2 Synopsis

Trial Registration ID-number: NCT00612040 From www.clinicaltrials.gov	**IND Number – 76496** **EudraCT number – 2007-002474-60**
Title of Trial A 16 week randomised, open labelled, 3-armed, treat-to-target, parallel group trial comparing SIBA (D) once daily + NovoRapid®, SIBA (E) once daily + NovoRapid® and insulin glargine once daily + NovoRapid®, all in a basal/bolus regimen in subjects with type 1 diabetes	
Investigators There were 28 principal investigators in 5 countries: Australia (5), Germany (6), Norway (6), Sweden (5) and the USA (6). Dr. [redacted] was appointed as Signatory Investigator for the trial.	
Trial Sites A total of 28 centres participated: Australia (5), Germany (6), Norway (6), Sweden (5) and the USA (6)	
Publications None	
Trial Period From 04 January 2008 to 20 June 2008	**Development Phase** Phase 2

Objectives

Primary Objective:

- To assess glucose control with respect to HbA_{1c} after 16 weeks of treatment with SIBA (D) QD + NovoRapid® or SIBA (E) QD + NovoRapid® compared with that of insulin glargine QD + NovoRapid®, all in a basal/bolus regimen, in subjects with type 1 diabetes.

Secondary Objectives:

Between the treatment arms:

- To compare efficacy and safety after 16 weeks of treatment in terms of:
  - body weight
  - 9-point plasma glucose profiles
  - lipid profiles
  - frequency of hypoglycaemic episodes
  - waist and hip circumference
- To compare intra-subject variability based on self measured plasma glucose (SMPG)
- To compare patient reported outcome

Methodology

This was a randomised (1:1:1 to SIBA (D), SIBA (E) or insulin glargine), open labelled, treat-to-target, parallel-group, multicentre, multinational, efficacy and safety trial comparing SIBA and insulin glargine administered once daily, in the evening, to subjects with type 1 diabetes mellitus. All three treatment groups received insulin aspart as bolus insulin before main meals. Subjects previously treated on a once daily insulin regiment were switched to SIBA and insulin glargine on a unit to unit basis, while subjects transferred from a twice daily insulin regimen were to reduce the dose of SIBA and insulin glargine by 20%.

The trial consisted of a 1-week screening period, a 16-week treatment period and a 2-week follow-up period. The treatment period included a total of 14 visits to the clinical trial sites and 6 telephone contacts.

During the treatment period the insulin doses were titrated by the investigator based upon the subject's SMPG and a titration algorithm aiming for a prebreakfast plasma glucose target of 4.0 to 6.0 mmol/L. Due to the stable effect and long half-life of insulin 454, careful titration of the subsequent anti-diabetic treatment was to be carried out (based on blood glucose measurements) when stopping treatment with SIBA.

Number of Subjects Planned and Analysed

In order to have 150 subjects completing the trial, it was planned to randomise 177 subjects. In total, 200 subjects were screened, 22 of whom were screening failures. Subject disposition is tabulated below:

	SIBA (D) N (%)	SIBA (E) N (%)	IGlar N (%)	Total N (%)
Screened				200
Not Randomised				22
Screening Failures				22
Randomised	60 (100.0)	59 (100.0)	59 (100.0)	178 (100.0)
Exposed	60 (100.0)	59 (100.0)	59 (100.0)	178 (100.0)
Not Exposed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawals	5 (8.3)	7 (11.9)	7 (11.9)	19 (10.7)
Adverse Event	0 (0.0)	2 (3.4)	1 (1.7)	3 (1.7)
Non-Compliance	1 (1.7)	2 (3.4)	1 (1.7)	4 (2.2)
Ineffective Therapy	2 (3.3)	1 (1.7)	0 (0.0)	3 (1.7)
Other	2 (3.3)	2 (3.4)	5 (8.5)	9 (5.1)
Completed Trial	55 (91.7)	52 (88.1)	52 (88.1)	159 (89.3)
Full Analysis Set	60 (100.0)	59 (100.0)	59 (100.0)	178 (100.0)
PP Analysis Set	52 (86.7)	51 (86.4)	52 (88.1)	155 (87.1)
Safety Analysis Set	60 (100.0)	59 (100.0)	59 (100.0)	178 (100.0)

