Synopsis

Identifier: HM2007/00025/00 **Study Number:** SB-705498/008

Title: A single blind, placebo controlled, multi-centre study to investigate the pharmacokinetics, safety, tolerability and pharmacodynamics of the TRPV1 antagonist SB-705498 against the pain of acute migraine

Investigators: Dr [redacted] Dr [redacted] Dr [redacted] Dr [redacted]

Study centers: [redacted]
UK; [redacted]
Canada; [redacted] Australia; and, [redacted] The Netherlands.

Publications: None at the time of this report.

Study period: 9 Jan 2006 - 22 Aug 2006.

Phase of development: II

Objectives: The **primary objective** was to assess the efficacy of SB-705498 in treating moderate-severe migraine headache.

Secondary objectives were:

- To investigate the safety and tolerability of single 400 mg and 800 mg doses of SB-705498 during a migraine attack.
- To investigate the pharmacokinetics of SB-705498 during a migraine attack.
- To explore the pharmacokinetic/pharmacodynamic (PK / PD) relationship for SB-705498 in a migraine attack.

Endpoints: The **primary endpoint** was the percentage of subjects who were pain-free at 2 h post-dose (e.g., had moderate to severe pain at baseline and no pain at 2 h post-dose)

Secondary endpoints were:

- Percentage of subjects pain-free at 30 min, 1 h, 3 h, 4 h, 5 h and 6 h.
- Percentage of subjects sustained pain-free (e.g., pain-free at 2 h and no return of headache pain and no use of additional migraine medications within 24 h post-dose).
- Percentage of subjects with headache relief at 30 min, 1 h, 2 h, 3 h, 4 h, 5 h and 6 h (e.g., had moderate to severe pain at baseline and mild pain or no pain at the post-dose time point).
- Sustained relief (headache relief at 2 h followed by no return of moderate or severe pain and no use of additional migraine medication within 2 to 24 h post-dose).

- Percentage of subjects experiencing associated symptoms: nausea, vomiting, photophobia and phonophobia at 30 min, 1 h, 2 h, 3 h, 4 h, 5 h and 6 h.
- Percentage of subjects migraine-free at 30 min, 1 h, 2 h, 3 h, 4 h, 5 h and 6 h (e.g., pain-free with no photophobia, phonophobia, nausea or vomiting).
- Time to pain-free.
- Time to headache relief.
- Percentage of subjects who used additional migraine medication within 24 h after treatment.
- Pharmacokinetic parameters for SB-705498, based on limited sampling, Cmax, tmax, AUC(0-2), AUC(0-4) and AUC(0-t).
- Safety Endpoints:
    - Adverse events (AEs),
    - Vital signs (blood pressure and heart rate),
    - 12-Lead electrocardiogram (ECG),
    - Continuous ECG monitoring,
    - Safety laboratory tests (haematology, clinical biochemistry, steroid hormones, urinalysis, pregnancy test).
- Heat pain thresholds on periorbital skin pre-dose and at approximately 2 h 30 min post-dose.

Methodology: This was a randomised, single-blind, placebo-controlled, multiple centre, 2-way crossover design in which migraine subjects attended a clinical pharmacology unit during a migraine attack, for supervised administration of a single dose of SB-705498 or placebo. Subjects and the investigational sites were blinded to treatment allocation but the sponsor study team were unblinded for ongoing review of safety data and the 2h headache response data. In addition to the blinded review of subject's cardiovascular safety data by the investigator, the ECG data were subjected to additional review on an ongoing basis by the medical monitor who was unblinded to the study medication. After 12 subjects had been dosed on 400 mg, the protocol included a review of all safety data after which, if supported, a dose of 800 mg was included for the remainder of the study. Dosing continued on 400 mg during the review period. Following the review, in accordance with the protocol, the 400 mg dose was increased to 800 mg. In addition, the protocol included that if 2 h post-dose headache pain severity data suggested a positive treatment effect at 800 mg, the study may have been extended so that 42 subjects completed the study at the 800 mg dose level to allow a fully powered comparison

Subjects were asked to attend the unit the next time that they believed a migraine attack was imminent, they were then dosed once the migraine head pain had reached moderate to severe intensity. If a subject did not treat an attack within 8 weeks of enrolment they were able to be re-screened to reconfirm eligibility and were then given a further 8 weeks to treat the first attack. If after this second 8 week period they had still not treated a migraine, they were considered to have withdrawn from the study. Subjects were

requested not to take rescue medication until 2 h post-dose. Use of triptans was excluded from the study. Subjects were required to remain in the unit until 6 h post-dose, and were then allowed to leave the unit at the investigator's discretion. Diary cards were used to monitor study parameters between 6 h and 24 h post-dose. There was at least 2 weeks washout between dosing sessions. After completion of both treatment sessions, or early withdrawal, subjects attended a safety follow up visit. No formal interim analysis was planned for this study, however in accordance with the protocol the cardiovascular data and headache pain severity 2 hours post dose were reviewed on an ongoing basis. When it became clear that measures of efficacy were numerically worse for the drug treatment group relative to the placebo treatment group, the study was suspended whilst available efficacy data was collected from all sites and analysed for the primary efficacy endpoint and important secondary efficacy endpoints. Having conducted an analysis it was concluded that it was not reasonable to continue the study and the study was immediately terminated in accordance with the protocol.

On each SB-705498 dosing occasion, blood samples for the determination of SB-705498 concentrations were taken pre-dose and up to 6 h post-dose.

Number of subjects: A sufficient number of subjects were planned to be enrolled to ensure that at least 42 migraineurs completed the study, i.e. two treated migraine attacks, and provide efficacy evaluations in both treatment periods. Fifty-one subjects were randomised (25 to receive placebo in Period 1 and 26 to receive SB-705498 in Period 1) and 27 subjects completed the study as planned (i.e. treated two migraine attacks and provided efficacy evaluations in both treatment periods). The disposition of the enrolled subjects is summarised below:

Number of Subjects	Placebo	SB-705498	Total
Planned, N	42	42	42
Randomized in Period 1, N	25	26	51
Entered Period 2 (from alternative treatment group in Period 1 above, as indicated by the arrows), N	13	15	28
Received at least one dose of treatment, N[a]	38	41	51
Total Withdrawn (any reason), n (%)	10 (26)	14 (34)	24 (47)
Withdrawn due to Adverse Events, n (%)	0	1 (2)	1 (2)
Withdrawn due to subject's decision, n (%)	0	1 (2)	1 (2)
Withdrawn due to 24-hour Holter findings, n (%)	1 (3)	0	1 (2)
Withdrawn due to Sponsor termination of the study, n (%)	9 (24)	12 (29)	21 (41)
Completed two periods of treatment, N[b]	27	27	27

a. Intent-to-treat (ITT) population
b. Per protocol (PP) population

Fifty-one subjects were randomised into the study, of these 38 were dosed with placebo and 41 were dosed with SB-705498. Of the 25 subjects who received placebo in Period 1, 15 went on to receive SB-705498 in Period 2. [redacted]

Of the 26 subjects who received SB-705498 in Period 1, 13 went on to receive placebo in Period 2. Of the 13 subjects withdrawn after SB-705498 in Period 1, 11 were withdrawn

due to the sponsor terminating the study, one subject was withdrawn at the subject's own request and one subject was withdrawn due to an AE of mild non-sustained ventricular tachycardia (VT). The VT consisted of a run of three ventricular ectopic beats occurring approximately 1 h 58 min after dosing, with a rate of 100 bpm. The subject was asymptomatic. This event was considered by the investigator to be related to study medication.

One additional subject was identified as having been withdrawn from the study due to the sponsor terminating the study, however the subject completed the 24h efficacy assessments in period 2 (SB-705498) and the follow-up visit and therefore appears not to have been withdrawn.

Overall, therefore, 51 subjects received at least one dose of study medication (intent-to-treat (ITT) population) and 27 subjects completed the study (per protocol (PP) population).

Diagnosis and main criteria for inclusion: Female or male subjects aged 18 to 65 years, inclusive, who were otherwise healthy but were suffering from moderate to severe migraine headache, with or without aura, were enrolled. The subjects had to have at least a 1 year history of migraine and an age of onset less than 50 years as well as one to six migraine attacks per month for at least the last 3 months, which had at least 48 h free of headache between migraine attacks.

Treatment administration: SB-705498 was supplied by GlaxoSmithKline, Harlow as white, round convex tablets containing 100 mg active dose (batch numbers 051111155, 051111158, 051113781 and 061115214) with matching placebo (batch numbers 051111163, 051113776 and 061115215). Each SB-705498 dose or placebo dose was achieved using either 4 x 100 mg tablets plus 4 placebo tablets for the 400 mg dose, or 8 x 100 mg tablets, or 8 placebo tablets, as appropriate. Each dose was achieved using eight tablets in order to maintain the study blind.

Criteria for evaluation: The primary comparison of interest was the percentage of subjects treated with SB-705498 (both 400 mg and 800 mg doses grouped together) achieving pain-free at 2 h post-dose, versus those treated with placebo. A significance level of 0.05 was used for the comparison. The intent-to-treat (ITT) population was the primary population of interest, and the analysis was carried out on the last-observation-carried-forward data set.

