2 Synopsis

Trial Registration ID-number: NCT00613951	**EudraCT number – EU only: 2007-002462-35**
Title of Trial A 16 week randomised, open labelled, 3-armed, parallel group, treat-to-target trial comparing twice daily (BID) injections of SIAC 30 (B), SIAC 45 (B) and NovoMix®30, all in combination with metformin in subjects with type 2 diabetes failing on OAD treatment.	
Investigator(s) There were 27 principal investigators in 5 countries: Finland (4), France (4), Germany (6), Poland (9) and Spain (4).	
Trial Site(s) The trial was conducted at 27 sites in 5 countries: Finland (4 sites), France (4 sites), Germany (6 sites), Poland (9 sites) and Spain (4 sites).	
Publications None	
Trial Period 23 January 2008 to 27 August 2008	**Development Phase** Phase 2
Primary Objective To assess glucose control with respect to HbA_{1c} after 16 weeks of treatment with BID soluble insulin analogue combination SIAC 30 (B), SIAC 45 (B) or NovoMix® 30 (biphasic insulin aspart, BIAsp 30), all in combination with metformin, in subjects with type 2 diabetes, failing on oral antidiabetic drug (OAD) treatment. ***Secondary Objectives*** Between the treatment arms: • To investigate the timing and the extent of blood glucose excursions, measured by continuous glucose measurement (CGM) after 8 and 16 weeks • To compare plasma glucose profiles obtained at meal test after 16 weeks of treatment • To compare efficacy and safety after 16 weeks of treatment in terms of: – 9-point plasma glucose profile – Lipid profile – Hypoglycaemic episodes and adverse events (AEs) – Body weight – Waist and hip circumference • To compare intra-subject variability in self-measured plasma glucose (SMPG) • To assess pharmacokinetics for insulin 454 and insulin aspart • To assess and compare patient reported outcome	
Methodology This was a multi-national, multi-centre, 3-armed, randomised, stratified, open labelled, parallel group trial comparing the efficacy and safety of SIAC 30 (B), SIAC 45 (B) and NovoMix® 30 (all treatments given twice daily), all treatments in combination with metformin. The trial consisted of a 1-week screening period, a metformin up-titration period of up to 2 weeks, a 1-week maintenance period prior to randomisation and, after randomisation, a 16-week treatment period and a 2-week follow-up period. The treatment period included a total of 10 visits to the clinical trial site and 6 telephone contacts. Subjects who had tolerated 1500 mg or 2000 mg of metformin for a week and still had fasting plasma glucose (FPG) $\geq$ 7.5 mmol/L were randomised 1:1:1 to SIAC 30 (B), SIAC 45 (B) or NovoMix® 30 BID. The FPG value used to determine the randomisation criterion was the median of three SMPG values taken before breakfast on three consecutive days just prior to the randomisation visit. Subjects were stratified according to their previous OAD treatment. During treatment, insulin doses were titrated weekly throughout the trial according to a pre-defined titration algorithm, based upon the subjects' SMPG, with the main goal of reaching an FPG of 4.0-6.0 mmol/L. SIAC 30 (B),	

SIAC 45 (B), NovoMix® 30, as well as metformin, were administered twice-daily before breakfast and dinner. Due to the stable effect and long half-life of insulin 454, careful titration of the subsequent anti-diabetic treatment was carried out (based on blood glucose measurements) when stopping treatment with SIAC.

Number of Subjects Planned and Analysed

In order to have 150 subjects completing the trial, it was planned to randomise a total of 177 subjects. Of the 246 subjects screened, 64 were not randomised (60 were screening failures and 4 were run-in failures). Subject disposition is tabulated below:

Subject Disposition

	SIAC 30 (B) N (%)	SIAC 45 (B) N (%)	BIAsp 30 N (%)	Total N (%)
Randomised	61 (100.0)	59 (100.0)	62 (100.0)	182 (100.0)
Exposed	60 (98.4)	59 (100.0)	62 (100.0)	181 (99.5)
Not Exposed	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Withdrawals	7 (11.5)	5 (8.5)	5 (8.1)	17 (9.3)
Adverse Event	1 (1.6)	0 (0.0)	1 (1.6)	2 (1.1)
Non-Compliance	1 (1.6)	1 (1.7)	1 (1.6)	3 (1.6)
Ineffective Therapy	0 (0.0)	1 (1.7)	1 (1.6)	2 (1.1)
Other	5 (8.2)	3 (5.1)	2 (3.2)	10 (5.5)
Completed Trial	54 (88.5)	54 (91.5)	57 (91.9)	165 (90.7)
Full Analysis Set	61 (100.0)	59 (100.0)	62 (100.0)	182 (100.0)
PP Analysis Set	51 (83.6)	55 (93.2)	57 (91.9)	163 (89.6)
Safety Analysis Set	60 (98.4)	59 (100.0)	62 (100.0)	181 (99.5)

