2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00184574	2004-002778-50
Title of Trial A multi-national, open labelled, randomised, stratified, parallel 36 week comparison of twice daily Biphasic Insulin Aspart 30 versus thrice daily Biphasic Insulin Aspart 50 and 70 all in combination with metformin in subjects with type 2 diabetes.	
Investigator Dr [redacted] and Professor [redacted] were designated as signatory Investigators	
Trial Sites The trial was carried out in 88 sites in 18 countries	
Publications None	
Trial Period 19-Apr 2005 – 24-Mar 2006	**Development Phase** Phase 3b

Objectives

Primary Objective:

To investigate if BIAsp 50-50-50(30) and BIAsp 70-70-70(30) is non-inferior, and superior in the event of non-inferiority, compared with BIAsp 30-30 all in combination with metformin with respect to glycaemic control as measured by HbA_{1c} after 36 weeks of treatment in subjects with type 2 diabetes;

- where BIAsp 50-50-50(30) is BIAsp 50 administered before breakfast, lunch and dinner in combination with stable dose of metformin as prior to randomisation, with the possibility of switching the dinner injection to BIAsp 30, if subjects after 12 weeks of treatment do not reach a pre-breakfast plasma glucose (PG) ≤ 7.0 mmol/L and
- BIAsp 70-70-70(30) is BIAsp 70 administered before breakfast, lunch and dinner in combination with stable dose of metformin as prior to randomisation, with the possibility of switching the dinner injection to BIAsp 30, if subjects after 12 weeks of treatment do not reach a pre-breakfast PG ≤ 7.0 mmol/L and
- BIAsp 30-30 is BIAsp 30 administered before breakfast and dinner in combination with stable dose of metformin as prior to randomisation

Secondary Objectives:

- Compare the glycaemic control of BIAsp 70-70-70(30) and BIAsp 50-50-50(30) with that of BIAsp 30-30 all in combination with metformin, as measured by 8-point plasma glucose profiles after 36 weeks of treatment
- Compare the safety profiles of BIAsp 70-70-70(30) and BIAsp 50-50-50(30) with that of BIAsp 30-30 all in combination with metformin, as measured by the incidence of hypoglycaemic episodes and AEs
- Compare changes in body weight and change in total daily insulin dose in the BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups, with that in the BIAsp 30-30 treatment group after 36 weeks of treatment
- Compare the percentages of subjects achieving the treatment target of $HbA_{1c} \leq 6.5\%$ in the BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups, with the percentage of subjects in the BIAsp 30-30 treatment group after 36 weeks of treatment
- Compare the percentages of subjects achieving the treatment target of $HbA_{1c} < 7.0\%$ in the BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups, with the percentage of subjects in the BIAsp 30-30 treatment group after 36 weeks of treatment
- Compare the percentages of subjects achieving a HbA_{1c} reduction of more than 1.0 % from baseline in the BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups, with the percentage of subjects in the BIAsp 30-30 treatment group after 36 weeks of treatment
- Compare the percentages of subjects in the BIAsp 70-70-70(30), BIAsp 50-50-50(30) and BIAsp 30-30 treatment groups reaching a pre-breakfast PG ≤ 7.0 mmol/L after 12 weeks of treatment
- Compare the percentages of subjects in the BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups switching the dinner injection to BIAsp 30 after 12 weeks of treatment

- Compare the percentages of subjects in the BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups with the percentage in the BIAsp 30-30 treatment group achieving the treatment target of $HbA_{1c} \leq 6.5\%$ after 36 weeks of treatment without experiencing hypoglycaemic episodes during the last 12 weeks of treatment
- Compare the percentages of subjects in the BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups with the percentage in the BIAsp 30-30 treatment group achieving the treatment target of $HbA_{1c} < 7.0\%$ after 36 weeks of treatment without experiencing hypoglycaemic episodes during the last 12 weeks of treatment
- Compare the prandial blood glucose increments over each of the 3 main meals as well as the average prandial blood glucose increments in the BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups with that in the BIAsp 30-30 treatment group after 36 weeks of treatment
- Compare BIAsp 70-70-70(30) and BIAsp 50-50-50(30) treatment groups with the BIAsp 30-30 treatment group, with respect to Treatment Satisfaction (Insulin Treatment Satisfaction Questionnaire (ITSQ-22)) and well being (Well-Being Index (WHO (Five))) after 36 weeks of treatment.

Methodology

- BIAsp-1440 was a multi-national, open-label, randomised, stratified parallel group, 'Treat to Target' trial in subjects with type 2 diabetes. The total duration of the trial was 36 weeks. Subjects were randomised 1:1:1 to treatment with either BIAsp 30 twice daily (BID), BIAsp 50 three times daily (TID) or BIAsp 70 TID. Subjects in the TID groups were switched to BIAsp 30 at dinner if their pre-breakfast PG exceeded 7 mmol/L after 12 weeks of treatment. The treatment groups were denoted BIAsp 30-30, BIAsp 50-50-50(30) and BIAsp 70-70-70(30), respectively. The term High Mix was used as a collective term for the BIAsp 50-50-50(30) and the BIAsp 70-70-70(30) groups.

Number of Subjects Planned and Analysed

A total of 749 subjects were screened, 603 subjects were randomised and 507 subjects completed the trial.

	BIAsp 30-30 N	(%)	BIAsp 50-50-50(30) N	(%)	BIAsp 70-70-70(30) N	(%)	Total N	(%)
Screened							749	
Randomised	201		202		200		603	
Randomised, not exposed	1		1		2		4	
Strata								
Once daily, metformin and SUs	36	(18.0)	37	(18.4)	38	(19.2)	111	(18.5)
Once daily, metformin without SUs	12	(6.0)	15	(7.5)	9	(4.5)	36	(6.0)
Twice daily, metformin and SUs	24	(12.0)	20	(10.0)	19	(9.6)	63	(10.5)
Twice daily, metformin without SUs	128	(64.0)	129	(64.2)	132	(66.7)	389	(64.9)
Exposed	200	(100.0)	201	(100.0)	198	(100.0)	599	(100.0)
Withdrawals								
Adverse Event	5	(2.5)	6	(3.0)	6	(3.0)	17	(2.8)
Ineffective Therapy	10	(5.0)	2	(1.0)	2	(1.0)	14	(2.3)
Non-compliance with Protocol	5	(2.5)	6	(3.0)	9	(4.5)	20	(3.3)
Other	11	(5.5)	11	(5.5)	19	(9.6)	41	(6.8)
Total	31	(15.5)	25	(12.4)	36	(18.2)	92	(15.4)
Completed	169	(84.5)	176	(87.6)	162	(81.8)	507	(84.6)
Intention-To-Treat (ITT)	200	(100.0)	201	(100.0)	198	(100.0)	599	(100.0)
Per Protocol (PP)	170	(85.0)	165	(82.1)	153	(77.3)	488	(81.5)

N: Number of subjects %: Proportion of exposed subjects
%: Proportion of exposed subjects

More than 50% of the screening failures were due to HbA_{1c} being outside the inclusion range; liver or renal

abnormalities and treatment-requiring retinopathy accounted for approximately 17% of the failures and current treatment with human insulin or insulin analogues for 9% of the failures. The fraction of the screened subjects who withdrew informed consent before treatment start (15%), was also accounted for as screening failures. More than 80% of the subjects in all three treatment groups completed the trial. Withdrawal due to adverse events and non-compliance was comparable for the treatment groups; ineffective therapy was the most frequent reason in the BIAsp 30-30 treatment groups and 'other' the most frequent in the BIAsp 70-70-70(30) treatment group. The most frequent 'others' were *wish to withdraw* (19), *protocol violations* (11) and *compliance-like problems* (6).

Diagnosis and Main Criteria for Inclusion

Subjects with type 2 diabetes.
Currently treated with human or analogue insulin once or twice daily for at least 3 months.
Currently treated with metformin within the interval of 1000 - 2550 mg daily. The metformin dose should have remained unchanged for a period of 2 months prior to randomisation and should remain unchanged throughout the trial period
Male or female age ≥ 18 years of age and with HbA_{1c} ≥ 7.5% and ≤12.0%.
Total daily insulin dose < 1.80 U/kg body weight.
Subjects should be able and willing to perform self measured plasma glucose (SMPG);
Subjects should be willing to take up to 3 insulin injections per day:
Subjects should be willing to eat 3 main meals (breakfast, lunch and dinner) per day.

Test Product, Dose and Mode of Administration, Batch Number

The test products were Biphasic insulin aspart 50 (BIAsp 50) (batch numbers RP50120 and RP50434) biphasic insulin aspart 70 (BIAsp 70) (batch numbers RP 50122 and RP 50433). The products were injected immediately before the main meals (breakfast, lunch and dinner). Subjects in the BIAsp 50 and BIAsp 70 groups were also treated with metformin, either taken as 500 mg Tablets (batch number B000008654 and B000008755) or 850 mg Tablets (batch numbers B000008652, B000008757 and B000010158). The subjects in the test group were initially treated with BIAsp 50 or BIAsp 70 thrice daily (BIAsp 50-50-50 or BIAsp-70-70-70); after 12 weeks of treatment subjects with a pre-breakfast PG > 8 mmol/L had to switch to BIAsp 30 at dinner (BIAsp 50-50-30 or BIAsp 70-70-30).

Duration of Treatment

The treatment period was 36 weeks in all treatment groups.

Reference Therapy, Dose and Mode of Administration, Batch Number

The reference treatment was BIAsp 30 twice daily, injected immediately before breakfast and dinner. Batch numbers (RP50024 andRP51556). Subjects in this treatment group were also treated with metformin (same batch numbers as used in the BIAsp 50 and BIAsp 70 treatment groups).

Criteria for Evaluation – Efficacy

HbA_{1c}, 8-point PG profiles, insulin dose, treatment satisfaction, weight and body mass index (BMI).

Criteria for Evaluation – Safety

Adverse event, hypoglycaemic episodes, vital signs, and biochemical and haematological laboratory measurements.

Statistical Methods

Efficacy endpoints

- The primary efficacy endpoint was HbA_{1c} after 36 weeks of treatment.

The primary analysis was made by an analysis of variance (ANOVA) model with treatment, strata and country as fixed effects and the baseline HbA_{1c} as a covariate. The analysis was based on comparison of the BIAsp 50-50-50(30) treatment with the BIAsp 30-30 treatment and comparison of the BIAsp 70-70-70(30) treatment with the BIAsp 30-30 treatment.

The non-inferiority criterion for HbA_{1c} was in both analyses set to 0.4%.

The null hypothesis (H_0) for non-inferiority of BIAsp 50-50-50(30) and BIAsp 30-30 was

H_0 BIAsp 50-50-50(30) – BIAsp 30-30 ≥ 0.40%

and it was tested against the alternative hypothesis (H_A) that BIAsp 50-50-50(30) is non-inferior to BIAsp 30-30 that is

H_A: BIAsp 50-50-50(30) – BIAsp 30-30 < 0.40%

Two-sided 95% confidence intervals (CI) were constructed for the difference, BIAsp 50-50-50(30) – BIAsp 30-30, between the means in the BIAsp 50-50-50(30) and BIAsp 30-30 treatment groups. BIAsp 50-50-50(30) was to be declared non-inferior to BIAsp 30-30 if the upper limit of the 95% CI for this difference was less than 0.40%. If non-inferiority was shown (that is if H_0 is rejected), then superiority of BIAsp 50-50-50(30) compared to BIAsp 30-30 would be claimed if the upper limit of the 95% CI for the difference was lower than 0%.

Exactly the same hypothesis and non-inferiority criterion was used for the analysis of BIAsp 70-70-70(30) versus BIAsp 30-30.

For both comparisons, BIAsp 70-70-70(30) versus BIAsp 30-30 and BIAsp 50-50-50(30) versus BIAsp 30-30 the models were run with all subjects (all three treatments) included, also the ones given the treatment which is not in the current comparison.

The primary analyses made for absolute HbA_{1c} were repeated for the change from baseline in HbA_{1c}.

Secondary endpoints derived from the HbA_{1c} data:

- The percentages of subjects achieving the treatment target of $HbA_{1c} \leq 6.5\%$ after 36 weeks of treatment.
- The percentages of subjects achieving the treatment target of $HbA_{1c} \leq 6.5\%$ after 36 weeks of treatment without experiencing hypoglycaemic episodes during the last 12 weeks of treatment. The last 12 weeks of treatment is defined as the last 12 weeks before the HbA_{1c} value used in the analyses was recorded.
- The percentages of subjects achieving the treatment target of $HbA_{1c} < 7.0\%$ after 36 weeks of treatment
- The percentages of subjects achieving the treatment target of $HbA_{1c} < 7.0\%$ after 36 weeks of treatment without experiencing hypoglycaemic episodes during the last 12 weeks treatment
- The percentages of subjects achieving an HbA_{1c} reduction of more than 1.0% after 36 weeks of treatment

Secondary endpoints derived from the 8 point plasma glucose

- The individual time points and average of individual 8-point (pre-breakfast, 120 minutes after breakfast, pre-lunch, 120 minutes after lunch, pre-dinner, 120 minutes after dinner, bedtime, 02.00) glucose measurements
- Prandial increment at breakfast, lunch and dinner
- Average prandial increment (the average of the increments at breakfast, lunch and dinner)
- Pre-breakfast plasma glucose values in the sub-groups defined by switching or not switching to BIAsp 30 after 12 weeks
- The percentage of subjects reaching the pre-breakfast target PG ≤ 7.0 mmol/l
- The percentage of subjects switching the dinner injection to BIAsp 30 after 12 weeks of treatment

Safety endpoints

Hypoglycaemia related endpoints:

- Endpoints included total number of episodes, major, minor and symptoms only episodes. Nocturnal episodes defined as episodes occurring in the period from 12 p.m. to 6 a.m., both times included.
- AE related endpoints.
- Vital signs and Laboratory parameters.

Demographic characteristics

As shown in the Table, the subjects were well matched regarding sex ratio (slightly more women than men) ethnicity, age, height and BMI. Many subjects were overweight (mean BMI > 31 kg/m2), mean age was about 60 years and most subjects had diabetes for more than 10 years (data not shown).

Demography of Trial Population

	BIAsp 30-30	BIAsp 50-50-50(30)	BIAsp 70-70-70(30)
Number of Subjects in ITT	200	201	198
Sex (N, (%))			
Female	104 (52.0)	117 (58.2)	110 (55.6)
Male	96 (48.0)	84 (41.8)	88 (44.4)
Ethnic Origin (N, (%))			
White	199 (99.5)	200 (99.5)	194 (98.0)
Black	1 (0.5)	0 (0.0)	2 (1.0)
Asian/Pacific Islander	0 (0.0)	0 (0.0)	2 (1.0)
American Indian - Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.5)	0 (0.0)
Age (years)			
N	200	201	198
Mean (SD)	60.7 (9.0)	60.4 (9.2)	60.4 (8.6)
Median	60.3	60.0	60.4
Min-Max	36.1 - 85.4	31.7 - 82.9	36.0 - 79.5
Weight (kg)			
N	200	201	198
Mean (SD)	88.6 (14.2)	87.6 (14.2)	88.0 (14.0)
Median	88.0	86.9	87.4
Min-Max	51.0 - 138.2	55.0 - 135.0	60.0 - 127.6
BMI (kg/m/m)			
N	200	201	198
Mean (SD)	31.9 (3.9)	31.9 (4.1)	31.9 (4.3)
Median	31.3	31.6	31.6
Min-Max	21.8 - 43.7	22.9 - 40.2	23.3 - 41.1