Statistical methods: The primary null hypothesis of no difference in migraine pain-free (Grade 2 or 3 reduced to Grade 0) at 2 h post-dose, between subjects treated with placebo and subjects treated with SB-705498, was to be tested using the generalized estimating equations (GEE) approach for the analysis of repeated measurements, with adjustment for period effects.

In addition, comparisons of SB-705498 and placebo were planned for each secondary endpoint. The proportion of subjects who achieved pain-free, headache relief, migraine-free, and presence of associated symptoms at each time point (0.5, 1, 2, 3, 4, 5, 6, and 24 h post-dose), proportion of subjects taking rescue medication, and the proportions of subjects achieving sustained pain-free and sustained headache relief from 2 to 24 h were

to be analyzed using generalized estimating equations (GEE) adjusted for period effects. The proportion of subjects experiencing return of migraine headache pain and recurrence of headache pain were summarized. Migraine pain-free at 2 h also was summarized by age group, gender, race, baseline pain severity, and presence of aura.

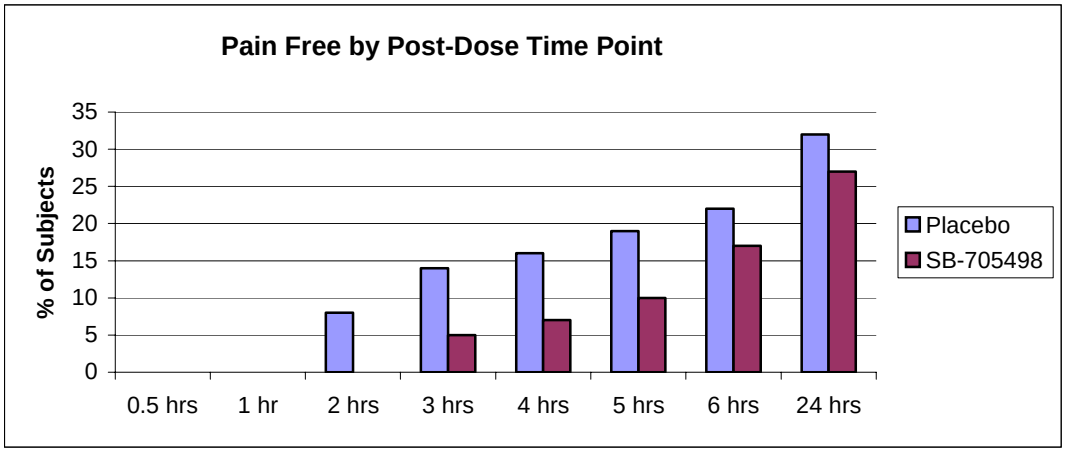
Descriptive summaries of AE rates and clinical laboratory, ECG and vital signs data were generated to evaluate the safety of SB-705498 compared to placebo.

Summary: The demographic data for the 51 subjects randomised in this study are summarised in the following table:

		Placebo/ SB-705498 (N = 25)	SB-705498/ Placebo (N = 26)	Total (N = 51)
Sex, n (%)	Males	3 (12)	5 (19)	8 (16)
	Females	22 (88)	21 (81)	43 (84)
Age, years	Mean	33.8	36.5	35.2
	SD	9.15	10.38	9.79
Height, cm	Mean	167.5	164.2	165.8
	SD	8.99	9.91	9.52
Weight, kg	Mean	73.91	67.98	70.89
	SD	16.48	17.28	16.99
Body Mass Index, kg/m^2	Mean	26.64	24.85	25.73
	SD	6.14	4.20	5.27
Race, n (%)	African American/African Heritage	2 (8)	5 (19)	7 (14)
	Asian – Central/South Asian Heritage	2 (8)	0	2 (4)
	Asian –South East Asian Heritage	0	1 (4)	1 (2)
	White – White/Caucasian/European Heritage	20 (80)	17 (65)	37 (73)
	White – Arabic/North African Heritage	0	1 (4)	1 (2)
	White – Mixed Race	1 (4)	0	1 (2)
	Mixed Race	0	2 (8)	2 (4)
Ethnicity, n (%)	Hispanic or Latino	0	3 (12)	3 (6)
	Not Hispanic or Latino	25 (100)	23 (88)	48 (94)

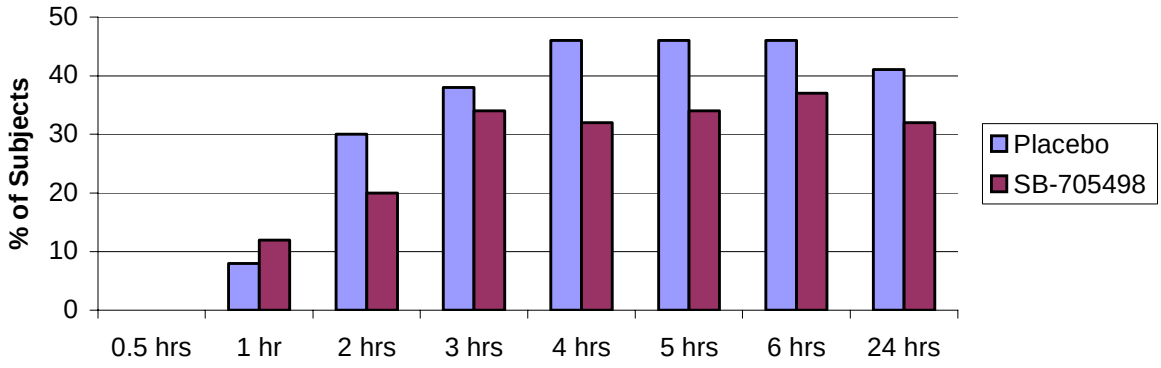
Efficacy: The majority of treated migraine attacks were without aura (76% SB-705498; 73% placebo) and were treated after > 4 h since pain onset (73% SB-705498; 74% placebo). The distribution of time between migraine pain onset and study drug administration was very similar across treatment groups. Approximately 73% (71% SB-705498; 76% placebo) of the treated attacks were moderate at baseline and 25% (24% SB-70598; 26% placebo) of the treated attacks were severe at baseline. One subject treated an attack with placebo while baseline pain was mild, this subject was excluded from the analysis of the pain endpoints as this subject did not meet the definition to be evaluated.

Pain-free rates for the ITT population at all post-dose time points are graphically displayed below:



Pain-free was not achieved by any subject at 0.5 h, 1 h, or 2 h post-dose for attacks treated with SB-705498, therefore, GEE analysis of the primary endpoint, pain-free at 2 h, could not be carried out. Three subjects on placebo (8%), however, were pain-free at 2 h post-dose. There were no significant differences between placebo and SB-705498 in the proportions of subjects pain-free at time points from 3 h to 24 h post-dose. Results were similar for the PP population.

Headache relief rates for the ITT population at all post-dose time points are graphically displayed below:



Headache relief was not achieved by any subject at 0.5 h post-dose, for migraine attacks treated with SB-705498 or placebo. In addition, there were no significant differences between placebo and SB-705498 in the proportion of subjects with headache relief at time points between1 h and 24 h post-dose in the ITT population. In the PP population, however, there were statistically significant differences between the proportion of subjects treated with placebo and SB-705498 who had pain relief at 2 h, 5 h and 6 h post-dose (at the 5% level) and at 4 h post-dose (at the 1% level, $p = 0.005$). All of these

differences showed SB-705498 to be inferior to placebo for the endpoint of headache relief following a migraine headache.

The proportion of subjects with sustained pain-free for placebo vs. SB-705498 could not be analysed since sustained pain-free was not achieved for any of the SB-705498 treated attacks. There was no significant difference in sustained headache relief between placebo (14%) and SB-705498 (7%). Headache recurrence occurred at a rate of 45% in placebo treated attacks and at a rate of 25% in SB-705498 treated attacks.

There were no statistically significant differences between placebo and SB-705498 in the incidence of nausea at any post-dose time point. There were statistically significant differences between placebo and SB-705498 in the incidence of photophobia at 3 h and 4 h post-dose and phonophobia at 2 h, 3 h and 4 h post-dose. In all cases, placebo-treated attacks had a significantly lower rate of these symptoms than the SB-705498 treated attacks.

In 61% of placebo-treated attacks, the subject took rescue medication within 24 h of study drug, compared to 68% of SB-705498-treated attacks. The mean time to rescue medication was approximately 4.5 h for attacks treated by both placebo and SB-705498.

Safety:

Adverse event (preferred term)	Treatment period, Number of Subjects (%)	
	Placebo (N = 38)	SB-705498 (N = 41)
Any event	23 (61)	25 (61)
Any AE related to Investigational Product	7 (18)	7 (17)
Most Common AEs: (≥ 5% in any treatment group):		
Headache	8 (21)	9 (22)
Migraine	5 (13)	5 (12)
Abdominal pain upper	1 (3)	4 (10)
Electrocardiogram QT corrected interval prolonged	2 (5)	3 (7)
Nasopharyngitis	2 (5)	2 (5)
Rash	2 (5)	2 (5)
Dizziness	1 (3)	2 (5)
Vomiting	1 (3)	2 (5)
Nausea	5 (13)	1 (2)
Diarrhoea	2 (5)	1 (2)
Dysmenorrhoea	2 (5)	1 (2)
Pharyngolaryngeal pain	3 (8)	0
Application site rash	2 (5)	0
Pruritus	2 (5)	0

There were no SAEs. The same proportion of subjects (61%) reported AEs after treatment with SB-705498 (400 mg or 800 mg) as on placebo. The reporting frequencies for headache and migraine were similar in the two treatment groups. The pattern of AEs was similar between the active and placebo treatment sessions, except that upper abdominal pain was reported by more subjects on SB-705498 (10%) than on placebo (3%), but nausea was reported by more subjects on placebo (13%) than on SB-705498 (2%). Pharyngolaryngeal pain, pruritus and application site rash were only reported by

subjects following dosing with placebo. All AEs were rated as mild or moderate (119 AEs, 92%) apart from 11 AEs (8%) that were rated as severe. Ten severe AEs were reported by five subjects on placebo (13%). The remaining one AE was an episode of migraine which was experienced 11 days after the administration of SB-705498. None of the severe AEs was considered to be related to study medication.

Four subjects had cardiovascular (ECG, Holter or Continuous Lead II monitoring) abnormalities that were reported by the investigator as AEs. In one subject, an abnormality was only seen after dosing with placebo. In two subjects abnormalities were seen only after dosing with SB-705498, although one of these subjects did not complete the placebo session. In the final subject, abnormalities were seen after both the active and placebo doses. The cardiovascular AEs were:

- [redacted]
- [redacted]
- [redacted]
- Subject 100620 (a 31-year-old female with BMI 32.4 kg/m^2) had QTc prolongation at 2 h (463 msec) and 4 h (458 msec) post-dose in Period 1 (SB-705498 400 mg) which did not meet the criteria for PCC (> 470 msec for females) but were considered by the investigator to be clinically significant. In addition, this subject had non-conducted P-waves and second degree atrioventricular block on the 0 – 6 h Holter recording taken during Period 1 (SB-705498 400 mg). No abnormalities were reported during Period 2 (placebo).

In addition, four other subjects had ECG parameters which met the criteria for PCC. However, one of these was in the screening phase at the time and one was pre-dose in Period 1. For the other two subjects, the same ECG abnormality of PCC was recorded at the same time post-dose on both SB-705498 and placebo treatment. There were no other clinically significant safety findings.

Pharmacokinetics: Following single oral administration of 400 mg and 800 mg SB-705498 in subjects experiencing acute migraine, concentrations of SB-705498 were observed in the first post-dose pharmacokinetic sample, 1 h after dosing, with peak concentrations observed between 1 h and 6 h post-dose at both dose levels. Systemic exposure to SB-705498 at a dose of 800 mg was less than proportionally higher than seen for the 400 mg dose, with Cmax and AUC(0-6) increasing, on average, by approximately 14% and 25%, respectively, when the SB-705498 dose was doubled. The pharmacokinetics of SB-705498 were highly variable, with between-subject variability for Cmax and AUC(0-2) ranging from 56% to 198%.

Pharmacodynamics: The mean heat pain threshold on SB-705498 was numerically greater than that of placebo. The difference was not statistically significant, but the study was not powered on this endpoint.

Conclusions:

- The primary endpoint, pain-free at 2 h post-dose, was not achieved by any subject following treatment with SB-705498.
- There were no statistically or clinically significant differences between placebo and SB-705498 in the proportion of subjects pain-free at time points from 3 h to 24 h post-dose
- On a number of secondary endpoints, headache relief, photo-and phono-phobia, placebo was more effective than SB-705498
- No SAEs or fatalities were reported. SB-705498 was well tolerated, the same proportion of subjects (61%) reported AEs after treatment with SB-705498 (400 mg or 800 mg) as on placebo.
- The post-dose ECG changes were similar between placebo and SB-705498 treatments, consistent with known changes in ECG characteristics during a migraine attack in the literature.
- Peak plasma SB-705498 concentrations were observed between 1 h and 6 h post-dose. SB-705498 Cmax and AUC(0-6) increased, on average, approximately 14% and 25%, respectively, with a doubling of the SB-705498 dose from 400 mg to 800 mg.
- There was no trend for increased pain relief at 2 h with higher AUC(0-2) values for SB-705498.
- The mean heat pain threshold on SB-705498 was numerically greater than that of placebo, although the difference was not statistically significant.

Date of Report: June 2007