N, Number of Subjects

Diagnosis and Main Criteria for Inclusion

- Informed consent obtained before any trial-related activities.
- Male or female, age 18-75 years (both inclusive)
- Type 2 diabetes (as diagnosed clinically) ≥ 3 months
- Treatment with one or two OADs: metformin, sulfonylurea, other insulin secretagogue (e.g. repaglinide, nateglinide), α-glucosidase inhibitors for at least 2 months at a stable maximally tolerated dose or at least half maximally allowed dose according to locally approved SPC
- Insulin-naïve subjects (no previous insulin treatment or previous short-term insulin treatment ≤ 14 days within the last 3 months)
- HbA_{1c}, 7.0-11.0 % (both inclusive) by central laboratory analysis
- BMI, 25.0–37.0 kg/m^2 (both inclusive)

Test Product, Dose and Mode of Administration, Batch Number

The number assigned to the SIAC product refers to the percentage by volume of insulin aspart

Trial Product	Strength	Dose	Mode of administration	Batch Number
SIAC 30 (B), 3 mL FlexPen®	100 DU/mL (100 DU = 600 nmol)	Treat-to-Target	Solution for subcutaneous administration (abdomen)	TP51345
SIAC 45 (B), 3 mL FlexPen®	100 DU/mL (100 DU = 600 nmol)	Treat-to-Target	Solution for subcutaneous administration (abdomen)	TP51344

Duration of Treatment

Prior to randomisation, subjects underwent a run-in period of up to 3 weeks (including a 1-week maintenance period) where metformin was up-titrated to 1500 or 2000 mg/day. Following randomisation, subjects were treated with trial product for approximately 16 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

Reference Product	Strength	Dose	Mode of administration	Batch Number
Biphasic insulin aspart (NovoMix®30) FlexPen®	100 DU/mL (100 DU = 600 nmol)	Treat-to-Target	Suspension for subcutaneous administration (abdomen)	TP51603
Metformin	500 mg	1500-2000 mg/day	Tablets taken with main meals	102908

Criteria for Evaluation – Efficacy

Primary Efficacy Variable

- HbA_{1c}

Secondary Efficacy Variables

- Interstitial glucose profiles
- SMPG 9-point profiles
- SMPG used for dosing
- Meal test
- Insulin dose
- Laboratory assessments:
  - FPG
  - Blood lipids
  - High sensitive c-reactive protein (hs CRP)
  - Serum insulin 454 concentration for subjects randomised to trial product (SIAC 30 (B) and SIAC 45 (B))
  - Serum insulin aspart concentration for subjects randomised to comparator (BIAsp 30)
- 1.5-anhydroglucitol concentration

Criteria for Evaluation – Safety

- Adverse events (AEs)
- Hypoglycaemic episodes
- Safety and tolerability by
  - Clinical evaluations (physical examination and vital signs)
  - Laboratory tests (urine (stick), haematology, biochemistry, antibodies)
  - Fundoscopy/fundusphotography
  - Electrocardiogram (ECG)
  - Injection site disorders
- Body weight and body mass index (BMI)
- Waist and hip circumference
- Patient reported outcome

Statistical Methods

This was an explorative trial in which the SIAC products were compared with each other and with BIAsp 30 with respect to HbA_{1c} after 16 weeks of treatment. The aim was to estimate the difference between the treatments and not to do formal hypothesis testing.

Analysis Sets

The following analysis sets were defined:

- Full Analysis Set (FAS): Includes all randomised subjects. Analyses followed the intention-to-treat (ITT) principle
- Per Protocol (PP) Analysis set: Includes subjects without any major protocol violations that may affect the primary endpoint. Subjects must be exposed to trial insulin for at least 12 weeks. Analyses followed the as-treated principle
- Safety Analysis Set: Includes all subjects with exposure information of at least one dose of randomised trial insulin. Analyses followed the as-treated principle

The primary and secondary efficacy endpoints as well as the analysis of hypoglycaemic episodes were based on the FAS, while all other endpoints related to safety was based on the Safety Analysis Set.

Primary Endpoint Analysis: HbA_{1c} after 16 Weeks of Treatment

HbA_{1c} after 16 weeks of treatment was analysed using an analysis of variance (ANOVA) model with treatment, country, sex and OAD treatment at screening (3 levels according to stratification) as fixed factors, and age and baseline HbA_{1c} as covariates. The sensitivity of the results of the primary analysis was explored in two additional analyses. The primary analysis was repeated on the PP analysis set and all scheduled HbA_{1c} measurements were jointly analysed in linear mixed model using the FAS.The primary analysis explored all pairwise treatment differences between SIAC 30 (B), SIAC 45 (B) and BIASp 30 concerning HbA_{1c} after 16 weeks of treatment. The aim was to estimate the difference between treatments and not to show formal superiority or non-inferiority. Subjects who met the HbA_{1c} targets of (<7%) and (≤6.5%) with and without hypoglycaemia was summarised by descriptive statistics.

Secondary Efficacy Analyses:

Secondary efficacy endpoints included assessments of: SMPG 9-point profiles, SMPG dosing endpoints and titration targets, FPG, interstitial glucose, meal test, lipids, free fatty acid, hs CRP, 1,5-anhydroglucitol, insulin 454 concentrations, insulin doses and change in patient reported outcomes.

- SMPG from the 9-point profile after 16 weeks of treatment:
  - The 9-point plasma glucose profiles after 16 weeks were analysed using a linear mixed model with an unstructured residual covariance structure and with treatment, country, and sex as fixed factors, and age and baseline HbA_{1c} as covariates.
  - The mean and the CV were analysed separately using the same model as described for the primary endpoint
  - The mean increment of all meals as well as the breakfast, the lunch and the dinner increments were analysed separately using a model similar to that described for the primary endpoint with the addition of the relevant baseline value as a covariate
- SMPG for dosing
  - The SMPG for dosing was used to assess the within-subject variability after 16 weeks of treatment in separate analysis for all meals (before and after breakfast, lunch and dinner). The log-transformed SMPG values were analysed with a mixed effect model with treatment, country and sex as fixed effects, and subject as random effect, and age and baseline HbA_{1c} as covariates
  - Mean of all meal increments (2 hours after start of meal), breakfast, lunch and dinner increments (baseline is defined as the pre-meal value) were analysed separately using a model similar to that described for the primary endpoint with the addition of the baseline value as a covariate.
  - The time to reach the titration targets (visit weeks) was analysed in a Cox proportional hazards model for each target separately with treatment, country and sex as fixed factors, and age and baseline HbA_{1c} as covariates.
- Central laboratory endpoints after 16 weeks: FPG, lipids, FFA, hs CRP and 1,5-anhydroglucitol were analysed separately using a model similar to that described for the primary endpoint with the addition of the baseline value as a covariate.
- Mean interstitial glucose (IG) after 16 weeks of treatment was analysed with the same model as used for the primary endpoint. CV, M-value and Fluctuation of the IG profiles after 16 weeks of treatment were log-transformed and analysed separately with a similar model as used for the primary endpoint but with the addition of

the profile mean value as a covariate. Meal related endpoints and duration of near hypo- and hyperglycaemic episodes were analysed separately with a similar model as used for the primary endpoint but with the pre-meal value as an additional covariate. The number of near hypo- and hyperglycaemic episodes were analysed using a negative binomial model using the same explorative variables as in the primary analysis.

- The meal test PG AUC(0-240min), PG peak and PG increment were analysed separately using a model similar to the one described for the primary endpoint including the mean prior meal PG value as an additional covariate.
- Change in PRO scores after 16 weeks of treatment were analysed separately using a model similar to that described for the primary endpoint with the addition of the relevant baseline value as a covariate.

No formal statistical analyses were made for insulin 454 concentrations, mean SMPG for dosing, status of titration targets and the dosing endpoints.

Secondary Safety Analyses

Secondary safety endpoints included: adverse events (AEs), hypoglycaemic episodes, physical examination, vital signs, haematology, biochemistry, urinalysis, insulin antibodies, pregnancy, fundoscopy/fundusphotography, ECG, injection site disorders, body weight, BMI and hip and waist circumference.

- An AE was defined as treatment emergent (TEAE) if the onset of the AE was on or after the first day of randomised treatment and no later than 5 days after the last day of randomised treatment. The incidence of TEAEs was compared between treatment groups by means of descriptive statistics.
- Hypoglycaemic episodes: a hypoglycaemic episode was defined as treatment emergent if the onset of the episode was on or after the first day of randomised treatment, and no later than 5 days after the last day of randomised treatment. Treatment emergent hypoglycaemic episodes were categorised according to severity and time of onset. Episodes were defined as nocturnal if the time of onset was between 23:00 and 05.59 hours (both inclusive). The number of treatment emergent hypoglycaemic were analysed using a negative binomial regression model using a log link function and the logarithm of the available collection time as offset. The model included treatment, country and sex as fixed factors, and age and baseline HbA_{1c} as covariates.
- Insulin antibodies (insulin aspart specific, insulin 454 specific and antibodies cross-reacting between insulin aspart and insulin 454) were assessed and possible correlations to relevant variables such as HbA_{1c} and basal insulin dose were investigated using descriptive statistics.
- Weight, BMI and waist-to-hip ratio after 16 weeks of treatment were analysed separately using a model similar to that described for the primary endpoint with the addition of the relevant baseline value as a covariate. Other safety endpoints including standard laboratory parameters and vital signs were listed and summarised using descriptive statistics. Any clinically relevant deterioration in physical examination, fundoscopy/fundusphotography or ECG since the screening visit was reported as an AE. The number of injection site disorders and the percentage of subjects with at least one disorder were summarised by treatment.

Demography of Trial Population

Demographics and Baseline Characteristics

Demographic characteristics were generally similar between the three treatment groups, except that males were somewhat over represented in the BIAsp 30 group at 63 %. Other baseline characteristics were similar across treatment groups, except for small differences in mean weight and duration of diabetes.

	SIAC 30 (B) N (%)	SIAC 45 (B) N (%)	BIAsp 30 N (%)	Total N (%)
Number of Subjects	61	59	62	182
Age Group				
Adults (below 65)	44 (72.1)	39 (66.1)	42 (67.7)	125 (68.7)
Elderly (65 or older)	17 (27.9)	20 (33.9)	20 (32.3)	57 (31.3)
Sex				
Female	32 (52.5)	30 (50.8)	23 (37.1)	85 (46.7)
Male	29 (47.5)	29 (49.2)	39 (62.9)	97 (53.3)
Country of Residence				
Germany	14 (23.0)	12 (20.3)	17 (27.4)	43 (23.6)
Spain	11 (18.0)	10 (16.9)	13 (21.0)	34 (18.7)
Finland	7 (11.5)	6 (10.2)	7 (11.3)	20 (11.0)
France	5 (8.2)	7 (11.9)	5 (8.1)	17 (9.3)
Poland	24 (39.3)	24 (40.7)	20 (32.3)	68 (37.4)
Race				
White	60 (98.4)	58 (98.3)	61 (98.4)	179 (98.4)
Black or African	1 (1.6)	1 (1.7)	1 (1.6)	3 (1.6)

N, number of subjects

Baseline and Diabetes Characteristics

	Treatment	FAS	Descriptive statistics N	Mean	SD	Min	Max
Age (yrs)							
	SIAC 30	61	61	58.7	8.5	41.0	75.0
	SIAC 45	59	59	60.5	8.9	34.0	75.0
	BIAsp 30	62	62	59.7	8.0	41.0	74.0
	Total	182	182	59.6	8.4	34.0	75.0
Weight (kg)							
	SIAC 30	61	61	87.8	16.3	54.0	127.0
	SIAC 45	59	59	84.9	14.3	61.0	115.5
	BIAsp 30	62	62	91.8	13.5	68.5	128.7
	Total	182	182	88.2	14.9	54.0	128.7
BMI (kg/m^2)							
	SIAC 30	61	61	31.5	3.6	24.5	36.9
	SIAC 45	59	59	30.8	3.6	24.9	37.2
	BIAsp 30	62	62	31.9	3.5	24.7	37.0
	Total	182	182	31.4	3.6	24.5	37.2
Waist-to-Hip Ratio							
	SIAC 30	61	60	1.0	0.1	0.8	1.2
	SIAC 45	59	58	1.0	0.1	0.8	1.1
	BIAsp 30	62	62	1.0	0.1	0.8	1.2
	Total	182	180	1.0	0.1	0.8	1.2
Duration of Diabetes (yrs)							
	SIAC 30	61	61	9.0	6.1	1.3	36.2
	SIAC 45	59	59	10.7	6.4	1.1	29.1
	BIAsp 30	62	62	8.6	6.3	0.6	28.1
	Total	182	182	9.4	6.3	0.6	36.2
HbA_{1c} (%)							
	SIAC 30	61	60	8.5	1.2	6.4	12.3
	SIAC 45	59	58	8.5	0.9	6.6	10.7
	BIAsp 30	62	62	8.6	1.0	6.9	10.9
	Total	182	180	8.5	1.1	6.4	12.3
FPG (mmol/L)							
	SIAC 30	61	61	11.4	2.7	5.0	17.1
	SIAC 45	59	59	11.8	2.9	6.8	20.8
	BIAsp 30	62	62	11.7	3.1	6.7	19.9
	Total	182	182	11.6	2.9	5.0	20.8
1.5 AG (mg/L)							
	SIAC 30	61	56	7.1	5.2	1.0	26.1
	SIAC 45	59	56	6.8	4.7	1.1	22.6
	BIAsp 30	62	59	7.9	5.5	1.0	24.5
	Total	182	171	7.3	5.1	1.0	26.1

FAS: full analysis set, N: number, SD: standard deviation, Min: minimum, Max: maximum
1.5 AG: 1.5 anhydroglucitol

Efficacy Results

Primary Efficacy Endpoint

HbA_{1c} (%)	**SIAC 30** Mean (SE)	**SIAC 45** Mean (SE)	**BIAsp 30** Mean (SE)
N	60	58	62
LS Means			
End of treatment	6.69 (0.13)	6.61 (0.13)	6.70 (0.13)
Estimated change from baseline (% points)	-1.82 (0.13)	-1.90 (0.13)	-1.80 (0.13)
Treatment difference vs. BIAsp 30 (% points)	-0.02 [-0.27; 0.24]	-0.10 [-0.35; 0.16]	0
Proportion of subjects reaching HbA_{1c} target after 16 weeks			
$HbA_{1c} < 7.0$ %	74%	77%	77%
$HbA_{1c} \leq 6.5$ %	48%	42%	48%
Proportion of subjects reaching HbA_{1c} target after 16 weeks without major or minor hypoglycaemic episodes			
$HbA_{1c} < 7.0$ %	67%	53%	40%
$HbA_{1c} \leq 6.5$ %	40%	28%	25%

- Twice daily treatment with SIAC 30, SIAC 45 or BIAsp 30, all combined with metformin, led to similar glycaemic control, as determined by HbA_{1c}, after 16 weeks of treatment in subjects with type 2 diabetes, inadequately controlled on oral antidiabetic treatment.
  - After 16 weeks of treatment with SIAC 30, SIAC 45 or BIAsp 30 twice daily, all in combination with metformin, mean HbA_{1c} was 6.7 % with SIAC 30, 6.6 % with SIAC 45 and 6.7% with BIAsp 30. The statistical analysis showed no difference between treatments in HbA_{1c}.
  - A clinically relevant decrease in HbA_{1c} from baseline to trial end was seen in all three treatment groups; observed mean change in HbA_{1c} being -1.79 %-points for SIAC 30, -1.87 %-points for SIAC 45 and -1.84 %-points for BIAsp 30.
  - After 16 weeks of treatment, $HbA_{1c} < 7\%$ was met by 74%, 77% and 77% of subjects in the SIAC 30, SIAC 45 and BIAsp 30 groups, respectively, and 67%, 53% and 40% of subjects treated with SIAC 30, SIAC 45 and BIAsp 30, respectively, reached this target without minor or major hypoglycaemic episodes within the last four treatment weeks.
  - After 16 weeks of treatment, $HbA_{1c} \leq 6.5\%$ was met by 48%, 42% and 48% of subjects treated with SIAC 30, SIAC 45 and BIAsp 30 respectively. This target was achieved without minor or major hypoglycaemic episodes within the last four treatment weeks for 40%, 28% and 25% of subjects treated with SIAC 30, SIAC 45 and BIAsp 30, respectively.
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Secondary Efficacy Endpoints