Efficacy Results

- The analysis of the primary endpoint (HbA_{1c} after 36 weeks treatment) showed that both High Mix treatment regimens were non-inferior to BIAsp 30-30, and that BIAsp 50-50-50(30) was superior to BIAsp 30-30.
- Analyses with a logistic regression model showed that the odds for meeting the HbA_{1c} target of the American Diabetes Association(< 7%) and the HbA_{1c} target of the American Association of Clinical Endocrinology (≤ 6.5%) were significantly higher for the BIAsp 50-50-50(30) treatment than for the BIAsp 30-30 and the BIAsp 70-70-70(30) treatments. Odds for a decrease of $HbA_{1c} \geq 1\%$ were also higher with BIAsp 50-50-50(30) than with any of the other treatments
- 8-point PG profiles after 36 weeks showed significantly lower PG values with BIAsp 50-50-50(30) than with BIAsp 30-30 from after lunch until 02.00 but no significant differences from before breakfast until lunch. Similar results were obtained with BIAsp 70-70-70(30) versus BIAsp 30-30. However, fasting (pre-breakfast) PG was significantly higher with BIAsp 70-70-70(50).Average PG and prandial increment at lunch was significantly lower with both High Mix regimens compared to BIAsp 30-30.
- Quality of life evaluations showed no differences between treatments regarding general wellbeing (WHO (5) Questionnaire). As for treatment satisfaction, no significant differences were found between BIAsp 50-50-50(30) and BIAsp 30-30 whereas BIAsp 70-70-70(50) scored significantly lower than BIAsp 30-30 in relation to hypoglycaemic control and regimen convenience.
- Insulin dose increased substantially in all treatment groups, but significantly more in the High Mix groups than in BIAsp 30-30. Total dose tended to increase more in the High Mix subpopulations who switched to BIAsp 30 at dinner than in those who did not switch to BIAsp 30.
- Exploratory analyses showed that both High Mix regimens reduced HbA_{1c} significantly more than BIAsp 30-30 after 12 weeks. Pre-breakfast PG was significantly lower in the BIAsp 30-30 group than in any of the High Mix groups, and lower in BIAsp 50-50-50 than in BIAsp 70-70-70 after 12 weeks.

- Body weight increased in all treatment groups. Mean weight increase was in the range 3.2 – 3.7%. No significant between group differences were found with respect to weight change

Safety Results

- AEs occurred with a comparable frequency in all treatment groups. The large majority of events were of mild or moderate severity. Serious AEs included 6 hypoglycaemic episodes and 2 episodes with hypoglycaemic coma; these SAEs were all seen in the BIAsp 70-70-70(30) treatment group and were all evaluated as severe events and considered possibly related to the trial. Other severe AEs considered related to the treatment included oedema, weight increase, injection site reactions, vertigo and visual disturbance.
- SAEs occurred with a similar frequency in all treatment groups. They included a total of 60 events, the most frequent being *cardiac disorders*, *nervous system disorders* (including two events with hypoglycaemic coma) and *metabolism and nutrition disorders* and six episodes with major and serious hypoglycaemic episodes.
- Eighteen subjects withdrew from the trial due to AEs, 14 of these due to SAEs; four subjects withdrawn due to SAEs subsequently died.
- Four subjects died during the trial. None of these deaths were considered related to treatments.
- Hypoglycaemic episodes were more frequent with the BIAsp 70-70-70(30) treatment than with BIAsp 30-30 and the risk of episodes was significantly higher with BIAsp 70-70-70(30). In both High Mix groups the rate of episodes appeared to be higher in the subjects who switched their dinner dose to BIAsp 30 than in those who did not switch.
- No abnormal findings and no significant differences between treatment groups were found for laboratory measurements and vital signs.

Conclusions

High Mix treatment with BIAsp 50-50-50(30) was superior to BIAsp 30-30 with respect to total glycaemic control and prandial glycaemic control. AEs did not differ between these two regimens; hypoglycaemic episodes were less frequent with BIAsp 30-30 but the difference was not significant. Substitution of BIAsp 50 at dinner with BIAsp 30 in the High Mix group improved the fasting PG, but in general and in spite of a higher insulin use, the subjects who made the dinner switch did not achieve the same glycaemic control as those who did not switch.

The BIAsp 70-70-70(30) regimen was non-inferior to but not significantly different from BIAsp 30-30 regarding HbA_{1c} but average PG and prandial PG increment was significantly lower with BIAsp 70-70-70(30) whereas fasting PG was significantly higher. Except for hypoglycaemic episodes, the two regimens were associated with the same number of mostly mild AEs.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice