The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: AXO110461

Title : A single-blinded, randomized, placebo-controlled, staggered-parallel, escalating single dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of orally administered SB756050 in healthy volunteers and in subjects with Type 2 Diabetes Mellitus.

Rationale: This study represented the first administration of SB-756050 in humans to establish initial safety, tolerability, PK and effects on PD markers of single escalating doses.
Two formulation types of SB-756050 were used in this study: an immediate-release (IR) capsule formulation and a modified-release (MR) capsule formulation.

Phase: I

Study Period: 16 November 2007 – 17 March 2008

Study Design: Single-blinded, randomized, placebo-controlled, staggered-parallel, escalating single dose study.

Centres: One center in the United States

Indication: None

Treatment: Two formulations of SB-756050: IR capsules and MR capsules, and matching placebo were supplied for use in this study. Doses of study drug were determined prior to each dose escalation based on ongoing review of PK, PD and safety data. The dosing schedule for the SB-756050 capsules is presented below:

Cohort	Dose #	Formulation – Capsules	SB-756050 Dose
A1	1	Immediate Release	5 mg (1x5 mg)
	2		15 mg (3x5 mg)
	3		50 mg (2x25 mg)
	4		100 mg (4x25 mg)
A2	1	Immediate Release	100 mg (1x100 mg)
	2		200 mg (2x100 mg)
	3		400 mg (4x100mg)
	4		800 mg (8x100mg)
A3	1	Modified Release	200 mg (2x100 mg)
	2	Immediate Release – Fed	200 mg (2x100 mg)
	3	Immediate Release	200 mg (2x100 mg)
	4	Modified Release - Fed	200 mg (2x100 mg)

Objectives: The primary objectives of this study were:

- To investigate the safety and tolerability of single ascending oral doses of SB-756050.
- To determine the pharmacokinetic (PK) parameters of oral doses of SB-756050, and to compare these parameters between immediate-release and modified-release capsule formulations.

Statistical Methods:
The Safety Population included all enrolled subjects who received at least one dose of study drug. The PK Population included all subjects from the Safety Population who had plasma SB756050 PK parameter estimates.
No formal power/sample size calculations were performed. The sample size for each cohort was based on feasibility.

Study Population: Healthy male subjects aged ≥18 years and ≤60 years who had a BMI with the range of 20 – 30 kg/m2. Healthy subjects were defined as individuals who were free from clinically significant illness or disease as determined by a responsible physician, with no clinically significant abnormality identified on medical or laboratory evaluation. The study was designed to enroll both healthy volunteers and subjects with Type 2 Diabetes Mellitus, but only healthy subjects were enrolled.

Number of Subjects:	Cohort A1	Cohort A2	Cohort A3
Planned, N	12 per cohort	12 per cohort	12 per cohort
Dosed, N	12	12	12
Completed, n (%)	11 (92)	11 (92)	12 (100)
Total Number Subjects Withdrawn, n (%)	1 (8)	1 (8)	0

Withdrawn Due to Adverse Events, n (%)	0	0	0
Withdrawn Due to Lack of Efficacy, n (%)	0	0	0
Withdrawn for Other Reasons, n (%)	1 (8)	1 (8)	0
Demographics			
N (Safety)	12	12	12
Females: Males	0:12	0:12	0:12
Mean Age in Years (SD)	28.0 (9.2)	32.6 (14.4)	23.8 (5.12)
Mean Weight in Kg (SD)	84.3 (12.2)	75.2 (6.52)	81.0 (12.7)
White, n (%)	10 (83)	10 (83)	11 (92)

Pharmacokinetics (PK) Endpoints:

Summary of Selected Plasma SB756050 Pharmacokinetic Parameters Following Single Dose Administration, geometric mean (CV%)

Treatment	n	AUC(0-t) (ng·hr/mL)	AUC(0-∞) (ng·hr/mL)	Cmax (ng/mL)	tmax (hr)2	t1/2 (hr)	tlag (hr) 2	CL/F (L/hr)	V/F (L)
5 mg IR	9	49.5 (70.0)	51.2 (69.8)	20.5 (50.8)	1.00 (0.50-1.50)	1.36 (49.1)	0.00 (0.00-0.25)	97.6 (69.8)	191 (32.0)
15 mg IR	9	188 (56.8)	194 (57.0)	51.5 (42.6)	1.50 (0.50-2.00)	2.93 (54.9)	0.00 (0.00-0.25)	77.4 (57.0)	327 (63.4)
50 mg IR	9	571 (34.0)	778[2] (57.0)	74.2 (36.9)	1.50 (1.00-4.00)	7.08[2] (0.20)	0.00 (0.00-0.25)	64.2[3] (57.0)	656[2] (57.2)
100 mg IR (4 x 25mg)	8	1098 (42.1)	1077[3] (50.9)	162 (30.2)	1.00 (1.00-2.00)	5.73[3] (27.5)	0.00 (0.00-0.25)	92.8[3] (50.9)	767[3] (37.5)
100 mg IR (1 x 100mg)	9	1062 (34.3)	2459[4]	144 (27.3)	1.50 (0.50-3.00)	8.05[4]	0.25 (0.00-0.50)	40.7[4]	472[4]
200 mg IR	9	1109 (27.9)	1452[4]	159 (33.8)	1.50 (0.50-4.00)	7.02[4]	0.25 (0.00-0.50)	138[4]	1395[4]
400 mg IR	9	1278 (28.9)	ND	204 (29.9)	1.50 (1.00-2.00)	ND	0.00 (0.00-0.25)	ND	ND
800 mg IR	8	1747 (36.7)	3475[4]	328 (41.4)	1.50 (1.00-2.00)	11.8[4]	0.00 (0.00-0.25)	230[4]	3932[4]
200 mg MR	9	1207 (45.4)	1781[4]	62.3 (67.3)	4.00 (2.00-5.00)	18.8[4]	0.25 (0.00-1.00)	112[4]	3050[4]
200 mg IR Fed	9	2272 (25.6)	2553[5] (10.5)	233 (24.4)	4.00 (2.00-4.00)	14.0[5] (55.8)	0.25 (0.00-0.50)	78.3[5] (10.5)	1587[5] (59.8)
200 mg IR	8	2069 (44.8)	2938[2] (45.0)	189 (45.2)	1.54 (1.00-4.00)	15.6[4] (4.92)	0.00 (0.00-0.25)	68.1[2] (45.0)	1532[2] (39.5)
200 mg MR Fed	9	1881 (28.7)	2073[6] (9.79)	102 (33.1)	12.00 (6.00-16.0)	10.5[6] (44.6)	0.50 (0.25-2.00)	96.5[6] (9.79)	1461[6] (56.0)

1. median (range)
2. n=2;
3. n=4;
4. n=1;
5. n=6;
6. n=3

Pharmacodynamic (PD) Endpoints

The analysis of covariance (ANCOVA) showed that there were no significant treatment effects for any of the PD parameters.

Safety results: The time period for the collection and recording of AEs and SAEs into the CRF began with receipt of the first dose of investigational product and continued until the post-treatment follow-up visit. Adverse events reported in 2 or more subjects are reported in the table below.

		SB756050			
	Placebo	5 mg IR	15 mg IR	50 mg IR	100 mg IR
	N=12	N=9	N=9	N=9	N=8
Adverse Events – Cohort 1:	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with Any Event, n (%)	1 (8)	2 (22)	1 (11)	3 (33)	0
Headache	1 (8)	0	0	2 (22)	0

		SB756050			
	Placebo	100 mg IR	200 mg IR	400 mg IR	800 mg IR
	N=12	N=9	N=9	N=9	N=8
Adverse Events – Cohort 2:	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with Any Event, n (%)	3 (25)	0	1 (11)	7 (78)	1 (13)
Rash	1 (8)	0	0	6 (67)	0
Pruritus	1 (8)	0	0	3 (33)	0
Ecchymosis	0	0	0	2 (22)	0

		SB756050			
	Placebo	200 mg MR	200 mg IR - Fed	200 mg IR	200 mg MR - Fed
	N=12	N=9	N=9	N=9	N=8
Adverse Events – Cohort 1:	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with Any Event, n (%)	1 (8)	3 (33)	3 (33)	2 (25)	1 (11)

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: None

Publications: None at the time of this summary.