CTR synopsis

Trial registration ID-number: NCT01427920	**UTN – U1111-1118-4096** **EudraCT number – 2010-024303-27**

TITLE OF TRIAL

A 20 weeks randomised, multinational, open labelled, 2 armed, parallel group comparison of twice daily subject driven titration of biphasic insulin aspart (BIAsp) 30 versus twice daily investigator driven titration of biphasic insulin aspart (BIAsp) 30 both in combination with metformin in subjects with type 2 diabetes inadequately controlled on basal insulin analogues

INVESTIGATOR(S)

There were 33 principal investigators (1 at each site).

[redacted], MD was the appointed signatory investigator (Address: [redacted])

TRIAL SITE(S)

A total of 33 sites in 5 countries enrolled subjects: Argentina (5), China (6), India (8), Poland (8) and United Kingdom (6)

PUBLICATIONS

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

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 01-Sep-2011 Completion date: 13-Jul-2012	Phase 4

OBJECTIVES

Primary objective:

- To confirm efficacy of subject-driven titration of BIAsp 30 twice daily in terms of glycaemic control assessed by change in HbA_{1c}, by showing that subject-driven titration of BIAsp 30 is non-inferior to investigator-driven titration of BIAsp 30 with respect to glycaemic control, as measured by HbA_{1c} after 20 weeks of treatment in subjects with type 2 diabetes inadequately controlled on basal insulin analogues.

Secondary objectives:

- To assess and compare efficacy in terms of:
  - Fasting plasma glucose values (FPG)
  - 7-point self-measured plasma glucose (SMPG) profile
- To assess and compare safety and tolerability in terms of:
  - Hypoglycaemic episodes
  - Adverse events (AEs)
  - Clinical and laboratory assessments
  - Change in body weight
- To assess time to plasma glucose (PG) target in terms of:
  - 2-point SMPG profile
- To evaluate insulin dose
- To assess diabetes treatment satisfaction
- To assess healthcare resource utilization

METHODOLOGY

This was a 20-week open labelled, randomised, two-armed, parallel group, stratified, multinational, multicentre trial comparing twice daily (BID) subject-driven titration of biphasic insulin aspart (BIAsp) 30 versus twice daily investigator-driven titration of BIAsp 30 both in combination with metformin in subjects with type 2 diabetes inadequately controlled on basal insulin analogues and oral antidiabetic drugs (OADs). The subjects titrated themselves in the subject-driven arm or the investigator performed the titration of BIAsp 30 BID in the investigator-driven arm according to a titration algorithm recommended by the European Union Summary of Product Characteristics.

The total duration of the trial was 22 weeks with a screening period of two weeks, training period of four weeks and

maintenance period of 16 weeks. After screening, eligible subjects were randomised to either BIAsp 30 subject-driven arm or BIAsp 30 investigator driven arm in 1:1 ratio both in combination with metformin.
At randomisation subjects discontinued their basal insulin analogue and OADs except for their pre-trial metformin (a total daily dose of at least 1500 mg metformin or maximum tolerated dose [minimum 1000 mg]) and were stratified based on their initial treatment into metformin monotherapy or metformin plus additional OADs.
The subject-driven arm had three mandatory visits to the site after randomisation, at Week 4, 12 and 20.
The investigator-driven arm had six mandatory visits to the site after randomisation; at Weeks 2, 4, 8, 12, 16 and 20.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 338 subjects were planned to be randomised and 286 subjects were planned to complete the trial. The total number of subjects randomised was 348; 174 subjects in each arm. Three hundred and forty eighty (348) subjects were included in the full analysis set, 324 subjects in the per-protocol (PP) analysis set and 347 subjects in the safety analysis set.

	Subject-driven arm N (%)	**Investigator-driven arm N (%)**	**Total N (%)**
Screened			463
• Screening failures			115
• Withdrawn before randomisation			0
• Randomised	174 (100.0)	174 (100.0)	348 (100.0)
• Exposed	174 (100.0)	173 (99.4)	347 (99.7)
• Withdrawals after randomisation	9 (5.2)	17 (9.8)	26 (7.5)
• - Adverse event	1 (0.6)	2 (1.1)	3 (0.9)
• - Ineffective therapy	1 (0.6)	0 (0.0)	1 (0.3)
• - Non compliance	1 (0.6)	3 (1.7)	4 (1.1)
• - Withdrawal criteria	4 (2.3)	4 (2.3)	8 (2.3)
• - Other	2 (1.1)	8 (4.6)	10 (2.9)
Completed trial	165 (94.8)	157 (90.2)	322 (92.5)
• Full analysis set	174 (100.0)	174 (100.0)	348 (100.0)
• PP analysis set	164 (94.3)	160 (92.0)	324 (93.1)
• Safety analysis set	174 (100.0)	173 (99.4)	347 (99.7)

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

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male and female subjects above 18 years of age with type 2 diabetes ($HbA_{1c} \geq 7.0\%$ and $\leq 10.0\%$ and body mass index ≤ 40.0 kg/m^2) were included in the trial: Treatment with any thiazolidinediones and glucagon-like peptide-1 receptor agonists or pramlintide within the last three months prior to Visit 1, or treatment with more than 1 IU/kg basal insulin analogue daily was not allowed. In addition subjects with impaired hepatic function alanine aminotransferase ≥ 2.5 times upper referenced limit) or impaired kidney function (serum creatinine ≥ 133 µmol/L [1.5 mg/dL]for males and ≥ 124 µmol/L [1.4 mg/dL]) for females were excluded.

INVESTIGATIONAL MEDICINAL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

BIAsp 30, 3 mL, batch no. AP51001, AP51647 and YP52099. BIAsp 30 was administered BID using Flexpen®, subcutaneously (s.c) in the abdomen, immediately before breakfast and immediately before dinner in equal doses. The starting dose of BIAsp 30 was subject's previous basal insulin analogue dose split into two equal daily doses. Dose titration was done based on SMPG values during the previous three days. Subjects in the subject-driven arm self-titrated the dose and had three mandatory visits to the clinic after randomisation. Titration was done once a week in the training period and once in two weeks during the maintenance period. All the subjects received metformin in combination with BIAsp 30.

DURATION OF TREATMENT

BIAsp 30 was administered for a period of 20 weeks in a BID regimen.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Subjects in the two treatment arms received the same investigational medicinal product, BIAsp 30, 3 mL, batch no. AP51001, AP51647 and YP52099. Subjects in the investigator-driven arm titrated the dose based on investigator's advice and had six mandatory visits to the clinic after randomisation.

CRITERIA FOR EVALUATION – EFFICACY

- HbA_{1c}
- FPG
- SMPG
- 7-point SMPG
- 2-point SMPG
- PRO questionnaire
- Number of contacts with health care professional
- Number of blood glucose strips used

CRITERIA FOR EVALUATION – SAFETY

- Hypoglycaemic episodes
- Adverse events
- Laboratory assessments
- Physical examination
- Vital signs
- Insulin dose
- Body weight

STATISTICAL METHODS

Sample size calculation was based on one sided t-test with a significance level of 2.5% and a power of 80%.

The following analysis sets were used:

- Full analysis set (FAS) included all randomised subjects.
- PP analysis set included subjects without any major protocol violations that could affect the primary endpoint.
- Safety analysis set (SAS) included all subjects receiving at least one dose of BIAsp 30.

All efficacy endpoints were based on the FAS; the primary efficacy analysis was repeated on PP analysis set. Safety endpoints were analysed using SAS.

Primary efficacy endpoint and analysis

The primary endpoint (change from baseline in HbA_{1c} after 20 weeks of treatment) was analysed using a normal linear regression model with treatment, strata (metformin monotherapy vs. metformin + additional OAD therapy) and region as factors and baseline HbA_{1c} as covariate. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.4% . Superiority was considered confirmed when the upper bound of the two-sided 95% CI, which was calculated using the FAS, was below 0%. The PP analysis was considered supportive.

