 (5.9)
Median	8.6	8.6	8.6
Min ; Max	0.8 ; 47.7	0.5 ; 31.7	0.5 ; 47.7
HbA_{1c} (%)			
N	197	197	394
Mean (SD)	8.5 (0.8)	8.3 (0.7)	8.4 (0.8)
Median	8.4	8.2	8.3
Min ; Max	6.8 ; 10.2	6.7 ; 9.9	6.7 ; 10.2
FPG (mmol/L)			
N	195	195	390
Mean (SD)	10.5 (2.4)	10.0 (2.3)	10.2 (2.3)
Median	10.2	9.7	9.9
Min ; Max	5.5 ; 17.3	4.3 ; 16.9	4.3 ; 17.3

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation
Full analysis set.

EFFICACY RESULTS

After 26 weeks of treatment with IDegAsp BID ± metformin or BIAsp 30 BID ± metformin in insulin-naïve subjects with T2DM, 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 mean treatment difference (IDegAsp-BIAsp 30) 0.02% point $[-0.12; 0.17]_{95\% CI}$. The estimated mean change in HbA_{1c} was –1.71% points with IDegAsp and –1.73% points with BIAsp 30. After 26 weeks of treatment, the observed mean (SD) HbA_{1c} was 6.6 (0.8)% with IDegAsp and 6.5 (0.7)% with BIAsp 30.

Secondary efficacy endpoints

Confirmatory efficacy endpoints

- **FPG**: Superiority of IDegAsp to BIAsp 30 was confirmed in terms of lowering FPG; estimated treatment difference (IDegAsp-BIAsp 30) -1.00 mmol/L $[-1.42; -0.59]_{95\% CI}$. The estimated mean change in FPG was -4.35 mmol/L with IDegAsp and -3.34 mmol/L with BIAsp 30. After 26 weeks of treatment, the observed mean (SD) FPG was 6.0 (2.0) mmol/L with IDegAsp and 7.0 (2.1) mmol/L with BIAsp 30.
- **Nocturnal confirmed hypoglycaemia**: Refer to the safety conclusions.
- **Confirmed hypoglycaemia:** Refer to the safety conclusions.
- **Body weight**: Refer to the safety conclusions.
- **HbA_{1c} <7.0% without confirmed hypoglycaemic episodes:** The observed proportion of subjects achieving HbA_{1c} <7.0% without confirmed hypoglycaemic episodes was 40.1% with IDegAsp and 31.6% with BIAsp 30. The estimated odds of achieving this target was significantly higher by 56% with IDegAsp compared to BIAsp 30; the odds ratio (IDegAsp/BIAsp 30) was 1.56 $[1.0035; 2.42]_{95\% CI}$. Hierarchical testing was stopped prior to testing this endpoint for superiority.

Supportive efficacy endpoints

- **Responder for HbA_{1c}**: The observed proportion of subjects achieving HbA_{1c} <7.0% was 74.6% with IDegAsp and 75.6% with BIAsp 30 with no statistically significant difference between treatments. The observed proportion of subjects with HbA_{1c} ≤6.5% was 56.3% with IDegAsp and 54.8% with BIAsp 30, with no statistically significant difference between treatments.
- **Responder for HbA_{1c} (≤6.5%) without confirmed hypoglycaemia**: The observed proportion of subjects achieving HbA_{1c} ≤6.5% without confirmed hypoglycaemic episodes was 31.8% with IDegAsp and 23.0% with BIAsp 30; the difference between treatments was statistically significant (odds ratio [IDegAsp/BIAsp 30] 1.70 $[1.05; 2.75]_{95\% CI}$).
- **Responder for HbA_{1c} without severe hypoglycaemia**: The observed proportion of subjects achieving HbA_{1c} <7.0% without severe hypoglycaemic episodes was 75.5% with IDegAsp and 78.6% with BIAsp 30, with no statistically significant difference between treatments. The observed proportion of subjects achieving HbA_{1c} ≤6.5% without severe hypoglycaemic episodes was 56.8% with IDegAsp and 56.7% with BIAsp 30, with no statistically significant difference between treatments.
- **9-point SMPG profiles**: The mean SMPG value before breakfast was lower for IDegAsp compared to BIAsp 30 (estimated difference [IDegAsp−BIAsp 30] −0.38 mmol/L $[-0.66; -0.10]_{95\% CI}$). This was also the case for the SMPG values 90 minutes after breakfast (estimated difference: −0.56 mmol/L $[-1.01; -0.11]_{95\% CI}$) and before breakfast the following day (estimated difference: −0.52 mmol/L $[-0.81; -0.24]_{95\% CI}$). There was no difference between the two treatment groups in the mean of the 9-point SMPG profile, fluctuation in SMPG, or in prandial increments (all meals, after breakfast, after lunch, and after the main evening meal).
- **SMPG for dosing**: After 26 weeks of treatment, mean SMPG values before breakfast and before the main evening meal were significantly lower with IDegAsp than with BIAsp 30 with an estimated treatment difference (IDegAsp−BIAsp 30) of −0.38 mmol/L $[-0.60; -0.16]_{95\% CI}$ before breakfast and −0.42 mmol/L $[-0.73; -0.12]_{95\% CI}$ before the main evening meal. A higher within-subject variability in prebreakfast SMPG was detected with IDegAsp than with BIAsp 30 (estimated treatment ratio [IDegAsp/BIAsp 30] 1.14 $[1.02; 1.25]_{95\% CI}$). The within-subject variability before the main evening meal was similar between IDegAsp and BIAsp 30. The observed proportion of subjects achieving the SMPG target <5 mmol/L with IDegAsp and BIAsp 30, respectively, was 34.5% and 20.4% prebreakfast, 15.7% and 15.3%, before the main evening meal, and 11.2% and 8.7% for both timepoints. Compared to BIAsp 30 subjects, IDegAsp subjects who had yet not achieved the titration target at a given visit had a 1.79 times higher chance of achieving the prebreakfast titration target at the next visit and a 1.41 times higher chance of achieving all titration targets at the next visit.

SAFETY RESULTS

After 26 weeks of treatment with IDegAsp BID ± metformin or BIAsp 30 BID ± metformin in treatment-naive subjects with T2DM, the following was concluded:

Confirmatory safety endpoints

- **Nocturnal confirmed hypoglycaemic episodes:** Superiority of IDegAsp to BIAsp 30 was demonstrated in terms of a lower rate of nocturnal confirmed hypoglycaemic episodes; estimated rate ratio (IDegAsp/BIAsp 30) 0.25 $[0.16; 0.38]_{95\% CI}$, reflecting a 75 % lower rate with IDegAsp than with BIAsp 30. The observed rate of nocturnal confirmed hypoglycaemic episodes per 100 PYE was 63 episodes with IDegAsp and 277 episodes with BIAsp 30.
- **Confirmed hypoglycaemic episodes:** Superiority of IDegAsp to BIAsp 30 was demonstrated in terms of a lower rate of confirmed hypoglycaemic episodes; estimated rate ratio (IDegAsp/BIAsp 30) 0.46 $[0.35; 0.61]_{95\% CI}$, reflecting a 54 % lower rate with IDegAsp than with BIAsp 30. The observed rate of confirmed hypoglycaemic episodes per 100 PYE was 580 episodes with IDegAsp and 1301 episodes with BIAsp 30.
- **Change in body weight**: Body weight increased during the trial to similar mean (SD) levels; 90.8 (15.8) kg with IDegAsp and 90.6 (15.0) kg with BIAsp 30. The estimated mean change in body weight was 3.5 kg with IDegAsp and 2.7 kg with BIAsp 30 and the estimated mean treatment difference (IDegAsp−BIAsp 30) was 0.79 kg $[-0.03; 1.61]_{95\% CI.}$ Superiority of IDegAsp compared to BIAsp 30 could not be confirmed and consequently, the hierarchical testing procedure was stopped. Therefore superiority could not be confirmed for the remaining confirmatory secondary efficacy endpoint.

Supportive safety endpoints

- **Hypoglycaemic episodes**:
  - The percentage of subjects who experienced severe hypoglycaemia during the treatment period was 2.0% with IDegAsp and 1.5% with BIAsp 30.
  - One episode of nocturnal severe hypoglycaemia was reported during the trial in each treatment group.
- **Adverse events**: A similar low percentage of subjects reported AEs in the IDegAsp and BIAsp 30 groups (40.3% and 36.4%, respectively). The rate of all AEs for the IDegAsp and BIAsp 30 groups was 207 and 146 events per 100 PYE, respectively. The majority of events were mild or moderate in severity. The rates of severe AEs were low: 14 and 9 events per 100 PYE, respectively. The rate of AEs assessed as possibly or probably related to investigational product by the investigator for the IDegAsp and BIAsp 30 groups was 20 and 11 events per 100 PYE, respectively.
- **Deaths, serious adverse events and other significant adverse events:** Three deaths were reported in this trial: two deaths in the IDegAsp group due to pulmonary oedema and pancreatic carcinoma metastatic and one death in the BIAsp 30 group due to myocardial ischaemia and coronary artery insufficiency. These fatal events were considered as unlikely related to investigational product by the investigator. A total of 13 subjects (6.6%) reported 20 SAEs in the IDegAsp group while 10 subjects (5.1%) reported 12 SAEs in the BIAsp 30 group. The event rate per 100 PYE of SAEs was 21 events per 100 PYE with IDegAsp and 13 events per 100 PYE with BIAsp 30. A similar low percentage of subjects withdrew from the trial due to AEs in the IDegAsp (1.0%) and BIAsp 30 (1.5%) groups.
- **Vital signs, ECG, fundoscopy**, **physical examination and laboratory values**: No clinically relevant changes from baseline to end of treatment or differences between the two treatment groups were observed.
- **Insulin dose**: The mean total daily dose after 26 weeks was similar between the IDegAsp group (74 U and 0.80 U/kg) and the BIAsp 30 group (74 U and 0.82 U/kg), producing a ratio (IDegAsp/BIAsp 30) of 1.00 in units and 0.97 in U/kg. However, at the end of the study, the mean morning dose was slightly higher (41 U vs. 38 U) and the mean evening dose slightly lower (33 U vs. 36 U) in the IDegAsp group compared with the BIAsp 30 group.

CONCLUSIONS

The results of this confirmatory, randomised, controlled, 26-week trial demonstrated the efficacy and safety of IDegAsp versus BIAsp 30, both administered twice daily with metformin in insulin-naïve subjects with type 2 diabetes mellitus. The data supports the following conclusions:

- IDegAsp effectively improved long-term glycaemic control as measured by HbA_{1c} (non-inferior to BIAsp 30) and the data confirmed superiority to BIAsp 30 with respect to lowering FPG.
- IDegAsp was superior to BIAsp 30 in terms of a lower rate of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia.
- More subjects achieved HbA_{1c} target <7.0% without confirmed hypoglycaemia with IDegAsp than with BIAsp 30.

- Body weight increased slightly more with IDegAsp than with BIAsp 30.
- The total daily dose of IDegAsp was similar compared to BIAsp 30.
- In this trial, no safety issues were identified with IDegAsp 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 the data available in the clinical database as of 17-Dec-2012.