- Estimated mean FPG after 16 weeks of treatment (central laboratory measurement) was approximately 1.0 mmol/L lower in both the SIAC 30 (6.79 mmol/L) (95% CI [-1.68; -0.29]) and the SIAC 45 (6.90 mmol/L) (95% CI [-1.58; -0.18]) group than in the BIAsp 30 group (7.77 mmol/L).
  - A clinically relevant decrease in FPG was seen in all three groups with observed mean changes from baseline to trial end of -5.07 mmol/L, -5.29 mmol/L and -4.28 mmol/L for subjects treated with SIAC 30, SIAC 45 and BIAsp 30, respectively.
- The statistical analyses of interstitial glucose showed that the estimated mean maximum post dinner peak in interstitial glucose and the mean maximum interstitial glucose increment at dinner and across 'all meals' were lower in the BIAsp 30 group than in either the SIAC 30 or the SIAC 45 group. No differences were seen after breakfast and lunch.
  - The statistical analyses showed no differences between the treatment groups after 16 weeks of treatment in mean interstitial glucose concentrations over 72 hours, variation in the IG profile (Determined by CV%,

fluctuation and M-value) as well as near hypoglycaemic and near hyperglycaemic episodes.

- After 16 weeks of treatment, mean 9-point SMPG profiles and mean variation in the 9-point SMPG profiles were similar for the three treatments.
  - Statistical analyses showed that the estimated mean SMPG was lower after breakfast with SIAC 30 (7.03 mmol/L) than with BIAsp 30 (7.97mmol/L) (95% CI [-1.83; -0.04]) and was higher after dinner with SIAC 30 (estimated mean = 8.44 mmol/L) than with BIAsp 30 (7.42) (95% CI [0.08; -1.97])
  - Mean postprandial SMPG increment after dinner was lower for BIAsp 30 than for SIAC 30 (estimated difference: 0.93 mmol/L; 95% CI [0.03; 1.83]).
  - Within-subject variation (CV%) based on SMPG after 16 weeks of treatment was shown in the statistical analyses to be similar for the three treatment groups before and after breakfast as well as before dinner, whereas it was higher after dinner for SIAC 45 than SIAC 30 (estimated mean: 27.2 vs. 21.9 %; 95% CI [1.01; 1.47]).
- After 16 weeks of treatment, the total daily insulin dose in units was 13% lower for subjects treated with SIAC 30 compared to subjects treated with either SIAC 45 or BIAsp 30.
- No differences were shown in the statistical analyses between the treatment groups in HDL, triglyceride or hs CRP after 16 weeks of treatment.
- Mean LDL concentrations at trial end were lower with SIAC 45 compared to BIAsp 30 (estimated treatment difference: -0.27mmol/L, 95% CI [-0.46; -0.07]).
- Mean total cholesterol levels were lower with SIAC 45 group compared to BIAsp 30 (estimated treatment difference: -0.31mmol/L; 95% CI [-0.60; -0.01]).
- Mean FFA concentrations at trial end was lower with SIAC 30 (estimated difference: -0.11mmol/L; 95% CI [-0.18; -0.04]) and SIAC 45 (estimated difference: -0.12mmol/L; 95% CI [-0.19; 0.05]).compared to BIAsp 30.
- 1,5-anhydroglucitol increased during the trial from 7.1, 6.8 and 7.9 mg/L to 11.9, 12.4 and 13.2 mg/L with SIAC 30, SIAC 45 and BIAsp 30 respectively
- No differences were shown in the statistical analyses of mean plasma glucose measured in the meal test.
- Mean dose adjusted insulin 454 concentrations appeared to be almost stable for both the SIAC 30 and SIAC 45 groups throughout the treatment period.
- Overall, patient reported outcomes were similar for the three treatment groups.

Safety Results

A summary of treatment emergent adverse events (TEAEs) are tabulated below:

	SIAC 30 N (%)	SIAC 30 E	SIAC 30 R	SIAC 45 N (%)	SIAC 45 E	SIAC 45 R	BIAsp 30 N (%)	BIAsp 30 E	BIAsp 30 R
Number of Subjects	60			59			62		
Total Exposure (yrs)	17.8			17.8			18.5		
Events	27 (45.0)	53	298	32 (54.2)	97	545	34 (54.8)	70	379
Serious							2 (3.2)	2	11
MESI									
Severity									
Severe							1 (1.6)	1	5
Moderate	8 (13.3)	10	56	10 (16.9)	12	67	5 (8.1)	7	38
Mild	25 (41.7)	43	242	26 (44.1)	85	477	30 (48.4)	62	335
Relationship to Insulin									
Probable	1 (1.7)	1	6	1 (1.7)	1	6	1 (1.6)	1	5
Possible	2 (3.3)	3	17	2 (3.4)	3	17			
Unlikely	24 (40.0)	48	270	30 (50.8)	91	511	34 (54.8)	69	373
Missing	1 (1.7)	1	6	2 (3.4)	2	11			
Relationship to Metformin									
Probable	1 (1.7)	1	6	1 (1.7)	1	6			
Possible	1 (1.7)	2	11	4 (6.8)	14	79	1 (1.6)	1	5
Unlikely	26 (43.3)	50	281	32 (54.2)	82	460	34 (54.8)	69	373
Missing									
Relationship to Device									
Outcome									
Recovered	24 (40.0)	45	253	28 (47.5)	88	494	32 (51.6)	63	341
Fatal							1 (1.6)	1	5
Recovering	1 (1.7)	1	6						
Not Recovered	7 (11.7)	7	39	7 (11.9)	8	45	6 (9.7)	6	32
Unknown				1 (1.7)	1	6			

N: number of subjects, %: percentage of subjects, E: number of events, R: event rate per 100 exposure years,
MESI: medical events of special interest

- Two (2) serious adverse events (SAEs) were reported, both in the BIAsp 30 group (*cardiac failure* (fatal) and *ischemic stroke*). Both SAEs were considered to be unlikely related to trial insulin.
- There two adverse events leading to withdrawal; one death from *cardiac failure*) and one SAE (*respiratory insufficiency*) which was not considered treatment emergent as it occurred after randomisation but before being exposed to trial insulin; (i.e., during the metformin titration period).
- No medical events of special interest (MESIs) occurred.
- Nine (9) AEs were considered probably or possibly related to trial insulin, 4 with SIAC 30 (*hunger*, *increased appetite*, *headache* and *lipodystrophy acquired*), four with SIAC 45 (2 *hunger*, 1 *increased appetite* and 1 *headache*) and 1 with BIAsp 30 (*oedema peripheral*).
- The most frequently reported AEs were *nasopharyngitis*, *headache, back pain, arthralgia* and *oedema peripheral*. and the proportion of subjects with *headache* events was higher for the SIAC 30 and SIAC 45 than for BIAsp 30.

Common Adverse Events (>5%) – by MedDRA System Organ Class and Preferred Term

	SIAC 30 N	(%)	E	R	SIAC 45 N	(%)	E	R	BIAsp 30 N	(%)	E	R
Subjects	60				59				62			
Total Exposure (yrs)	17.8				17.8				18.5			
Infections and infestations												
Nasopharyngitis	8	(13.3%)	9	51	4	(6.8%)	4	22	5	(8.1%)	5	27
Musculoskeletal and connective tissue disorders												
Back pain	2	(3.3%)	2	11	1	(1.7%)	4	22	4	(6.5%)	7	38
Arthralgia					3	(5.1%)	7	39	3	(4.8%)	3	16
Nervous system disorders												
Headache	6	(10.0%)	10	56	5	(8.5%)	7	39	1	(1.6%)	1	5
General disorders and administration site conditions												
Oedema peripheral					4	(6.8%)	4	22	1	(1.6%)	1	5

N, number of subjects; %, percentage of subjects; E, number of events; R, event rate per 100 exposure years

- Hypoglycaemic events were reported for 64%, 80% and 74% of subjects in the SIAC 30, SIAC 45 and BIAsp 30 groups, respectively. No major hypoglycaemic episodes were reported during the trial. An overview of hypoglycaemic episodes is presented in the table below:

Overview of Hypoglycaemia

	SIAC 30 N (%) E	**SIAC 45** N (%) E	**BIAsp 30** N (%) E
Number of subjects	61	59	62
Total Exposure (years)	17.8	17.8	18.5
All hypoglycaemic episodes	39 (64%) 159	47 (80%) 295	46 (74%) 313
Major	0 (0%) 0	0 (0%) 0	0 (0%) 0
Minor	22 (36%) 51	33 (56%) 121	37 (60%) 135
Symptoms only	34 (56%) 108	41 (69%) 174	35 (56%) 178
Nocturnal hypoglycaemia[1]	11 (18%) 16	15 (25%) 30	20 (32%) 43

Hypoglycaemic episodes based on Novo Nordisk definitions; N: number of subjects, %: percentage of subjects, E: number of events; [1] all hypoglycaemic episodes occurring between 23:00 and 05.59 hours (both inclusive)

- The observed number of all hypoglycaemic episodes was 159 with SIAC 30, 295 with SIAC 45 and 313 with BIAsp 30.
  - The risk of all hypoglycaemic episodes was 48% lower with SIAC 30 (7.66 events per subject per year) than with either SIAC 45 (14.89 events per subject per year, SIAC 45/SIAC 30 = 1.94 (95% CI; [1.24; 3.05]) or BIAsp 30 (14.85 events per subject per year, SIAC 30/BIAsp 30 = 0.52 (95% CI; [0.33, 0.81]).
  - The number of minor hypoglycaemic episodes 51 with SIAC 30, 121 with SIAC 45 and 135 with BIAsp 30.
  - The risk of minor hypoglycaemic episodes with SIAC 30 was 58% lower than with BIAsp 30 (SIAC 30/BIAsp 30 = 0.42, 95% CI [0.23; 0.75]) and 55% lower with SIAC 45 (SIAC 45/SIAC 30 = 2.21, 95% CI [1.22; 4.00]).

- The number of nocturnal hypoglycaemic episodes 16 with SIAC 30, 30 with SIAC 45 and 43 with BIAsp 30.
- The risk of nocturnal hypoglycaemic episodes in the SIAC 30 arm (0.47 events per year) was statistically significantly lower than for BIAsp 30 (1.39 events per year) (SIAC 30/BIAsp 30 = 0.34, 95% C I [0.15; 0.77]).

- Two (2) injection site disorders were reported. One (1) subject on BIAsp 30 had 1 mild, non-allergic reaction ([redacted]), and one subject on SIAC 45 had 1 reaction of moderate severity ([redacted]).
- Mean levels of both insulin aspart specific and insulin 454 specific antibodies remained low throughout the trial and antibody development did not give rise to any concerns.
- There were no obvious overall changes in ECG, vital signs, haematology or biochemistry.
- Safety data did not reveal any unexpected findings and no specific pattern or clustering of AEs were observed with SIAC or BIAsp 30. Antibody development did not give rise to any concerns and, in general, SIAC was well tolerated.

Conclusions

- In subjects with type 2 diabetes, twice daily treatment with SIAC 30, SIAC 45 or BIAsp 30, all combined with metformin, led to similar glycaemic control, as determined by HbA_{1c}, after 16 weeks of treatment in subjects with type 2 diabetes, inadequately controlled on oral antidiabetic treatment.
- The target of HbA_{1c} below 7% was met by 74%, 77% and 77% of subjects in the SIAC 30, SIAC 45 and BIAsp 30 groups, respectively, and 67%, 53% and 40% of subjects treated with SIAC 30, SIAC 45 and BIAsp 30, respectively, reached this target without minor or major hypoglycaemic episodes within the last four treatment weeks.
- The mean FPG concentrations after 16 weeks of treatment were approximately 1.0 mmol/L lower in both the SIAC 30 and the SIAC 45 groups than in the BIAsp 30 group and a clinically relevant decrease in mean FPG was observed in all three treatment groups.
- The extent of postprandial interstitial glucose excursions after dinner, measured by CGM after 16 weeks of treatment was lower with BIAsp 30 compared to SIAC 30 and SIAC 45.
- The mean 9-point SMPG profiles were similar for the three treatments after 16 weeks of treatment, except after dinner. Mean postprandial SMPG increment after dinner was lower for BIAsp 30 than for SIAC 30.
- Mean insulin 454 concentrations, adjusted for dose, remained almost stable for both SIAC 30 and SIAC 45 throughout the trial.
- The overall rate of all hypoglycaemic episodes was 48% lower with SIAC 30 compared to SIAC 45 and BIAsp 30 and that there were less than half the number of minor hypoglycaemic episodes with SIAC 30 than with SIAC 45 or BIAsp 30. The estimated number of nocturnal hypoglycaemic episodes was higher for the BIAsp 30 group compared with the SIAC 30 and SIAC 45 groups.
- Safety data did not reveal any unexpected findings and no specific pattern or clustering of AEs were observed with SIAC or BIAsp 30. Antibody development did not give rise to any concerns and, in general, SIAC was well tolerated.
- There were no obvious overall changes in ECG, vital signs, lipids, haematology or biochemistry.
- Only marginal differences in patient reported outcomes were observed between the three treatments after 14 weeks of treatment.

The trial was conducted in accordance with the Declaration of Helsinki(52 WMA, October 2000, last amended in Washington 2002 and Tokyo 2004) and ICH Good Clinical Practice (May 1996).

The results presented reflect data available in the clinical database as of 14-NOV-2008.