Synopsis

Identifier: HM2007/00627/00 **Study Number:** VRA107438

Title: A double-blind, randomised, placebo controlled, single dose, two-period crossover study to investigate the therapeutic potential of the TRPV1 antagonist SB-705498 in treatment of subjects with rectal hypersensitivity including irritable bowel syndrome.

Investigator: Professor [redacted]

Study centre: [redacted]

Publication: None at the time of this report.

Study period:

Initiation Date:	26 Jan 2007
Completion Date:	18 Sept 2007
Early Termination Date:	18 Sept 2007

Phase of development: IIa

Objectives: The primary objective of this study was to investigate the effects of a single dose of SB-705498 on rectal pain thresholds and ongoing pain in patients with rectal hypersensitivity and irritable bowel syndrome (IBS). The secondary objective was to further investigate efficacy and improvements in symptoms and quality of life.

Methodology: This was a double-blind, placebo-controlled, two-way crossover study. A sufficient number of patients were to be enrolled into this trial to obtain 21 evaluable IBS patients.

There were to be four study visits. Subjects attended a screening visit (Visit 1) to assess their eligibility for the study. Subjects who were eligible were then randomised to one of two treatment sequences, AB or BA, where A is SB705498 and B is placebo. Study medication was to be administered at visits 2 and 3.

Subjects were dosed in the unit and pain thresholds to rectal distension and thermal stimulation were measured pre- and post-dose. On-going rectal pain, faecal urgency and frequency were also assessed pre-dose and post-dose. Safety measurements were undertaken. Subjects stayed in the hospital for 6 h post-dose. On completion of the study procedures, subjects were discharged if the attending physician was satisfied with their medical condition. The two treatment sessions were to be between 21 to 28 days apart to allow sufficient wash-out of study medication. A follow-up visit (Visit 4) took place 14-28 days after Visit 3.

The dose of SB-705498 was 800 mg, which was the highest single dose used in other Phase IIa clinical trials at the time of the conduct of this study. Safety review was on-going for all subjects throughout the study. The GlaxoSmithKline Medical Monitor reviewed the electrocardiogram (ECG) data as they became available during the study.

Number of subjects: A sufficient number of subjects with IBS were planned to be recruited such that at least 21 evaluable patients were available for analysis. Only one subject was successfully recruited to the study but, due to a protocol violation of a positive drugs of abuse test result, this subject was withdrawn. The subject was randomized to sequence BA. She received placebo in the first treatment period but was withdrawn before any further investigational products were given. Due to difficulties with recruitment, the study was terminated.

Demographics: The demographic characteristics of the subject in this study are presented in the Table below.

Demographics	Total (N = 1)
Age in Years	21
Sex, n (%)	
Female:	1 (100)
Male:	0
Body Mass Index, kg/m^2	29.38
Height, cm	150
Weight, kg	66.1
Ethnicity, n (%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	1 (100)
Race, n (%)	
White – White/Caucasian/European Heritage	1 (100)

Diagnosis and main criteria for inclusion: Subjects were included in the study if they were female or male subjects aged 18 to 65 who had IBS as defined by Rome II criteria [Drossman, 2000] and rectal hyperalgesia as defined by [Chan, 2003] and determined using the protocol outline in barostat study [Akbar, 2007].

Subjects were to be excluded from the study if they had other gastrointestinal or pain conditions that in the opinion of Investigator may interfere with study procedures or confound data interpretation, a history of alcohol, substance or drug abuse within the last year and any clinical or biological abnormality found at screening (other than those related to the disease under investigation) which, in the opinion of the investigator, was clinically significant [e.g., major depression (within the past 3 months)].

Treatment administration: The treatment sequences for study visits 2 and 3 were AB or BA, where:

A – SB705498 800 mg (Provided as SB705498 100 mg: batch number 061121225).

B – Placebo (batch number 031008152).

Subjects were assigned to study treatment in accordance with the randomisation schedule, generated in advance of the study by Clinical Pharmacology Statistics and Programming, using RandAll, an in-house validated computer system.

Criteria for evaluation:

Primary Efficacy Endpoints: Visual analogue scale pain score to rectal distensions (at 12, 24, 36 and 48 mmHg above baseline operating pressure threshold) pre-dose and 6 h post-dose.

Secondary Efficacy Endpoints:

- Visual analogue scale scores to rectal distensions for gas, urgency and discomfort (at 12, 24, 36 and 48 mmHg above threshold) pre-dose and 6 h post-dose.
- Rectal sensory thresholds to **thermal stimulation** (contact heat device, values reported as in study by [Chan, 2003]) assessed pre-dose and 6 h post-dose.
- Ongoing rectal pain intensity (11-point numeric rating scale (NRS), where 0=Unnoticeable/No Pain, 10=Unbearable/Worst Pain Imaginable:

a. Average of daily scores over 1 week pre-dose and 1 week post-dose.

b. Single measurements pre-dose and at hourly intervals within 6 h post-dose.

- Peak Pain Intensity Difference (PPID6), as derived from maximum pain intensity (NRS) difference from baseline (single measurement) recorded over 0–6 h (see Pain Intensity Assessments).
- Summary of Pain Intensity Difference (SPID6), as derived from pain intensity (NRS) difference from baseline (single measurement) recorded over 0–6 h (see Pain Intensity Assessments).
- Somatic heat pain thresholds (hand and foot) assessed pre-dose and 6 h post-dose.
- Contact heat-evoked potentials (CHEPs) – optional, assessed pre-dose and 6 h post-dose.
- Frequency of defecation over 24 h and over 1 week following a dose of SB-705498 (monitored using Bristol Stool Scoring Diary kept 1 week pre- and 1 week post-dose).
- Irritable bowel syndrome symptom severity score calculated over approximately 10 days pre- and post-dose.

Safety Endpoints: The safety and tolerability of SB-705498 were assessed by monitoring subjects for changes in 12-lead ECG, 24 h Holter, vital signs, biochemistry, haematology, urinalysis, plasma and serum hormone levels as well as recording reported adverse events.

Pharmacokinetic/Pharmacodynamic Endpoints: The relationship between measures of exposure to SB-705498 and efficacy and safety outcomes may have been investigated where appropriate, with the potential to use the following endpoints as required or as supported by study data:

- Plasma concentrations and other pharmacokinetic parameters for SB-705498, based on serial sampling (Maximum observed concentration (Cmax), time of occurrence of Cmax, area under concentration-time curve).
- Expression of Transient Receptor Potential Vanilloid 1 (TRPV1) and exploratory biomarkers of rectal hypersensitivity in rectal biopsies

Statistical methods: Due to the early termination of this study, no formal statistical analysis was performed. Following database release, Excel .csv data listings directly from the inform eCRF system were provided.

Summary:

Safety: The recruited subject had a serious adverse event (SAE) of abdominal (iliac fossa) pain 19 days after dosing with placebo. The subject was hospitalised for one day for additional tests and surgical examination. The ultra-sound scan and pregnancy test were negative and there were no results reported for the unspecified blood tests. The surgical team advised that there was no acute surgical reason for the pain. The SAE was moderate in intensity and resolved after approximately 10 days. The subject received oral co-codamol (paracetamol 500 mg plus codeine phosphate 30 mg) as required for approximately 4 days to treat the SAE. The SAE was not judged related to the investigational product by the Investigator and did not lead to subject withdrawal.

No clinically significant abnormalities were detected in vital signs, