2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00469092	2006-003288-29

Title of Trial

A multi-national, open-labelled, randomised, parallel group, 4 week run-in and 26 weeks treat-to-target comparison of biphasic insulin aspart 30 once daily versus insulin glargine once daily both in combination with metformin and glimepiride in insulin naïve subjects with type 2 diabetes

Investigator(s)

A total of 64 investigators in 15 countries. Dr [redacted] was appointed as Signatory Investigator

Trial Site(s)

64 sites in 15 countries: Argentina (4), Austria (4), Czech Republic (2), France (3), India (4), Malaysia (3), Mexico (3), Netherlands (4), Philippines (4), Poland (13), Romania (5), Serbia and Montenegro (4), South Africa(4), Spain (4) and Sweden (3)

Publications

None

Trial Period	**Development Phase**
07 May 2007 to 10 April 2008	4

Objectives

Primary Objective:

- To investigate if biphasic insulin aspart (BIAsp) 30 once daily (OD) in combination with metformin and glimepiride is non-inferior and superior in the event of non-inferiority, compared with insulin glargine OD in combination with both metformin and glimepiride with respect to glycaemic control, as measured by HbA_{1c} after 26 weeks of treatment in subjects with type 2 diabetes, failing on oral anti-diabetic drugs (OADs).

Secondary Objectives:

To compare the following parameters in the BIAsp 30 group with those in the glargine group, both in combination with metformin and glimepiride after 26 weeks treatment:

- the glycaemic control as measured by 9-point plasma glucose (PG) profiles
- the safety profile as measured by the incidence of hypoglycaemic episodes, adverse events, laboratory tests and clinical evaluations
- change in body weight
- change in waist circumference (WC)
- total daily insulin dose
- the percentage of subjects achieving the treatment target of $HbA_{1c} < 6.5\%$
- the percentage of subjects achieving the treatment target of $HbA_{1c} < 7.0\%$
- the percentage of subjects achieving a HbA_{1c} reduction of > 1.0 % from baseline
- the prandial glucose increment over each of the 3 main meals
- the average prandial glucose increments
- the cardiovascular (CV) risk marker as measured by the lipid profile (total cholesterol, HDL, LDL, TG) and the high sensitive C-reactive protein (hs CRP)
- Treatment Satisfaction as measured by the Diabetes Medication Satisfaction questionnaire (Diab MedSat)

Methodology

This was a two-armed, open-label, randomised, parallel group, multi-centre, multinational, treat-to-target trial comparing the efficacy and safety of a once daily regimen of BIAsp 30 or insulin glargine, both in combination with a fixed dose of metformin and glimepiride, in subjects with type 2 diabetes. Following screening, eligible subjects entered a 4 week run-in period where during the first 3 weeks metformin was titrated to maximum 2550 mg (or 1700 mg if 2550 mg was not tolerated) and glimepiride to 4 mg, at the discretion of the Investigator. Subjects who were

already taking 4, 6 or 8 mg glimepiride continued on this dose. During the last week prior to randomisation, the doses of both metformin and glimepiride were kept constant. For subjects taking maximum doses of metformin and glimepiride prior to the trial, the 3 weeks OAD titration period was omitted. Eligible subjects were randomised (1:1) into two treatment groups, BIAsp 30 OD or insulin glargine OD. During the insulin treatment period of 26 weeks, titration was based upon pre-breakfast plasma glucose measurements with the aim to achieve fasting plasma glucose of 5-6.1 mmol/L (90-110mg/dL). The titration was performed once a week for the first 10 weeks of insulin treatment, and every 2 weeks for the remainder of the treatment period.

Number of Subjects Planned and Analysed

It was planned to screen 700 subjects in order to randomise 480 and obtain 382 evaluable subjects. In total, 802 subjects were screened, of whom 246 were screening failures and 76 were randomisation failures. The subject disposition is shown below:

	BIAsp 30 n (%)	Glargine n (%)	Total n (%)
Screened			802
Entered run-in			556
Randomised	239(100.0%)	241(100.0%)	480(100.0%)
Exposed	231(96.7%)	238(98.8%)	469(97.7%)
Withdrawals	26(10.9%)	21(8.7%)	47(9.8%)
Adverse event	5(2.1%)	4(1.7%)	9(1.9%)
Non-compliance with Protocol	3(1.3%)	3(1.2%)	6(1.3%)
Ineffective Therapy	1(0.4%)	0(0.0%)	1(0.2%)
Withdrawal Criteria	3(1.3%)	4(1.7%)	7(1.5%)
Other	14(5.9%)	10(4.1%)	24(5.0%)
Completed	213(89.1%)	220(91.3%)	433(90.2%)
ITT Analysis Set - SAP	225(94.1%)	232(96.3%)	457(95.2%)
PP Analysis Set - SAP	207(86.6%)	205(85.1%)	412(85.8%)
Safety Analysis Set			
Run-in Period	239	241	556
Treatment Period	231(96.7%)	238(98.8%)	469(97.7%)

Diagnosis and Main Criteria for Inclusion

Male and female subjects with type 2 diabetes aged ≥ 18years, with a BMI ≤ 40kg/m^2, and an $HbA_{1c} \geq 7.0\%$ and ≤ 11.0%. Subjects must have been treated with a maximum of 3 OADs for more than 6 months; an unchanged total daily dose of at least 1500 mg (850 mg for Asian subjects) metformin for at least two months and an unchanged total daily dose of at least half maximum recommended daily dose of any insulin secretagogue for the last two months. Subjects were to be insulin naïve and must not have been treated with any TZD for 5months, nor systemic corticosteriods for 3 months prior to the trial. Subjects were not to have known hypoglycaemia unawareness or recurrent major hypoglycaemic episodes, blood disorders, cardiac disease, renal disorders, proliferative retinopathy or maculopathy requiring acute treatment, or any other disease or medication known to interfere with the trial.

Test Product, Dose and Mode of Administration, Batch Number

BIAsp 30, 3ml, 100 U/ml, FlexPen®. The dose was individually titrated and administered as subcutaneous injections preferably in the abdomen. Batch number was SP52261.

Metformin hydrochloride tablets, 850 mg were administered orally. Batch numbers were 107319 and 105172.

Glimepiride tablets, 2mg were administered orally. Batch number N479.

Duration of Treatment

Subjects were treated with metformin and glimepiride for a maximum of 30 weeks, and with BIAsp 30 or insulin glargine for 26 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

Insulin glargine cartridges 3 ml 100 U/ml, OptiSet®. The dose was individually titrated and administered as subcutaneous injections, preferably in the abdomen. Batch number was 40N032.

Metformin hydrochloride tablets, 850 mg were administered orally. Batch numbers were 107319 and 105172.

Glimepiride tablets, 2mg were administered orally. Batch number N479.

Criteria for Evaluation – Efficacy

HbA_{1c},9-point plasma glucose profiles, prandial increment over three main meals, average prandial increment, percentage of subjects achieving the treatment targets of: HbA_{1c} <6.5%, HbA_{1c}<7.0%, percentage of subjects achieving HbA_{1c} <6.5% and HbA_{1c}<7.0% without hypoglycaemia, percentage of subjects achieving an HbA_{1c} reduction of 1%, treatment satisfaction

Criteria for Evaluation – Safety

Adverse events, hypoglycaemic episodes, laboratory analyses (haematology, biochemistry and cardiovascular risk markers), insulin dose, body weight, waist circumference, pregnancy test, vital signs, physical examination, ECG and funduscopy/fundusphotography.

Statistical Methods

Three analysis sets were defined: the safety population consisting of all subjects exposed to trial products grouped after actual treatment, the ITT population defined as all randomised subjects exposed to trial product and who have at least a baseline HbA_{1c} measurement and at least one post-randomisation HbA_{1c} measurement, and the PP population defined as all randomised subjects exposed to trial product who completed the trial and who did not significantly violate the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the primary endpoint. Analyses based on the ITT population were considered primary while analysis based on the PP was considered supportive and only applied for the primary endpoint. All tests were two sided at a significance level of 5%. In all analyses except for the primary efficacy analysis, the null hypothesis was that the two treatment groups do not differ, against the alternative that they differ.

The primary endpoint, HbA_{1c} after 26 weeks of treatment was analysed using a linear regression model with treatment and country as factors and baseline HbA_{1c} as continuous covariate. The treatment comparison (BIAsp 30 versus insulin glargine) was based on a non-inferiority criterion, where BIAsp 30 was shown to be non-inferior if the upper limit of the 95% confidence interval of the BIAsp 30-glargine difference was less than 0.4%. If non-inferiority of BIAsp 30 is shown, a subsequent test for superiority was to be performed based on the ITT population. Superiority of BIAsp 30 over insulin glargine was to be claimed if the upper limit of the 95% confidence interval for the difference was lower than 0%.

In the test of superiority of BIAsp 30 OD over insulin glargine OD the lower limit of the 95% confidence interval must also be considered. If this lower limit is greater than -0.4% then insulin glargine OD is non-inferior to BIAsp 30 OD by symmetry and a conclusion of equivalence between the two treatments is more appropriate.

The primary analysis was repeated on the change in HbA_{1c} from baseline.

Secondary endpoints: The frequencies of subjects achieving $HbA_{1c} \leq 6.5\%$ and < 7.0% and of subjects who achieve an HbA_{1c} reduction of more than 1.0% were analysed using logistic regression including effects of treatment and country and with baseline HbA_{1c} as an explanatory continuous variable. In the case of some categories having only a few observations, Fisher's Exact Test was to be used instead.

The 9-point SMPG profiles after 26 weeks of treatment were analysed using a repeated measures mixed model including treatment, time, the treatment-by-time interaction and country as fixed effects, and subject as random effect. The prandial increments after the three main meals after 26 weeks of treatment were analysed using a similar model to the 9-point profiles.

The relative risk of having a hypoglycaemic episode in the two groups was analysed using a negative binomial regression model. The model included the number of episodes as the dependent variable, the log-transformed exposure time as an offset variable, and country and treatment as categorical variables. Nocturnal (episodes occuring 24.00h – 06.00h) and diurnal episodes were analysed separately. Two composite endpoints were applied to describe

the percentages of subjects achieving the treatment target of HbA_{1c} < 7.0% after 26 weeks treatment without nocturnal (00:00-06:00) hypoglycaemia (minor+major), and the percentages of subjects achieving the treatment target of HbA_{1c} < 7.0% after 26 weeks treatment without daytime (06:01-23:59) hypoglycaemia (minor+major). Adverse events, Physical Examination, Vital Signs, ECG and Fundoscopy/fundusphotography were summarised by descriptive statistics. Biochemistry, haematology and blood lipids (Cardiovascular risk markers) and Hs CRP were evaluated by shift tables at baseline and end of trial. The change in body weight from baseline visit 22 (week 26) was analysed using a linear normal model including treatment and country as factors, and baseline body weight as continuous covariate. The treatment difference was estimated and a 95% confidence interval for the difference was calculated. Likewise the change in average waist circumference from baseline visit 22 (week 26) was analysed using a linear normal model including treatment and country as factors, and baseline waist circumference as continuous covariate. Treatment satisfaction was analysed using a linear normal model including treatment and country as factors and the corresponding baseline score as continuous covariate.

Demography of Trial Population

The demography of all exposed subjects is shown below. The overall subject characteristics were comparable between the two groups. Slightly more females were included (56%). Subjects were predominantly of White or Asian origin (55% and 33% respectively) with a mean age of 56.0 years and BMI of 29.1. The mean duration of diabetes was 9.3 years and mean HbA_{1c} at screening was 9.0%.

	BIAsp 30	Glargine	Total
Number exposed (n)	231	238	469
Males, n (%)	108 (46.8)	98 (41.2)	206 (43.9)
Females, n (%)	123 (53.2)	140 (58.8)	263 (56.1)
Race n (%)			
American Indian/Alaska native,	13 (5.6)	11 (4.6)	24 (5.1)
Asian	76 (32.9)	79 (33.2)	155 (33.0)
Black or African American	10 (4.3)	7 (2.9)	17 (3.6)
Other	3 (1.3)	6 (2.5)	9 (1.9)
White	125 (54.1)	133 (55.9)	258 (55.0)
Missing	4 (1.7)	2 (0.8)	6 (1.3)
Mean (SD)			
Weight (kg)	77.5 (14.6)	77.3 (15.4)	77.4 (15.0)
BMI (kg/m^2)	29.0 (4.6)	29.1 (4.6)	29.1 (4.6)
Age (yrs)	55.9 (9.7)	56.1 (10.0)	56.0 (9.9)
Diabetes duration (yrs)	9.1 (5.8)	9.5 (6.1)	9.3 (6.0)
HbA_{1c} (%)	8.9 (1.0)	9.0 (1.1)	9.0 (1.1)

Efficacy Results

Primary endpoint

- Analysis of HbA_{1c} showed that BIAsp 30 was non-inferior to glargine. BIAsp 30 was demonstrated to be superior to glargine, however according to the predefined limits the treatments are considered to be clinically equivalent.

Primary Endpoint Analysis	BIAsp 30 mean (SE)	Glargine mean (SE)	p-value
Estimated mean end of trial HbA_{1c} (%)	7.08 (0.07)	7.23 (0.07)	0.029
Estimated mean reduction in HbA_{1c} from baseline (%)	1.41 (0.07)	1.25 (0.07)	
BIAsp 30 – Glargine Estimated Mean and 95% C.I.	-0.16 [-0.30;-0.02]		

Secondary Endpoints based on self measured Plasma Glucose and Treatment Satisfaction

- 9 point plasma glucose profiles were lower after 26 weeks of treatment in both groups. At the end of trial, the profiles differed between BIAsp 30 and glargine, where significantly lower SMPGs were observed post dinner ($p=0.04$) and at bedtime ($p<0.01$) with BIAsp 30.
- The overall mean prandial increment over breakfast, lunch and dinner after 26 weeks of treatment was not significantly different between treatments; $p= 0.28$.
- The average prandial increment, mean (SD) mmol/L at baseline was 2.1(1.9) with BIAsp 30 and 2.0 (2.0) with glargine, decreasing to 1.7(1.6) with BIAsp 30 versus 1.9(1.9) with glargine after 26 weeks of treatment.
- Analysis of treatment satisfaction scores showed that subjects had a similar level of satisfaction with BIAsp 30 and glargine; mean BIAsp 30 - glargine = -0.11, 95% CI [-2.36; 2.14].

Subjects Achieving Treatment Targets

Secondary Endpoint	BIAsp 30	Glargine	p-value
HbA_{1c} <7% at 26 weeks n (%)	101 (45)	106 (46)	0.948
HbA_{1c} <7% at 26 weeks with no nocturnal hypoglycaemia, n (%)	82 (36)	92 (40)	0.640
HbA_{1c} <7% at 26 weeks with no daytime hypoglycaemia, n (%)	52 (23)	50 (22)	0.481
HbA_{1c} <7% at 26 weeks with no overall hypoglycaemia, n (%)	45 (20)	45 (19)	0.640
HbA_{1c} ≤6.5% at 26 weeks, n (%)	54 (24)	60 (26)	0.713
Number with more than 1% reduction in HbA_{1c}, n (%)	134 (60)	132 (57)	0.593

Safety Results

- The distribution of adverse events was comparable in the two groups. The most frequent events in both groups were nasopharyngitis, upper respiratory tract infection and headache.
- In both treatments groups, 2 (<1%) of subjects had serious adverse events considered to have a possible or probable relation to trial products, all were related to hypoglycaemia (BIAsp 30: hypoglycaemic unconsciousness and hypoglycaemic coma and glargine: 2 events of hypoglycaemia).
- Three deaths were reported, two in the run-in period (myocardial infarction and cerebrovascular accident) and one treatment emergent event of myocardial infarction in the glargine group. All were considered as having an unlikely relation to trial products.
- Five subjects in the BIAsp 30 group and four subjects in the glargine group were withdrawn from the trial due to treatment emergent adverse events. Apart from one death, the subjects were withdrawn due to the following events: BIAsp 30: cerebral infarction, chronic renal failure, visual acuity reduced, acute pulmonary oedema, pneumonia, and glargine: cerebrovascular accident, perianal abcess and vascular graft occlusion. None of these events were considered related to trial products.

Summary of Treatment Emergent Adverse Events

	BIAsp 30 n (%)	E	Glargine n (%)	E
Subjects	231		238	
All Adverse Events	117 (50.6)	288	115 (48.3)	309
Serious Adverse Events	13 (5.6)	15	10 (4.2)	14
Deaths	0 (0.0)	0	1 (0.4)	1
Non-Serious Adverse Events	111 (48.1)	273	110 (46.2)	295
Adverse Events by Relation to trial product				
Missing	2 (0.9)	2	1 (0.4)	1
Probably or possibly related	7 (3.0)	7	12 (5.0)	14
Unlikely Related	115 (49.8)	279	113 (47.5)	294
Adverse Events leading to Withdrawal	5 (2.2)	5	4 (1.7)	4

n: number of subjects with an AE, E: number of events

Hypoglycaemic Episodes

Endpoint	**BIAsp 30**	**Glargine**	**Relative Risk BIAsp 30/ Glargine**	**p- value**
All hypoglycaemic episodes n (%)	133 (58)	122 (51)	1.41	0.034
Number of episodes/subject year	6.5	4.8		
Minor hypoglycaemic episodes n (%)	112 (49)	99 (42)	1.46	0.041
Major hypoglycaemic episodes n (%)	3 (1.3)	2 (0.8)		
Nocturnal hypoglycaemic episodes n (%)	54 (23)	34 (14)	2.41	0.003
Number of nocturnal episodes/subject year	1.1	0.5		
Daytime hypoglycaemic episodes n (%)	122 (53)	112 (47)	1.33	0.101
Number of daytime episodes/subject year	5.4	4.3		

n: number of subjects with a hypoglycaemic episode

- The incidence of hypoglycaemia was low with both treatments.
- The mean weight gain after 26 weeks was similar with BIAsp 30, 1.74 kg compared with 1.67 kg for glargine. This difference was not statistically significant; p= 0.81.
- The mean increase in waist circumference after 26 weeks was 1.42 cm with BIAsp 30 and 1.45 cm with glargine. This difference was not statistically significant; p= 0.95.
- No clinically relevant differences between treatment groups were observed in standard laboratory parameters or cardiovascular risk markers after 26 weeks.
- No clinically significant changes were observed in vital signs and physical examination.
- After 26 weeks of treatment the mean total daily insulin dose at end of trial was slightly higher in the BIAsp 30 group (0.32U/kg), than for glargine (0.29U/kg), an increase of 0.14U/kg versus 0.11U/kg, respectively.

Conclusions

In a population of poorly controlled insulin naïve subjects with type 2 diabetes, once daily treatment with BIAsp 30 or insulin glargine, both in combination with metformin and glimepride for 26 weeks resulted in the following:

- Analysis of HbA_{1c} showed that BIAsp 30 was non-inferior to glargine. Furthermore, BIAsp 30 was demonstrated to be superior to glargine. However, according to the predefined limits the treatments are considered to be clinically equivalent.
- Similar proportions of subjects reached the treatment targets of <7.0% and <6.5% and a reduction of HbA_{1c} of more than 1% in both treatment groups.
- Self measured 9 point plasma glucose profiles showed significantly lower SMPG values after dinner and at bedtime with BIAsp 30 compared to glargine, although mean postprandial glucose increments over the three main meals were not significantly different.
- The absolute hypoglycaemia rates were low in both treatments. BIAsp 30 OD was associated with a significantly higher relative risk of hypoglycaemia overall compared with glargine. The higher relative risk with BIAsp 30 was significant for minor hypoglycaemia and nocturnal hypoglycaemia, but not for daytime hypoglycaemia. Major hypoglycaemia was rare. A similar proportion of subjects achieved the HbA_{1c} target of <7.0% without hypoglycaemia.
- No statistically significant differences between BIAsp 30 and glargine were observed with respect to body weight and waist circumference. Total daily dose increased over 26 weeks up to 0.32U/kg and 0.29U/kg with BIAsp 30 and glargine respectively.
- The proportion of subjects with adverse events and distribution of events was comparable between the two groups, while the proportion of subjects with possibly or probably related adverse events was slightly lower with BIAsp 30 compared to glargine. There were 5 withdrawals due to adverse events with BIAsp 30 and 4 with glargine. The safety profile as reflected by vital signs, physical examination and clinical laboratory parameters did not show any differences between the two groups.
- Treatment satisfaction scores indicated a similar degree of satisfaction with both treatments.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Amended with note of Clarification on Paragraph 29, Washington 2002).