2 Synopsis

Trial Registration ID-number: NCT00614055 From www.clinicaltrials.gov	**EudraCT number: 2007-002476-33**
Title of Trial A 16 week randomised, open labelled, 3-armed, parallel group, treat-to-target trial comparing once daily injection of SIAC 30 (B), SIAC 45 (B) and insulin glargine, all in combination with metformin in subjects with type 2 diabetes failing on OAD treatment.	
Investigator(s) There were 22 principal investigators in 5 countries: France (4), Germany (5), Norway (5), Romania (3) and Spain (5)	
Trial Site(s) The trial was conducted at 22 sites in 5 countries: France (4 sites), Germany (5 sites), Norway (5 sites), Romania (3 sites) and Spain (5 sites)	
Publications None	
Trial Period From 23 January 2008 to 23 July 2008	**Development Phase** Phase 2

Objectives

***Primary Objective*:**

To assess glucose control with respect to HbA_{1c} after 16 weeks of treatment with SIAC 30 (B) or SIAC 45 (B) QD or insulin glargine QD, all in combination with metformin, in subjects with type 2 diabetes mellitus, failing on OAD treatment.

***Secondary Objectives*:**

Between the treatment arms:

- To investigate timing and the extent of blood glucose excursions, measured by CGM after 8 and 16 weeks
- 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
  - Body weight
  - Waist and hip circumference
- To compare intra-subject variability in self measured plasma glucose
- To assess the pharmacokinetic (PK) of insulin 454
- To assess and compare patient reported outcome

Methodology

This was a multi-national, multi-centre, 3-armed, randomised, stratified, open labelled, parallel group trial in which the efficacy and safety of the soluble insulin analogue combination SIAC 30 (B), SIAC 45 (B) and insulin glargine were compared (all treatments given once 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 trial period included a total of 14 visits to the clinical trial sites 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 insulin glargine. Subjects were stratified according to their previous treatment with oral antidiabetic drugs (OAD). During treatment, insulin doses were titrated weekly 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 or insulin glargine was administered once daily before dinner, while metformin was taken in connection with main meals. Due to the stable effect and long half-life of insulin 454 (the

basal component of the insulin combination product, SIAC), 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 completers, it was planned to randomise a total of 177 subjects. Subject disposition is tabulated below:

Subject Disposition

	SIAC 30 (B) N	(%)	SIAC 45 (B) N	(%)	IGlar N	(%)	Total N	(%)
Screened							226	
Not Randomised							48	
Screening Failures							46	
Run-in Failures							2	
Randomised	59	(100.0)	59	(100.0)	60	(100.0)	178	(100.0)
Exposed	59	(100.0)	59	(100.0)	60	(100.0)	178	(100.0)
Not Exposed	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Withdrawals	4	(6.8)	6	(10.2)	5	(8.3)	15	(8.4)
Adverse Event	1	(1.7)	0	(0.0)	0	(0.0)	1	(0.6)
Non-Compliance	2	(3.4)	2	(3.4)	1	(1.7)	5	(2.8)
Ineffective Theraphy	0	(0.0)	0	(0.0)	2	(3.3)	2	(1.1)
Other	1	(1.7)	4	(6.8)	2	(3.3)	7	(3.9)
Completed Trial	55	(93.2)	53	(89.8)	55	(91.7)	163	(91.6)
Full Analysis Set	59	(100.0)	59	(100.0)	60	(100.0)	178	(100.0)
PP Analysis Set	47	(79.7)	48	(81.4)	48	(80.0)	143	(80.3)
Safety Analysis Set	59	(100.0)	59	(100.0)	60	(100.0)	178	(100.0)

N: Number of Subjects

Diagnosis and Main Criteria for Inclusion

- Eligible subjects were men and women aged 18-75 years and diagnosed with type 2 diabetes for ≥3 months. Subjects were to be insulin naïve, treated with one or two OADs (metformin, sulfonylurea, other insulin secretagogue (e.g. repaglinide, nateglinide), α-glucosidase inhibitors for ≥ 2 months at a stable maximum tolerated dose), having HbA_{1c} of 7.0 – 11.0 % (both inclusive) and body mass index (BMI) of 25.0 – 37.0 kg/m^2 (both inclusive).

Test Product, Dose and Mode of Administration, Batch Number

- SIAC 30 (B) in 3 mL FlexPen® (100 DU/mL; 1 DU = 6 nmol), solution for subcutaneous (s.c.) injection (abdomen). Starting dose was 10 DU followed by treat-to-target dosing. Batch no. TP51345.
- SIAC 45 (B) in 3 mL FlexPen® (100 DU/mL; 1 DU = 6 nmol), solution for s.c. injection (abdomen). Starting dose was 10 DU followed by treat-to-target dosing. Batch no. TP51344.

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

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

- Insulin glargine (Lantus®) in 3 mL Optiset® (100 U/mL), solution for s.c. injection (thigh). Starting dose was 10 U followed by treat-to-target dosing. Batch no. 40B301.
- Metformin (500 mg), 1500-2000 mg/day given as tablets for oral administration. Batch no. 102908.

Criteria for Evaluation – Efficacy

Primary Efficacy Variable

- HbA_{1c} after 16 weeks of treatment

Secondary Efficacy Variables

- Interstitial glucose profiles
- SMPG 9-point profiles
- FPG
- Blood lipids
- Free fatty acids
- High sensitive c-reactive protein (hs CRP)
- Serum insulin 454 concentration for subjects randomised to SIAC 30 (B) or SIAC 45 (B)
- Insulin dose
- Patient reported outcome

Criteria for Evaluation – Safety

- Adverse events (AEs)
- Hypoglycaemic episodes
- Safety and tolerability by
  - Clinical evaluations (physical examination and vital signs)
  - Laboratory tests (urine, haematology, biochemistry and antibodies)
  - Fundoscopy/fundusphotography
  - Electrocardiogram (ECG)
  - Injection site disorders
- Body weight and BMI
- Waist and hip circumference and waist-to-hip ratio

Statistical Methods

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 analyses of hypoglycaemic episodes were based on the FAS, while all other endpoints related to safety were based on the safety analysis set.

Primary Efficacy Analysis

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, lipids, free fatty acid, hs CRP, insulin 454 concentrations, insulin doses and 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, sex and OAD treatment at screening 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, but CV was log transformed.
  - 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 and dinner). The log-transformed SMPG values were analysed with a mixed effect model with treatment, country, sex and OAD treatment at screening 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 the same fixed factors and covariates as used in the primary analysis.
- Central laboratory endpoints after 16 weeks: FPG, lipids, FFA and hs CRP 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 in the analysis of the meal related endpoints. The number of near hypo- and hyperglycaemic episodes were analysed using a negative binomial model using the same fixed factors and covariates as in the primary analysis.
- Change in PRO scores after 14 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. Diabetes medication compliance scores were not measured at baseline and were analysed after 14 weeks of treatment.
- No formal statistical analyses were made for insulin 454 concentrations, mean SMPG for dosing, status of titration targets and the dosing endpoints.

Safety Endpoints

Formal statistical analyses were only performed for the number of hypoglycaemic episodes, body weight and waist-to-hip ratio. The remaining safety endpoints were listed and analysed using descriptive statistics.

- An adverse event (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. All TEAEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) and individual data were listed. TEAEs were summarised descriptively.
- 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 (included) and 06:00 (not included). The number of treatment emergent hypoglycaemic episodes were analysed in 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, sex and OAD treatment at screening as fixed factors, and age and baseline HbA_{1c} as covariates.

- The number of injection site disorders and the percentage of subjects with at least one disorder were summarised by treatment.
- Body weight and waist-to-hip ratio after 16 weeks of treatment was analysed using an ANOVA model including treatment, country, sex and OAD treatment at screening as fixed factors, and age, baseline HbA_{1c} and baseline value 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 HbA1c and basal insulin dose were investigated using descriptive statistics.
- Laboratory safety parameters and vital signs were listed and summarised using descriptive statistics. Any clinically relevant deterioration in physical examination, funduscopy/fundusphotography or ECG since the screening visit was reported as an AE.

Demography of Trial Population

Demographics Characteristics

The majority of subjects in all three groups were below 65 years of age, the proportion of elderly subjects being lower in the insulin glargine group (21.7%) than in the SIAC 30 (B) group (28.8%) and SIAC 45 group (33.9%). Fewer women were included in the insulin glargine group (26.7%) than in the SIAC 30 (B) group (37.3%) and SIAC 45 group (42.4%). All subjects were white. Treatment regimens with oral antidiabetic drugs at screening were evenly distributed in the three treatment groups Approximately 50% of subjects in each group received metformin and/or α-glucosidase. The other subjects received metformin together with sulfonylurea (SU), except for one subject in the SIAC 30 group, who received SU and/or α-glucosidase.