Secondary efficacy endpoints and analyses

- Responders for HbA_{1c} $\leq$6.5% and <7%/ responders without severe and documented symptomatic hypoglycaemia/responders without severe and minor hypoglycaemia were analysed separately based on a logistic regression model using treatment, strata and region as factors, and baseline HbA_{1c} as covariate.

- Change from baseline in FPG after 20 weeks of treatment was analysed using a normal linear regression model using treatment, strata and region as factors, and baseline FPG as covariate.
- A mixed effect model was fitted to the 7-point SMPG profile data. The model included treatment, time, interaction between treatment and time, strata and region as fixed factors and subject as random effect. The time corresponded to the expected measurement times during the 24 period. Mean differences between the two treatments arms and corresponding 95% CI were to be estimated for each time point only when the treatment-by-time interaction effect was statistically significant. If the treatment by-time interaction effect was not statistically significant, the model was fitted without the interaction term, and the overall treatment effect was estimated.
- Prandial PG increment for each meal was analysed using a normal linear regression model with treatment, strata and region as factors, and the relevant baseline value as covariate.
- Mean PG increment over all meals was analysed using a normal linear regression model with treatment, strata and region as factors, and the mean PG increment at baseline as covariate.
- Time to reach PG target using 2-point SMPG profile during the treatment period: The survival endpoint was analysed using a Cox proportional hazards model including treatment, strata and region as factors.

Safety endpoints and analyses

- Hypoglycaemic episodes were classified based on American Diabetes Association (ADA) classification. The number of hypoglycaemic episodes were 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, strata and region as factors. For each class of hypoglycaemic episodes a separate sensitivity analyses were conducted comparing number of episodes pair-wise in the two treatment groups using the Wilcoxon-Mann-Whitney method.
- AEs were evaluated based on descriptive statistics. AEs and hypoglycaemic episodes were also presented as the rate of the events per 100 patient years of exposure (PYE).
- Change from baseline in body weight after 20 weeks of treatment was analysed using a normal linear regression model with treatment, strata and region as factors, and baseline body weight as covariate.
- Remaining laboratory parameters, physical examination, vital signs and insulin dose were evaluated based on descriptive statistics.

Other endpoints and analyses

- The patient reported outcome questionnaire included Treatment-Related Impact Measures for Diabetes and Devices (TRIM-D) questionnaire with five subscale scores. Each of the subscale scores and the overall score were analysed separately using a normal linear regression model including treatment, strata and region as factors, and the corresponding baseline score as covariate.
- The number of healthcare resources utilized was compared descriptively between treatment groups, in terms of number of contacts, number of blood glucose strips, medication prescribed, dose of insulin used and referral to hospital and reason for referral.

DEMOGRAPHY OF TRIAL POPULATION

The baseline characteristics are presented below for the two arms. The mean age was 58.5 years, mean duration of type 2 diabetes 9.9 years and the mean BMI 29.4 kg/m^2. The mean HbA_{1c} was 8.3% and mean FPG 9.0 mmol/L suggesting inadequate glycaemic control. Majority of the subjects were White (53.4%) and Asian (42.8%) and of non-hispanic or latino origin (74.1%). The mean body weight in the subject-driven arm (81.0 [16.2] kg) was slightly higher than the investigator-driven arm (78.0 [15.0] kg) and so was the FPG; 9.1 (2.7) mmol/L in the subject-driven arm and 8.8 (2.8) mmol/L in the investigator-driven arm. The duration of diabetes was slightly longer in the investigator-driven arm (10.6 [6.8] years) than the subject-driven arm (9.3 [5.8] years).

	Subject-driven Mean (SD)	**Investigator-driven Mean (SD)**	**Total Mean (SD)**
Number of subjects	174	174	348
Age (years)	58.9 (9.8).	58.0 (9.5)	58.5 (9.6)
Ethnicity	N (%)	N (%)	N (%)
Hispanic or Latino	42 (24.1)	48 (27.6)	90 (25.9)
Not Hispanic or Latino	132 (75.9)	126 (72.4)	258 (74.1)

Ethnic origin			
White	96 (55.2)	90 (51.7)	186 (53.4)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
Asian	73 (42.0)	76 (43.7)	149 (42.8)
American Indian or Alaska Native	4 (2.3)	8 (4.6)	12 (3.4)
Other	1 (0.6)	0 (0.0)	1 (0.3)
Weight (kg)	81.0 (16.2)	78.0 (15.0)7	79.5 (15.7)
BMI (kg/m^2)	29.7 (4.8)	29.2 (4.7)	29.4 (4.7)9
Duration of diabetes (years)	9.3 (5.8	10.6 (6.8)	9.9 (6.3)
HbA_{1c} (%)	8.3 (0.9)	8.3 (0.9)	8.3 (0.9)
FPG (mmol/L)	9.1 (2.7)	8.8 (2.8)	9.0 (2.7)

N: number of subjects; SD: standard deviation; BMI: body mass index

EFFICACY RESULTS

After 20 weeks of treatment with BIAsp 30, the following was concluded:

Primary endpoint:

- Non-inferiority could not be confirmed for the subject-driven arm in terms of reduction in HbA_{1c} from baseline compared with the investigator-driven arm. The estimated mean treatment difference was 0.25%-points $[0.04;0.46]_{95\% CI}$ with an estimated reduction of -0.72%-points in the subject-driven arm and -0.97%-points with investigator-driven arm. After 20 weeks of treatment, the estimated mean HbA_{1c} was 7.57% in the subject-driven arm and 7.32% in the investigator-driven arm.

Secondary endpoints:

Responders for HbA_{1c}

- A statistically significantly lower proportion of subjects in the subject-driven arm compared with the investigator-driven arm reached HbA_{1c} target of ≤6.5% and <7% after 20 weeks of treatment; for HbA_{1c} ≤6.5%, 12.1% vs 20.7% respectively reached HbA_{1c} target, estimated odds ratio 0.4959 $[0.2716; 0.9056]_{95\% CI}$ and for HbA_{1c} <7%, 28.7% vs 38.5% respectively reached HbA_{1c} target, estimated odds ratio 0.5941 $[0.3696; 0.9550]_{95\% CI}$.
- A statistically significantly lower proportion of subjects in the subject-driven arm compared with the investigator-driven arm reached HbA_{1c} target of ≤6.5% and <7% without severe and minor hypoglycaemia during the last 12 weeks of treatment; for HbA_{1c} ≤6.5%, 8.0% vs 16.1 % respectively reached the HbA_{1c} target, estimated odds ratio 0.4308 $[0.2144; 0.8657]_{95\% CI}$ and for HbA_{1c} <7%, 19.5 % vs 28.2% respectively reached the HbA_{1c} target, estimated odds ratio 0.5844 $[0.3480; 0.9814]_{95\% CI}$.
- There was statistically no significant difference between the two treatment arms in the proportion of subjects reaching the HbA_{1c} target of ≤6.5% and <7% without severe and documented symptomatic hypoglycaemia during the 12 weeks of treatment; for HbA_{1c} target ≤6.5%, estimated odds ratio 0.5474 $[0.2568; 1.1667]_{95\% CI}$ and for HbA_{1c} target <7%, estimated odds ratio 0.7011 $[0.3995; 1.2303]_{95\% CI}$.

Fasting plasma glucose

- There was no statistically significant difference between the two treatment arms with respect to change from baseline in FPG after 20 weeks of treatment, estimated treatment difference 0.13 $[-0.44;0.69]_{95\% CI}$.

Self-measured plasma glucose profile

- Overall, after 20 weeks of treatment, the subject-driven arm had statistically significant higher estimated overall mean of 7-point SMPG profile compared with the investigator-driven arm, estimated treatment difference 0.4530 $[0.0408; 0.8651]_{95\% CI}$.
- The prandial increments at breakfast, lunch, dinner and all meals were similar between the two treatment arms with statistically no significant difference.
- There was statistically no significant difference between the two treatment arms in time to reach the PG target [4.4; 6.1] mmol/L for the first time, estimated hazard ratio, 1.065 $[0.8123; 1.3963]_{95\% CI}$.

Patient reported outcome and healthcare utilisation

- No statistically significant differences were found between the subject- and the investigator-driven arms in any of the subscale TRIM-D scores and total TRIM-D score at end-of-trial.
- Overall, contacts between subject and site were less frequent in the subject-driven arm than investigator-driven arm both for mandatory contacts and also for additional contacts due to titration.
- Blood glucose strips appeared to be slightly less frequently used in the subject-driven arm than the investigator-driven arm.

SAFETY RESULTS

Insulin dose

- The increase in mean insulin dose was similar in both the arms throughout the trial.
- Both the breakfast and dinner dose of BIAsp 30 were similar at the beginning and end of trial.
- The prescribed and actual dose at the end of trial was similar.

Adverse events

- The rate of treatment emergent adverse events (TEAEs) was slightly lower in the subject-driven arm than the investigator-driven arm (157.8 vs. 225.2 events per 100 PYE).
- No TEAEs were reported by ≥5% subjects in both the treatment arms.

- There were few TEAEs which were probably or possibly related to trial product; one event in the subject-driven arm and seven events in the investigator-driven arm.
- There were few serious adverse events (SAEs) reported in the trial; two SAEs in the subject-driven arm and four SAEs in the investigator-driven arm; only one event of severe hypoglycaemia from the investigator-driven arm was reported as SAE probably related to BIAsp 30.
- Among the TEAEs reported, the majority were of mild to moderate severity. There were seven severe TEAEs in the investigator-driven arm compared with no severe TEAEs reported in the subject-driven arm.
- Three subjects withdrew from the trial due to AEs.

Laboratory safety, Physical examination and Vital signs

- No clinically relevant effects were observed with laboratory parameters related to haematology and biochemistry.
- No clinically relevant effects were observed with vital signs or physical examination.

Hypoglycaemia

- The observed rates of hypoglycaemic episodes according to the ADA classification were slightly higher for the investigator-driven arm (12.15 and 9.87 episodes per subject exposure year with the subject-driven arm and the investigator-driven arm respectively), however there was statistically no significant difference between the two treatment arms. There was statistically no significant difference between the two arms in the occurrence of nocturnal and minor or severe hypoglycaemic episodes.

Body weight

- There was a statistically significant higher weight gain in the subject-driven arm compared with the investigator-driven arm after 20 weeks of treatment, estimated treatment difference 0.68 kg $[0.03; 1.32]_{95\%CI.}$

CONCLUSIONS

- Efficacy of subject-driven titration in terms of reduction in HbA_{1c} at the end of trial could not be confirmed in comparison to investigator-driven titration (non-inferiority could not be confirmed).
- The overall proportion of subjects reaching the HbA_{1c} target of $\leq 6.5\%$ and $<7\%$ was statistically significantly lower in the subject-driven arm.
- There was statistically no significant difference between the two arms with respect to reduction in FPG after 20 weeks of treatment.
- The subject-driven arm had statistically significant higher estimated overall mean of 7-point SMPG profile, although there was no significant difference between the two arms with respect to prandial PG increment or in the time to reach PG target first time.
- There was similar increase in the mean insulin dose in both the arms throughout the trial.
- The number of contacts in the subject-driven arm was less frequent and so was the use of blood glucose strips. There was no difference in the perception of treatment between the two arms as assessed by TRIM-D scores.
- Overall, BIAsp 30 was safe and well tolerated as measured by laboratory parameters and AE profile, although with the subject-driven arm showing statistically significant higher weight gain compared with the investigator-driven arm.
- There was statistically no significant difference between the two arms in the occurrence of hypoglycaemic episodes.

The trial was conducted in accordance with the Declaration of Helsinki [World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 59th WMA Assembly, Seoul, October 2008] and ICH Good Clinical Practice [International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. 01-May-1996].

- The results presented reflect data available in the clinical database as of 08 August 2012.