Synopsis

Identifier: HM2007/00585/00 **Study Number:** NAA104606

Title: A Multi Centre, Double-Blind, Double-Dummy, Placebo-Controlled, Randomised, Adaptive, Dose-Range Study To Evaluate the Safety and Efficacy of SB-773812 Administered Once Daily for 12 Weeks in Adults With Schizophrenia.

Investigators: This was a multicentre study.

Study centres: Subjects were recruited at a total of 19 Investigator sites for Part A of the study and at 34 Investigator sites for Part B. The study was conducted in seven countries.

Publications: None at the time of this report.

Study Period: 20 September 2005 – 28 June 2007. **Phase of Development:** II.

Objectives: The primary objective was to compare the efficacy of SB-773812 with placebo in the treatment of subjects diagnosed with acute schizophrenia.

The secondary objectives were:

- To provide preliminary data on safety and tolerability of SB-773812 compared with olanzapine (15 mg) and compared with placebo in subjects with acute schizophrenia.
- To provide data on the efficacy of olanzapine (15 mg) compared with placebo in subjects with acute schizophrenia (for assay sensitivity).
- To measure the pharmacokinetics and to investigate preliminary pharmacokinetic/ pharmacodynamic relationships for SB-773812 in subjects with schizophrenia.

Methodology: This was a placebo-controlled, parallel-group, adaptive, dose-range study in subjects with schizophrenia, with olanzapine included as a positive control for assay sensitivity. Screening took place a maximum of 1 week before the baseline (BL) visit. Subjects were hospitalised from Screening for at least 14 days following randomisation in Part A and for the full 6-week treatment period (recommended) in Part B.

Subjects in Part A were randomised (2:2:1) to receive SB-773812 60 mg, placebo or olanzapine 15 mg once daily for 12 weeks. An interim analysis was performed once 72 subjects had been randomised in Part A and had either completed 6 weeks of treatment or had withdrawn early. The dose levels to be used in Part B were chosen at the time of this interim analysis. Subjects in Part B were randomised (1:1:1:1) to receive SB-773812 60 mg, SB-773812 120 mg, placebo, or olanzapine 15 mg once daily for 6 weeks.

In Part B, an interim analysis was performed once 104 subjects had completed the treatment phase or withdrawn early. These data were used in portfolio planning and also to review the variability in order to determine whether Part B was sufficiently powered.

A follow-up visit took place 21 days after the final dose of investigational product. The maximum duration of each subject's participation in the study was 17 weeks for Part A subjects and 11 weeks for Part B subjects.

Number of subjects: Subject disposition in Part A is summarised in the following table:

Number of Subjects	Placebo	SB-773812 60 mg	Olanzapine	Total
Number of subjects planned, N (maximum)	52	52	26	130
Number of subjects randomised, N	39	41	21	101
Number of subjects included in ITT population, n (%)	38 (97)	41 (100)	21 (100)	100 (>99)
Number of subjects completed as planned, n (%) [a]	7 (18)	11 (27)	10 (48)	28 (28)
Number of subjects withdrawn (any reason), n (%)	31 (82)	30 (73)	11 (52)	72 (72)
Reasons for subject withdrawal, n (%)				
Lack of efficacy	17 (45)	13 (32)	4 (19)	34 (34)
Subject decided to withdraw from study	9 (24)	11 (27)	4 (19)	24 (24)
Adverse events	2 (5)	5 (12)	1 (5)	8 (8)
Lost to follow-up	3 (8)	1 (2)	2 (10)	6 (6)

a. A subject was considered to have completed the study if they completed the Week 12 visit case report form.
ITT = Intention-to-Treat.

Subject disposition in Part B is summarised in the following table:

Number of Subjects	Placebo (Pt B)	SB-773812 60 mg (Pt B)	SB-773812 120 mg (Pt B)	Olanzapine (Pt B)	Total
Number of subjects planned, N (max)	52	52	52	52	208
Number of subjects randomised, N	52	54	54	57	217
Number included in ITT population, n (%)	52 (100)	54 (100)	54 (100)	57 (100)	217 (100)
Number completed as planned, n (%) [a]	25 (48)	36 (67)	39 (72)	43 (75)	143 (66)
Number withdrawn (any reason), n (%)	27 (52)	18 (33)	15 (28)	14 (25)	74 (34)
Reasons for subject withdrawal, n (%)					
Lack of efficacy	16 (31)	7 (13)	8 (15)	3 (5)	34 (16)
Adverse events	8 (15)	5 (9)	4 (7)	4 (7)	21 (10)
Subject decided to withdraw from study	2 (4)	2 (4)	2 (4)	4 (7)	10 (5)
Lost to follow-up	0	2 (4)	1 (2)	1 (2)	4 (2)
Other	0	1 (2)	0	2 (4)	3 (1)
Protocol violation	1 (2)	1 (2)	0	0	2 (<1)

a. A subject was considered to have completed the study if they completed the Week 6 visit case report form.
ITT = Intention-to-Treat.

Diagnosis and main criteria for inclusion: Male and female subjects aged 18–65 years with schizophrenia diagnosed per the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) were recruited for the study. Subjects had to be suffering from an acute exacerbation of schizophrenia and require inpatient hospitalisation. Subjects were required to have a PANSS Total score of at least 70 and a minimum score of 4 (moderate) on at least two defined PANSS parameters. Subjects had a body weight ≥46 kg (male) ≥41 kg (female) and a body mass index within the range 18.5–33.0 kg/m^2, inclusive. Subjects were not eligible if this was their first episode of schizophrenia or if they had any psychotic disorder other than schizophrenia.

Treatment administration: Investigational products were as follows: SB-773812 30 mg oral tablet (two batches); SB-773812 60 mg oral tablet (one batch); placebo to match SB-773812 (one batch); olanzapine 7.5 mg oral tablet (one batch); and placebo to match olanzapine (one batch).

Criteria for evaluation: Primary endpoint: The primary endpoint was the change from BL in the Positive and Negative Syndrome Scale (PANSS) Total score for each SB-773812 dose versus placebo at Week 6.

Secondary endpoints – Efficacy (all at Week 6):

- Change from BL in PANSS Positive, Negative, and General symptoms.
- Change from BL in Brief Psychiatric Rating Scale (BPRS) total and psychosis score.
- Change from BL in Clinical Global Impression – Severity (CGI-S) score.
- Proportion of responders: score of 1 or 2 on the Clinical Global Impression – Improvement (CGI-I) scale.
- Proportion of responders (≥20% decrease in the PANSS Total score).
- Change from BL in Calgary Depression Scale for Schizophrenia (CDSS) total score.
- Change from BL in five factor PANSS analysis components (negative, positive, cognitive, excitement, depression).

Safety and Tolerability: Change from BL in Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale and Simpson Angus Scale at Week 6; and other assessments including adverse events (AEs), physical examination (PE), vital signs (standing and supine systolic and diastolic blood pressure [BP] and heart rate [HR]), laboratory assessments (haematology panel, chemistry panel [including full fasting lipid profile], hormones [prolactin] and urinalysis), electrocardiogram (ECG), electron microscopy evaluation of peripheral lymphocytes as a marker for phospholipidosis, visual function tests and assessments for neurological function.

Pharmacokinetics and PK/PD: To develop a population pharmacokinetic model of SB-773812 in order to provide an estimate of steady state exposure in all subjects receiving SB-773812; to estimate the steady-state exposure of SB-773812 following chronic dosing in subjects with schizophrenia; and to estimate the relationship between plasma concentration/exposure of SB-773812 and safety/efficacy measurements.

Pharmacodynamics: Change from BL cognitive factor scores and in each cognitive test.

Health Outcomes: Change from BL in Motivation and Energy Inventory – Short Form (MEI-SF); scores from subject-reported Drug Attitude Inventory (DAI) at Week 6.

Statistical methods: The primary population was the Intention-to-Treat (ITT) Population and comparisons were made using the last observation carried forward (LOCF) dataset. Secondary comparisons on all endpoints were made using the observed case (OC) data and with a repeated measures model.

A hierarchical evaluation method was used to test the treatment effect on each SB-773812 dose in Part B. Firstly, the efficacy of the high dose of SB-773812 was compared with placebo at the 5% level of significance. If this comparison achieved statistical significance, the second comparison of the low dose of SB-773812 was tested at the 5% level of significance. If the first comparison of the SB-773812 doses vs. placebo was not significant at the 5% level, no further inferential testing was to be done.

Change from baseline in PANSS Total score was analysed using parametric analysis of covariance (ANCOVA). The statistical model included terms for baseline score, race, country and treatment group and other covariates found to be significant following the model-building approach. Since smoking history was found to be a significant covariate in Part B, this term was also included in the Part B analysis. No interactions were included in this primary model.

The original intention was to combine efficacy data from both parts of the study. Given the number of changes made following the interim analysis in Part A (reduction of the treatment period, increased hospitalisation and additional health outcomes and safety endpoints) the efficacy data were reported separately for each part of the study.

All safety data were reported separately for each part of the study, with key safety data also reported combined across both parts of the study. Given the changes made to the study design in response to failed interim in Part A, Parts A and B of the study may effectively be considered as two separate studies.

Summary:

Efficacy:

Part A: No significant treatment difference was observed in Part A Week 6 PANSS Total score between olanzapine and placebo or SB-773812 60 mg vs. placebo.

Treatment	N	n	Adjusted Mean	SE of Adjusted Mean	Difference vs. Placebo	95% CI	P value
Interim analysis							
Placebo	26	26	-7.9	2.99			
SB-773812 60 mg	31	31	-11.6	2.74	-3.7	(-11.8, 4.4)	0.369
Olanzapine	15	15	-12.5	3.94	-4.5	(-14.4, 5.4)	0.364
Final analysis							
Placebo	38	36	-4.7	5.09			
SB-773812 60 mg	41	40	-8.7	5.26	-4.0	(-10.9, 2.9)	0.247
Olanzapine	21	21	-13.0	5.34	-8.3	(-16.7, 0.1)	0.052

Part B: At Week 6 interim SB-773812 120 mg and 60 mg had a clinically meaningful effect on PANSS Total versus placebo and the difference between 120 mg and placebo was also statistically significant. At Week 6 final, PANSS Total for both SB-773812 60 mg and 120 mg as well as olanzapine showed clinically meaningful and statistically significant differences relative to placebo.

Treatment	N	n	Adjusted Mean	SE of Adjusted Mean	Difference vs. Placebo	95% CI	P value
Interim analysis							
Placebo (Part B)		25	-3.3	4.25			
SB-773812 60 mg (Part B)		25	-13.0	4.23	-9.8	(-21.7, 2.1)	0.107
SB-773812 120 mg (Part B)		25	-17.8	4.25	-14.5	(-26.5, -2.6)	0.018
Olanzapine (Part B)		29	-20.4	3.93	-17.1	(-28.6, -5.6)	0.004
Final analysis							
Placebo (Part B)	52	52	-3.8	3.22			
SB-773812 60 mg (Part B)	54	54	-12.6	3.24	-8.8	(-16.2, -1.4)	0.020
SB-773812 120 mg (Part B)	54	54	-12.3	3.08	-8.5	(-15.8, -1.1)	0.024
Olanzapine (Part B)	57	57	-20.3	3.09	-16.5	(-23.8, -9.3)	<0.001

Other Part B Week 6 final analyses are presented below (difference compared with placebo).

Parameter	SB-773812 60 mg (N = 54)	SB-773812 120 mg (N = 54)	Olanzapine (N = 57)
(Week 6)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)
PANSS Positive	-3.3 (-5.7, -0.9)	-3.5 (-5.9, -1.1)	-5.5 (-7.8, -3.1)
PANSS Negative	-1.6 (-3.5, 0.3)	-0.8 (-2.7, 1.0)	-2.9 (-4.7, -1.0)
PANSS General	-4.0 (-7.7, -0.2)	-3.9 (-7.6, -0.1)	-8.2 (-11.9, -4.5)
BPRS Total	-5.2 (-9.5, -0.9)	-5.7 (-10.0, -1.4)	-9.9 (-14.1, -5.6)
CGI-S Score	-0.5 (-1.0, -0.1)	-0.6 (-1.0, -0.2)	-0.9 (-1.3, -0.5)

Safety: Frequently reported AEs (≥5% in any group) in Part A are summarised below.

Adverse Event	Placebo (N = 38) n (%)	SB-773812 60 mg (N = 41) n (%)	Olanzapine (N = 21) n (%)
Any adverse event	21 (55)	20 (49)	13 (62)
Headache	6 (16)	6 (15)	2 (10)
Diarrhoea	3 (8)	3 (7)	0
Insomnia	3 (8)	1 (2)	1 (5)
Sedation	1 (3)	1 (2)	2 (10)
Dry mouth	0	0	3 (14)
Flatulence	0	0	3 (14)
Tremor	2 (5)	0	1 (5)
Vomiting	2 (5)	1 (2)	0
Constipation	2 (5)	0	0
Skin laceration	0	0	2 (10)
Weight increased	0	0	2 (10)

Frequently reported AEs in Part B (≥5% in any group) are summarised below.

Adverse Event	Placebo (Part B) N = 52 n (%)	SB-773812 60 mg (Part B) N = 54 n (%)	SB-773812 120 mg (Part B) N = 54 n (%)	Olanzapine (Part B) N = 57 n (%)
Any adverse event	34 (65)	36 (67)	43 (80)	39 (68)
Insomnia	14 (27)	11 (20)	13 (24)	7 (12)
Somnolence	4 (8)	7 (13)	11 (20)	13 (23)
Headache	8 (15)	9 (17)	7 (13)	6 (11)
Dizziness	6 (12)	3 (6)	7 (13)	4 (7)
Tremor	1 (2)	6 (11)	7 (13)	5 (9)
Diarrhoea	2 (4)	10 (19)	3 (6)	1 (2)
Agitation	6 (12)	0	2 (4)	4 (7)
Sleep disorder	4 (8)	3 (6)	3 (6)	2 (4)
Anxiety	3 (6)	2 (4)	2 (4)	3 (5)
Decreased appetite	1 (2)	5 (9)	4 (7)	0
Nausea	2 (4)	4 (7)	2 (4)	2 (4)
Psychotic disorder	4 (8)	3 (6)	1 (2)	1 (2)
Vomiting	2 (4)	5 (9)	1 (2)	1 (2)
Akathisia	0	1 (2)	3 (6)	4 (7)
Weight decreased	1 (2)	6 (11)	0	0
Abdominal pain	0	2 (4)	4 (7)	0
Paraesthesia	0	1 (2)	2 (4)	3 (5)
Sedation	0	3 (6)	2 (4)	1 (2)
Asthenia	0	0	5 (9)	0
Sinus bradycardia	1 (2)	1 (2)	3 (6)	0
Arthralgia	0	0	1 (2)	3 (5)
Weight increased	0	1 (2)	0	3 (5)

Across both parts of the study, treatment-limiting AEs were reported in eight subjects (9%) receiving placebo, five subjects (5%) receiving SB-773812 60 mg, five subjects (9%) receiving SB-773812 120 mg, and six subjects (8%) receiving olanzapine.

There was one fatal SAE, intestinal gangrene in a subject in the SB-773812 120 mg group in Part B (2%), which was considered as not related to investigational product.

All SAEs are summarised below across both parts of the study.

Serious Adverse Events	Placebo (Parts A and B) N = 90 n (%)	SB-773812 60 mg (Parts A and B) N = 95 n (%)	SB-773812 120 mg (Part B) N = 54 n (%)	Olanzapine (Parts A and B) N = 78 n (%)
Any SAE	4 (4)	4 (4)	2 (4)	5 (6)
Psychotic disorder	1 (1)	2 (2)	0	3 (4)
Schizophrenia	2 (2)	1 (1)	0	0
Delirium	1 (1)	0	0	0
Depressive symptom	0	0	0	1 (1)
Intestinal gangrene	0	0	1 (2)	0
Paraesthesia	0	0	0	1 (1)
Sciatica	0	1 (1)	0	0
Hyponatraemia	0	0	1 (2)	0

There was no evidence of SB-773812 treatment-related extrapyramidal symptoms as measured using AIMS, Barnes akathisia, and Simpson Angus scores. However, AEs of tremor and akathisia were reported at an incidence greater than placebo but similar to or slightly less than olanzapine.

An increase in mean inorganic phosphate was observed in Part B following administration of SB-773812 60 mg and 120 mg compared with placebo; this was not seen in Part A summary statistics by treatment group but an effect of SB-773812 was seen when analysed by exposure relationship in the exploratory pharmacokinetic/ pharmacodynamic analyses.

There was evidence of an increase in mean serum prolactin following SB-773812 administration compared with placebo in Parts A and B.

Both doses of SB-773812 in Part B showed a mean decrease in subject body weight compared with placebo and olanzapine. There was evidence of a decrease in serum lipids (triglycerides and cholesterol) in the placebo and SB-773812 groups in Part B compared with baseline over the treatment period, whereas increases were seen in the olanzapine group. Liver function test (alanine and aspartate aminotransferase) values ≥2 x the upper limit of the normal range were seen more frequently following olanzapine than either SB-773812 or placebo dosing.

There was no evidence of accumulation of lamellar bodies in peripheral lymphocytes examined by electron microscopy, and thus phospholipidosis.

In Part B, there was evidence of an asymptomatic decrease in mean supine systolic BP, diastolic BP and HR in the SB-773812 groups relative to placebo. Subjects in the SB-773812 60 mg and 120 mg groups showed an increase in uncorrected QT interval and a decrease in QTc(Bazett) average values at Week 6 relative to placebo. The increase in uncorrected QT interval was an expected finding, given that SB-773812 decreased mean HR. No trends were seen for other mean ECG interval values including QTc(Fridericia).

Pharmacokinetics & PK/PD: The pharmacokinetic parameters observed in this study at 2 weeks for SB-773812 were similar to those previously observed in Phase I studies at the 60 mg and 120 mg doses both as mean as well as between-subject variability.

Exploratory PK/PD analyses of Week 6 LOCF data in study NAA104606 Part B provided a significant link between SB-773812 PK levels and antipsychotic efficacy (the response increased with increasing plasma levels) on both primary endpoint (PANSS total score, P=0.0025) as well as a number of secondary endpoints (BPRS P=0.002, PANSS positive P=0.003 and PANSS General Psychopathology, P=0.001).

The split by tertile of SB-773812 exposure confirmed that the response correlated with pharmacokinetic levels: in the lower tertile (corresponding approximately to 30 mg) the separation from placebo was ~7 points, in the median tertile (corresponding approximately to 90 mg) the separation from placebo was ~12 points and in the upper tertile (corresponding approximately to 220 mg) separation from placebo was ~22 points.

Pharmacodynamics: There was no evidence of cognitive benefit of SB-773812 compared with placebo.

Health Outcomes: Analysis of Part B Week 6 DAI Total score is summarised below.

Treatment	N	n	Adjusted Mean	SE of Adjusted Mean	Difference vs. Placebo	95% CI
Placebo (Part B)	52	50	2.8	0.79		
SB-773812 60 mg (Part B)	54	54	2.5	0.77	-0.3	(-2.1, 1.5)
SB-773812 120 mg (Part B)	54	54	2.4	0.73	-0.4	(-2.2, 1.4)
Olanzapine (Part B)	57	57	4.9	0.74	2.1	(0.3, 3.8)

Analysis of Week 6 change from BL MEI-SF Total score is presented below.

Treatment	N	n	Adjusted Mean	SE of Adjusted Mean	Difference vs. Placebo	95% CI
Placebo (Part B)	52	46	4.7	3.28		
SB-773812 60 mg (Part B)	54	50	9.3	3.19	4.6	(-2.6, 11.8)
SB-773812 120 mg (Part B)	54	52	2.5	2.95	-2.2	(-9.4, 4.9)
Olanzapine (Part B)	57	56	11.9	2.92	7.2	(0.2, 14.3)

Conclusions:

- In the final analysis of Part B, SB-773812 showed anti-psychotic efficacy as measured by the PANSS rating scale for schizophrenia, at both 120 mg and 60 mg doses. Improvement at Week 6 was statistically superior to placebo at both doses, with a PANSS Total score treatment difference (95% confidence interval) of -8.8 (-16.2, -1.4) at the 60 mg dose (p=0.020) and -8.5 (15.8, -1.1) at the 120 mg dose (p=0.024).
- Week 6 PANSS Total score was lower in the olanzapine group than in the placebo group (difference -16.5; 95% confidence interval -23.8, -9.3) (p<0.001), demonstrating assay sensitivity in Part B.
- Both SB-773812 60 mg and 120 mg showed a clinically and statistically meaningful effect on most secondary efficacy measures (PANSS Positive and General Psychopathology subscale scores, CGI-S, BPRS Total and BPRS Psychosis scores) at Week 6 in Part B.
- Part A interim efficacy analyses showed a smaller effect of olanzapine than expected (a non-clinically relevant effect), and Part A was considered a failed study.
- SB-773812 was generally well tolerated over the 6- or 12-week treatment period.
- There was one fatal SAE, intestinal gangrene in a subject in the SB-773812 120 mg group in Part B, which was considered as not related to investigational product.
- Non-fatal SAEs were reported in 14 subjects across the study, four following placebo dosing, four with SB-773812 60 mg, one with SB-773812 120 mg, and five subjects following olanzapine administration.
- There was no indication of EPS associated with SB-773812 treatment as measured by specific scales. However, AEs of tremor and akathisia were reported at an incidence greater than placebo but similar to or slightly less than olanzapine.

- A favourable metabolic profile for SB-773812 over 6 weeks of treatment was demonstrated. There were slight reductions in body weight, decreases in triglycerides compared with olanzapine, decreases in total and LDL cholesterol compared with placebo and olanzapine, and no effects on HDL cholesterol or fasting glucose. Additionally, an earlier patient study (SB-773812/003) revealed no changes in fasting insulin (not measured in study NAA104606).
- SB-773812 appeared to cause a treatment- but not dose-related decrease in heart rate and blood pressure compared with placebo and olanzapine. This decrease was seen across all measurements (standing and supine systolic and diastolic blood pressure and heart rate). The findings were not associated with any patient-reported AEs. When compared with baseline values, subjects who had the highest baseline values showed the largest decreases.
- As expected, SB-773812 caused a dose-related increase in prolactin. SB-773812 60 mg was similar to olanzapine and towards the upper limit of normal (which was 18 ng/mL). The increases in the SB-773812 120 mg group were more marked than at 60 mg but were not associated with AEs. Mean concentration after 6 weeks' treatment at SB-773812 120 mg was 30 ng/mL.
- The pharmacokinetic parameters observed in this study at 2 weeks for SB-773812 were similar to those previously observed in Phase I studies at the 60 mg and 120 mg doses both for mean as well as between-subject variability. Likewise, the SB-773812 60 mg dose groups had similar mean pharmacokinetic parameters in the two study parts.
- Exploratory pharmacokinetic/pharmacodynamic analyses of Week 6 data in Part B provided a significant link between SB-773812 pharmacokinetic levels and antipsychotic efficacy (the response increased with increasing plasma levels) on the primary endpoint (PANSS Total score, p=0.0025) as well as a number of secondary endpoints (BPRS p=0.002, PANSS Positive p=0.003 and PANSS General Psychopathology, p=0.001).

Date of Report: June 2008.