Baseline and Diabetes Characteristics

		Descriptive statistics					
	Treatment	FAS	N	Mean	SD	Min	Max
Age (yrs)							
	SIAC 30 (B)	59	59	58.7	8.8	40.0	73.0
	SIAC 45 (B)	59	59	60.2	8.4	34.0	74.0
	IGlar	60	60	58.4	8.4	40.0	74.0
	Total	178	178	59.1	8.5	34.0	74.0
Weight (kg)							
	SIAC 30 (B)	59	59	85.1	11.7	60.5	117.5
	SIAC 45 (B)	59	59	83.9	15.7	58.0	123.5
	IGlar	60	60	86.8	11.3	63.0	110.0
	Total	178	178	85.3	13.0	58.0	123.5
BMI (kg/m^2)							
	SIAC 30 (B)	59	59	30.2	3.4	25.1	36.9
	SIAC 45 (B)	59	59	30.3	4.3	23.9	37.9
	IGlar	60	60	30.5	3.5	23.7	36.4
	Total	178	178	30.3	3.7	23.7	37.9
Waist-to-Hip Ratio	SIAC 30 (B)	59	59	1.0	0.1	0.9	1.1
	SIAC 45 (B)	59	59	1.0	0.1	0.8	1.1
	IGlar	60	59	1.0	0.1	0.8	1.1
	Total	178	177	1.0	0.1	0.8	1.1
Duration of Diabetes (yrs)	SIAC 30 (B)	59	59	9.1	8.0	1.1	43.1
	SIAC 45 (B)	59	59	9.5	5.8	0.7	26.1
	IGlar	60	60	8.5	4.8	2.3	24.1
	Total	178	178	9.0	6.3	0.7	43.1
HbA1c (%)							
	SIAC 30 (B)	59	59	8.3	1.2	5.6	12.0
	SIAC 45 (B)	59	59	8.6	1.5	6.0	15.5
	IGlar	60	60	8.4	1.3	5.5	11.8
	Total	178	178	8.5	1.3	5.5	15.5

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FPG (mmol/L)
                SIAC 30 (B)     59      59  11.1   3.3   5.8   18.9
                SIAC 45 (B)     59      59  11.5   3.2   5.9   19.4
                IGlar           60      60  12.1   3.5   3.7   20.2
                Total          178     178  11.6   3.3   3.7   20.2
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FAS, full analysis set; N, number; SD, standard deviation; Min, minimum; Max, maximum

Efficacy Results

Primary Efficacy Endpoint

	SIAC 30 (B)	SIAC 45 (B)	Insulin Glargine
HbA_{1c} (%)			
Baseline[1]	8.3 (1.2)	8.6 (1.5)	8.4 (1.3)
End of treatment[1]	7.0 (1.0)	7.2 (1.0)	7.1 (1.3)
Change from baseline (% points)[1]	-1.3 (1.0)	-1.5 (1.4)	-1.3 (1.1)
Estimated treatment difference vs. insulin glargine (% points)	-0.11 $[-0.41; 0.19]_{95\%CI}$	-0.03 $[-0.33; 0.27]_{95\%CI}$	0
Proportion of Subjects reaching HbA_{1c} target after 16 weeks			
$HbA_{1c} < 7.0$ %	56%	51%	52%
$HbA_{1c} \leq 6.5$ %	37%	24%	33%
$HbA_{1c} < 7.0$ % without hypoglyc.[2]	51%	47%	50%
$HbA_{1c} \leq 6.5$ % without hypoglyc.[2]	35%	24%	31%

[1] arithmetic mean (SD);[2] Proportion of subjects exposed for at least 8 weeks without any hypoglycaemia in the last 4 weeks of treatment

- After 16 weeks of treatment with SIAC 30, SIAC 45 or insulin glargine once daily, all in combination with metformin, mean HbA_{1c} was 7.0% with SIAC 30, 7.2% with SIAC 45 and 7.1% with insulin glargine. The statistical analysis showed no difference in HbA_{1c} between treatments.

Secondary Efficacy Endpoints

- Mean FPG concentrations at trial end were 6.8 mmol/L, 7.4 mmol/L and 7.0 mmol/L for SIAC 30, SIAC 45 and insulin glargine, respectively. The statistical analysis showed no difference between the three treatment groups in FPG (central laboratory measurement) after 16 weeks of treatment.
  - A clinically relevant decrease in FPG was seen in all three groups with mean changes from baseline to trial end of -4.3 mmol/L, -4.1 mmol/L and -5.1 mmol/L for subjects treated with SIAC 30, SIAC 45 and insulin glargine, respectively.
- The statistical analyses of meal related interstitial glucose endpoints showed that after dinner, the estimated mean postprandial IG concentrations over 2 hours, mean IG meal peak concentrations as well as the mean 2-hour IG meal increments and mean maximum IG meal increments were lower in the SIAC 30 and SIAC 45 groups compared to the insulin glargine group. No differences in IG endpoints were shown after breakfast and lunch and across all meals.
  - The statistical analyses showed no differences between the treatment groups after 16 weeks of treatment in mean interstitial glucose concentrations over 72 hours, as well as in the variation in the IG profile (determined by CV%, fluctuation and M-value).
- 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.
  - Mean SMPG values after dinner were 9.0 mmol/L, 8.8 mmol/L and 10.1 mmol/L for subjects treated with

SIAC 30, SIAC 45 and insulin glargine, respectively. The statistical analyses showed that the estimated mean value tended to be lower for SIAC 30 than for insulin glargine after dinner (estimated difference: -1.19 mmol/L; $[.-2.38; 0.01]_{95\%CI}$), and the estimated mean values for SIAC 45 were lower compared to insulin glargine after dinner (estimated difference: -1.44 mmol/L; $[.-2.64; -0.24]_{95\%CI}$) and before bedtime (estimated difference: -1.20 mmol/L; $[.-2.37; -0.03]_{95\%CI}$).

- Mean postprandial increment after dinner at trial end was 0.13 mmol/L, 0.24 mmol/L and 1.63 mmol/L for SIAC 30, SIAC 45 and insulin glargine, respectively. Statistical analyses showed that the estimated mean value was lower for SIAC 30 compared to insulin glargine (estimated difference: -1.34 mmol/L; $[-2.45; -0.23]_{95\%CI}$) and for SIAC 45 compared to insulin glargine (estimated difference: -1.33 mmol/L; $[-2.43; -0.23]_{95\%CI}$). This difference was reflected in the overall mean postprandial increment across all meals, which was lower in subjects treated with SIAC 30 compared to insulin glargine (estimated difference: -0.78 mmol/L; $[-1.47; -0.09]_{95\%CI}$).
- 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 30 than insulin glargine (treatment ratio: 1.29; $[1.05; 1.53]_{95\%CI}$) and for SIAC 45 compared to insulin glargine (treatment ratio: 1.54; $[1.24; 1.84]_{95\%CI}$).

- After 16 weeks of treatment, the total daily insulin dose (units/kg) was 16% lower for subjects treated with SIAC 30 compared to subjects treated with insulin glargine, and 21 % lower for SIAC 45 compared to insulin glargine.
- No differences were shown in the statistical analyses between the treatment groups in blood lipids and hs CRP after 16 weeks of treatment. Mean FFA concentrations at trial end was shown to be lower with SIAC 30 compared to SIAC 45 (estimated difference: 0.09; $[0.02; 0.17]_{95\%CI}$).
- 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. The estimated mean perception of life productivity increased during the trial in the SIAC 30 and insulin glargine groups, while it decreased in the SIAC 45 group. The statistical analyses showed that after 14 weeks of treatment, change in life productivity score was higher with SIAC 30 and insulin glargine than with SIAC 45.

Safety Results

A summary of adverse events by severity and relation to trial product is tabulated below.

Summary of Adverse Events

	SIAC 30 (B)			SIAC 45 (B)			IGlar			Total		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	59				59				60				178			
Total Exposure (yrs)	17.4				17.1				18.0				52.5			
Events	41	(69.5)	77	441	34	(57.6)	53	310	28	(46.7)	53	295	103	(57.9)	183	348
Serious	2	(3.4)	2	11	1	(1.7)	1	6					3	(1.7)	3	6
MESI																
Severity																
Severe	1	(1.7)	1	6									1	(0.6)	1	2
Moderate	18	(30.5)	24	138	16	(27.1)	21	123	6	(10.0)	11	61	40	(22.5)	56	107
Mild	27	(45.8)	52	298	27	(45.8)	32	187	27	(45.0)	42	234	81	(45.5)	126	240
Relationship to Insulin																
Probable	1	(1.7)	1	6					1	(0.6)	1	2				
Possible	4	(6.8)	4	23					4	(2.2)	4	8				
Unlikely	33	(55.9)	65	373	29	(49.2)	44	257	25	(41.7)	46	256	87	(48.9)	155	295
Missing	10	(16.9)	12	69	4	(6.8)	4	23	7	(11.7)	7	39	21	(11.8)	23	44
Relationship to Metformin																
Probable	2	(3.4)	2	12					2	(1.1)	2	4				

Possible	1 (1.7)	1	6	3 (5.1)	3	18	1 (1.7)	1	6	5 (2.8)	5	10
Unlikely	40 (67.8)	76	436	31 (52.5)	48	281	27 (45.0)	52	289	98 (55.1)	176	335
Missing												
Outcome												
Recovered	31 (52.5)	57	327	27 (45.8)	39	228	20 (33.3)	32	178	78 (43.8)	128	244
Fatal												
Recovering	2 (3.4)	3	17	1 (1.7)	1	6	3 (5.0)	3	17	6 (3.4)	7	13
Not Recovered	15 (25.4)	16	92	10 (16.9)	13	76	11 (18.3)	13	72	36 (20.2)	42	80
Unknown	1 (1.7)	1	6				4 (6.7)	5	28	5 (2.8)	6	11

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

- Overall, the incidence of adverse events was higher in the SIAC 30 group compared to SIAC 45 and insulin glargine, with the lowest incidence of adverse events reported for insulin glargine. Most AEs were mild or moderate in severity. Only 1 severe adverse event was reported (a fall in the SIAC 30 group), which was considered unlikely related to trial product.
- There were 3 serious adverse events ('depression' and 'transcient ischaemic attack' reported in the SIAC 30 group and 'epistaxis' reported in the SIAC 45 group), which were all considered unlikely related to trial product. One (1) subject in the SIAC 30 group was withdrawn due to a serious adverse event of 'transient ischemic attack'.
- Adverse events considered possibly or probably related to trial insulin were only reported in the SIAC 45 group (5 single events occurring in 5 subjects: nausea, diarrhoea, diabetic retinopathy, ecchymosis and haematoma).

Overview of Hypoglycaemia

	SIAC 30 (B) N (%) E	**SIAC 45 (B)** N (%) E	**Insulin glargine** N (%) E
Number of subjects	59	59	60
Total Exposure (years)	17.4	17.1	18.0
All hypoglycaemic episodes	18 (31%) 47	29 (49%) 91	15 (25%) 24
Major hypoglycaemia	0 (0%) 0	0 (0%) 0	0 (0%) 0
Minor hypoglycaemia	13 (22%) 20	18 (31%) 41	9 (15%) 12
Symptoms only hypoglycaemia	14 (24%) 27	21 (36%) 50	9 (15%) 12
Nocturnal hypoglycaemia[1]	3 (5%) 5	16 (27%) 48	5 (8%) 7

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 overall rates of hypoglycaemia were low in all treatment groups: no major hypoglycaemic episodes were reported, and more than 67% of subjects in each treatment arm, did not report any minor hypoglycaemic episodes during the trial.
  - The estimated rate of minor hypoglycaemic events was 1.22, 1.71 and 0.53 events per exposure year in the SIAC 30, SIAC 45 and insulin glargine groups, respectively. Statistical analyses of minor hypoglycaemic episodes showed no difference in the estimated rate of minor hypoglycacemia with SIAC 30 versus insulin glargine, or SIAC 30 versus SIAC 45, but a higher incidence in the SIAC 45 group compared with the insulin glargine group. The estimated rate of all hypoglycaemic events (including symptomatic hypoglycaemic episodes) was 2.80, 4.50 and 1.26 events per exposure year in the SIAC 30, SIAC 45 and insulin glargine groups, respectively. Statistical analysis of all hypoglycaemic episodes showed that the estimated rate was higher for the SIAC 30 and SIAC 45 groups compared with the insulin glargine group.
  - The estimated rate of nocturnal hypoglycaemic events was 0.16, 1.45 and 0.28 events per exposure year in the SIAC 30, SIAC 45 and insulin glargine groups, respectively. Statistical analyses showed that there was no difference between SIAC 30 and insulin glargine in the relative risk of all nocturnal hypoglycaemic episodes, whereas it was higher for the SIAC 45 group compared with the SIAC 30 and insulin glargine groups. The same result was seen, when nocturnal major and minor hypoglycaemic episodes were analysed.

- The time of occurrence of hypoglycaemia differed across treatments, with the highest number of hypoglycaemic episodes occurring in the early morning with insulin glargine, in the afternoon and evening with SIAC 30 and in the evening and first part of the night with SIAC 45.
- The proportion of subjects with hypoglycaemia was almost constant throughout the treatment period in the SIAC 30 group, whereas more hypoglycaemic episodes were reported after the initial 4 weeks in the SIAC 45 and insulin glargine groups.

- There were no obvious changes in weight, BMI or waist-to-hip ratio after 16 weeks of treatment.
- Overall levels of antibodies specific to insulin aspart and insulin 454 remained low or undetectable during the trial. There was a slight increase in antibodies cross-reacting between insulin aspart and insulin 454, and also for antibodies cross-reacting between insulin 454 and human insulin. The changes in antibody levels were not associated with changes in HbA_{1c} and insulin dose, and thus not considered clinically important.
- There were no obvious overall changes in ECG, vital signs, haematology or biochemistry

Conclusions

Efficacy

- Once daily treatment with SIAC 30, SIAC 45 or insulin glargine, 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 alone. A clinically relevant decrease in mean HbA_{1c} was observed in all three treatment groups at trial end.
- The mean FPG concentrations were similar for the three treatments after 16 weeks of treatment; a clinically relevant decrease in mean FPG during the treatment period was observed in all three treatment groups.
- The postprandial interstitial glucose excursions after dinner, measured by CGM, at the end of trial were lower with SIAC 30 and SIAC 45 compared to insulin glargine.
- Overall, mean 9-point SMPG profiles were similar for the three treatments after 16 weeks of treatment. After dinner, the mean SMPG concentration tended to be lower with SIAC 30 than with insulin glargine and was shown to be lower with SIAC 45 compared to insulin glargine. Before bedtime, the mean SMPG concentration was lower with SIAC 45 than with insulin glargine.
- Intra-subject variability, determined from the 9-point SMPG at trial end, was similar for the treatments, except after dinner, where the coefficient of variation was higher for SIAC 30 and SIAC 45 compared to insulin glargine.
- After 16 weeks of treatment, the total daily insulin dose (units/kg) was 16% lower for subjects treated with SIAC 30 compared to subjects treated with insulin glargine, and 21 % lower for SIAC 45 compared to insulin glargine.
- There were no apparent differences in the lipid profiles between SIAC and insulin glargine. The concentration of free fatty acids was lower with SIAC 30 compared to SIAC 45 at trial end.
- Mean insulin 454 concentrations, adjusted for dose, appeared to be almost stable for both SIAC 30 and SIAC 45 throughout the trial.
- Marginal differences in patient reported outcomes were observed between the three treatments after 14 weeks of treatment.
- Efficacy of SIAC was demonstrated.

Safety

- The overall rates of hypoglycaemia were low with all three treatments. No major hypoglycaemic episodes were reported, and more than two thirds (67%) of subjects in each treatment group did not report any minor hypoglycaemic episodes. Statistical analyses showed no difference in the estimated rates of minor hypoglycaemic episodes between SIAC 30 and insulin glargine, but a higher rate with SIAC 45 compared to insulin glargine. The estimated rate of nocturnal minor hypoglycaemic episodes was similar for SIAC 30 and insulin glargine, but higher with SIAC 45 compared to the two other treatments. The estimated rate of all hypoglycaemic episodes (events per year) was higher with SIAC 30 and SIAC 45 compared with insulin glargine.
- Safety data did not reveal any unexpected findings. No specific pattern or clustering of adverse events was observed with SIAC or insulin glargine. Antibody development did not give rise to any concerns and, in general, SIAC was well tolerated.
- There were no apparent differences between treatments in body weight and waist-to-hip ratio after 16 weeks of treatment.
- Safety of SIAC was demonstrated.

The trial was conducted in accordance with the Declaration of Helsinki(52nd VMA, 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