N: Number of Subjects

Diagnosis and Main Criteria for Inclusion

Eligible subjects were men and women 18-75 years of age, diagnosed with type 1 diabetes mellitus for a minimum of 12 months prior to inclusion in this trial, treated continuously with any insulin regimen and having an HbA_{1c} of 7.0%- 11.0% (both inclusive). Subjects were to have no clinically relevant renal, hepatic or cardiac diseases, recurrent major hypoglycaemia or proliferative retinopathy / maculopathy requiring active treatment.

Test Product, Dose and Mode of Administration, Batch Number

- SIBA (D) 100 DU/mL (100 DU = 900 nmol) solution in a 3 mL FlexPen®. The dose was individually titrated and administered in the evening as a subcutaneous (s.c.) injection, preferentially in the thigh. Batch number: TP51544.
- SIBA (E) 100 DU/mL (100 DU = 600 nmol) solution in a 3 mL FlexPen®. The dose was individually titrated and administered in the evening as a s.c. injection, preferentially in the thigh. Batch number: TP51545.
- Meal-related insulin: NovoRapid® (insulin aspart), 100 U/mL solution in a 3 mL FlexPen®. The dose was individually titrated and administered as s.c. injections in the abdomen. Batch number: TP51387.

Duration of Treatment

The treatment period with insulin was approximately 16 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

- Insulin glargine (Lantus®), 100 U/mL (600 nmol/mL) solution in a 3 mL OptiSet®. The dose was individually titrated and administered in the evening as s.c. injections preferentially in the thigh. Batch number: 40B305.
- Insulin glargine (Lantus®), 100 U/mL (600 nmol/mL) solution in 10 mL vials (US only).Batch number: 40B187
- Meal-related insulin: NovoRapid® (insulin aspart), 100 U/mL solution in a 3 mL FlexPen®. The dose was individually titrated and administered as s.c. injections in the abdomen. Batch number: TP51387.

Criteria for Evaluation – Efficacy

HbA_{1c}, fasting plasma glucose (FPG); SMPG recordings including 9-point profiles, lipids, free fatty acids (FFA), hs CRP, serum insulin 454 concentrations, basal and bolus insulin dose and patient reported outcomes (PRO).

Criteria for Evaluation – Safety

Adverse events, hypoglycaemic episodes, physical examination, vital signs, laboratory tests (haematology, biochemistry, urinalysis, pregnancy and insulin antibodies), fundoscopy/fundusphotography, electrocardiogram (ECG), injection site disorders, weight, body mass index (BMI) and waist and hip circumference.

Statistical Methods

Analysis Sets

The following analysis sets were defined:

- Full Analysis Set (FAS): including all randomised subjects.
- Per Protocol (PP) Set: Including subjects without any major protocol violations that may affect the primary endpoint. Subjects were to be exposed to the randomized trial medication (insulin) for at least 12 weeks, and must have valid assessments necessary for deriving the primary endpoint. Analyses followed the as-treated principle.
- Safety Analysis Set: including all subjects with exposure information of at least one dose of randomised trial medication (basal insulin).

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 as fixed factors and age and baseline HbA_{1c} as covariates. The robustness of the results was explored by stability analysis on the PP population. The primary analysis explored all pair wise treatment differences between SIBA (D), SIBA (E) and insulin glargine 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, lipids, FFA, hs CRP, insulin 454 concentrations, insulin doses and change in PRO.

- 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 a model similar to that 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 baseline value as a covariate
- SMPG for dosing
  - The SMPG for dosing were 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 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.
- 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 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.

Continued

- 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 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.

Demography of Trial Population

About 60% of subjects were males and the vast majority of subjects were White (98%) and of non-Hispanic-Latino origin (98%). At trial entry slightly more than half of the subjects were on a once daily basal insulin regimen, while the other half administered basal insulin twice daily in combination with bolus insulin. The overall subject characteristics were similar between the three groups apart from a slightly higher proportion of male subjects in the two SIBA groups compared to the insulin glargine group (62 vs. 54 %) and a slightly lower mean body weight in the insulin glargine group. The baseline and diabetes characteristics are shown in the table below:

Baseline and Diabetes Characteristics

	Treatment	FAS	Descriptive statistics N	Mean	SD	Min	Max
Age (yrs)							
	SIBA (D)	60	60	45.6	12.5	19.0	71.0
	SIBA (E)	59	59	44.5	12.7	20.0	72.0
	IGlar	59	59	47.2	13.5	20.0	74.0
Weight (kg)							
	SIBA (D)	60	60	80.5	14.5	54.9	115.2
	SIBA (E)	59	59	80.9	11.8	56.2	108.7
	IGlar	59	59	77.7	14.2	50.2	117.4
BMI (kg/m^2)							
	SIBA (D)	60	60	27.1	3.6	20.1	35.1
	SIBA (E)	59	59	27.2	3.4	19.6	38.5
	IGlar	59	58	26.3	3.9	19.5	34.7
Duration of Diabetes (yrs)							
	SIBA (D)	60	60	20.8	10.6	1.2	47.1
	SIBA (E)	59	59	22.7	14.6	1.8	55.0
	IGlar	59	59	19.1	10.8	1.3	47.0
HbA1c (%)							
	SIBA (D)	60	60	8.5	1.0	7.0	10.9
	SIBA (E)	59	59	8.4	0.9	7.3	10.9
	IGlar	59	59	8.3	0.8	7.0	10.1
FPG (mmol/l)							
	SIBA (D)	60	60	10.3	4.8	2.1	30.1
	SIBA (E)	59	59	9.9	3.3	3.3	17.2
	IGlar	59	59	9.5	3.8	2.2	18.1

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

Efficacy Results

Primary Efficacy Endpoint: HbA_{1c} after 16 weeks of treatment

HbA_{1c} (%)	**SIBA (D)** Mean (SE)	**SIBA (E)** Mean (SE)	**Insulin Glargine** Mean (SE)
N	60	59	59
LS Means			
End of treatment	7.94 (0.09)	7.87 (0.09)	7.76 (0.09)
Change from baseline (% points)	-0.46 (0.09)	-0.53 (0.09)	-0.64 (0.09)
Treatment difference vs. insulin glargine (% points)	0.18 [-0.06; 0.42]	0.10 [-0.14; 0.34]	0
Proportion of subjects reaching HbA_{1c} target after 16 weeks			
$HbA_{1c} < 7.0$ %	15%	15%	14%
$HbA_{1c} \leq 6.5$ %	5%	0%	5%

LS means: least square means, SE: standard error

- Once daily treatment with SIBA (D), SIBA (E) and insulin glargine, all in combination with insulin aspart at meals, resulted in comparable glycaemic control after 16 weeks of treatment. This was supported by analysis of the PP analysis set.
- Less than 4% of subjects in all three groups achieved an HbA_{1c} <7% and none of the groups achieved an HbA_{1c} ≤6.5% without minor or major hypoglycaemic episodes during the last 4 weeks of treatment.

Secondary Efficacy Endpoints

- Estimated mean FPG, centrally analysed, decreased by 1.82 mmol/L with SIBA (D), by 1.62 mmol/L with SIBA (E), and by 1.06 mmol/L with insulin glargine. Statistical analyses did not confirm any differences in FPG between treatments after 16-weeks
- Statistical analyses related to the 9-point SMPG profiles did not suggest any differences between the three treatment groups after 16 weeks.
- No differences were observed between treatments with respect to the within-subject variation in SMPG levels. A slightly larger proportion of subjects in the two SIBA groups (18%) achieved the pre-breakfast PG target without major or minor hypoglycaemic episodes during the last 4 weeks of treatment compared to subjects treated with insulin glargine (9%).
- A larger decrease in estimated mean FFA (-0.18 mmol/L) was observed in the two SIBA arms compared to insulin glargine (-0.09 mmol/L). Apart from this, no differences were observed between the groups with respect to lipid levels and hs CRP during the trial.
- Quality of life based on PRO showed marginal changes during the trial. The only difference observed between treatments, based on statistical analyses, was an improvement in mental component score in the SIBA (E) group compared to the insulin glargine group using the Health Related Quality of Life Questionnaire (SF-36).
- Mean daily basal insulin doses at baseline and after 16 weeks of treatment are tabulated below.

	SIBA (D)	SIBA (E)	IGlar
Baseline (U/kg)	0.34	0.36	0.30
End of trial (U/kg)	0.28	0.36	0.32
End of trial (nmol/kg)	2.50	2.19	1.92

- The mean dose of insulin aspart was approximately 0.38 U/kg at baseline in all three groups. At end of trial the mean daily dose was 0.32 U/kg in the SIBA (D) group, 0.37 U/kg in the SIBA (E) group and 0.33 U/kg in the insulin glargine group.

Safety Results

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

	SIBA (D)			SIBA (E)			IGlar		
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of Subjects	60				59				59			
Total Exposure (yrs)	17.3				17.0				16.6			
Events	40	(66.7)	113	653	45	(76.3)	149	874	39	(66.1)	152	914
Serious	1	(1.7)	1	6	2	(3.4)	2	12	1	(1.7)	1	6
MESI												
Severity												
Severe	1	(1.7)	1	6	4	(6.8)	5	29	1	(1.7)	1	6
Moderate	17	(28.3)	35	202	24	(40.7)	42	246	19	(32.2)	66	397
Mild	31	(51.7)	77	445	40	(67.8)	102	599	32	(54.2)	85	511
Relationship to Basal Insulin												
Probable	3	(5.0)	3	17					2	(3.4)	2	12
Possible	3	(5.0)	4	23	7	(11.9)	8	47	1	(1.7)	1	6
Unlikely	37	(61.7)	105	607	44	(74.6)	139	816	39	(66.1)	146	878
Missing	1	(1.7)	1	6	2	(3.4)	2	12	1	(1.7)	3	18
Relationship to Bolus Insulin												
Probable	1	(1.7)	1	6					2	(3.4)	2	12
Possible	3	(5.0)	4	23	4	(6.8)	5	29				
Unlikely	37	(61.7)	107	618	45	(76.3)	142	833	39	(66.1)	147	884
Missing	1	(1.7)	1	6	2	(3.4)	2	12	1	(1.7)	3	18
Outcome												
Recovered	38	(63.3)	104	601	45	(76.3)	140	822	39	(66.1)	139	836
Fatal												
Recovering					2	(3.4)	2	12				
Not Recovered	8	(13.3)	9	52	7	(11.9)	7	41	8	(13.6)	13	78

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

- The most common AEs were nasopharyngitis and headache in all three treatment groups.
- Four SAEs were reported: “hypoglycaemia”, in the SIBA (D) group, “hypoglycaemic unconsciousness” and “abdominal distension” in the SIBA (E) group and “diabetic ketoacidosis” in the insulin glargine group. All SAEs were severe and, except for the “abdominal distension”, considered possibly or probably related to trial products by the investigator.
- Three (3) subjects withdrew due to AEs. In the SIBA (E) group the withdrawals were related to respectively ”nausea” and “abdominal distension”. In the insulin glargine group the withdrawal was due to “diabetic ketoacidosis”.
- The proportion of subjects with AEs considered to have a possible or probable relation to trial product was higher in the two SIBA arms compared to the insulin glargine arm, being approximately 10% for the SIBA (D) group, 12% for the SIBA (E) group and 5% for the insulin glargine group. With the exception of nausea and rash, which each occurred in 2 subjects in the SIBA (E) group, these related events were single events occurring in single subjects.
- No clustering or specific pattern in the reported AEs was observed.

Continued

An overview of the hypoglycaemic episodes is presented in the table below:

Hypoglycaemia	**SIBA (D)** N (%) E	**SIBA (E)** N (%) E	**Insulin Glargine** N (%) E
Number of subjects	60	59	59
Total Exposure (years)	17.3	17.0	16.6
All hypoglycaemic episodes	58 (97) 2010	58 (98) 1798	55 (93) 1850
Major hypoglycaemia	4 (7%) 8	6 (10%) 7	4 (7%) 6
Minor hypoglycaemia	56 (93%) 1010	56 (95%) 904	54 (92%) 1104
Symptoms only hypoglycaemia	52 (87%) 992	57 (97%) 887	52 (88%) 740
Nocturnal hypoglycaemia[1]	46 (77%) 208	36 (61%) 161	47 (80%) 236

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)

- No marked differences were found between the three treatment groups with respect to overall hypoglycaemia, although the estimated rate appeared slightly lower for the SIBA (E) group than for the other two groups. When "major and minor" episodes were pooled, the rate was 28% lower with SIBA (E) compared to insulin glargine.
- The rate of nocturnal hypoglycaemic episodes was 43% lower with SIBA (E) than with insulin glargine. When "major and minor" episodes were pooled, the rate was 58% lower with SIBA (E) compared to insulin glargine. No marked differences were found between SIBA (D) and insulin glargine, although the rate of hypoglycaemia tended to be slightly lower for the SIBA (D) treated group.
- No injection site reactions were observed.
- Insulin 454 specific and insulin aspart specific antibody levels remained stable during the trial, while the mean level of antibodies cross-reacting between insulin 454 and insulin aspart increased (less than 2-fold). However, this did not appear to have any effect on HbA_{1c} or basal insulin dose following the 16 weeks of treatment with SIBA.
- Body weight increased by approximately 1.0 kg with SIBA (D), by 0.1 kg with SIBA (E) and 0.7 kg with insulin glargine, while the waist and hip circumference remained stable in all three groups during the trial.
- No clinically relevant differences in clinical laboratory tests (haematology, biochemistry and urinalysis) were reported between the treatment groups. No obvious differences in ECG, fundoscopy/fundusphotography, vital signs, or physical examination were observed between the three treatment groups.

Conclusions

- In subjects with type 1 diabetes mellitus, 16 weeks of basal-bolus treatment with SIBA (D) or SIBA (E) once daily, in combination with insulin aspart, resulted in comparable glycaemic control to that observed with insulin glargine administered once daily in combination with insulin aspart.
- No clinically relevant differences were found between treatments based on analyses of the 9-point SMPG profiles after 16 weeks.
- No clinically relevant differences were observed between treatments in the analyses of within-subjects variability based on SMPG after 16 weeks of treatment.
- Lipid profiles improved slightly or remained stable in all three treatment groups. Statistical analyses showed that subjects treated with SIBA (D) or SIBA (E) had a larger reduction in FFA levels during the trial compared to subjects treated with insulin glargine.
- The mean rate of all hypoglycaemic episodes was similar between treatments, while statistical analyses suggested that the mean rate of all nocturnal hypoglycaemia was lower with SIBA (E) compared to insulin glargine.
- Safety data did not reveal any unexpected findings and no specific patterns or clustering of AEs were observed with SIBA and insulin glargine. Antibody development did not give rise to any concerns and in general SIBA was well tolerated.
- Body weight increased slightly during the trial, while waist and hip circumference remained stable and no clinically relevant differences were observed between treatments with respect to body measurements after 16 weeks of treatment.
- Marginal changes were observed in the three treatment groups with respect to PRO.

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.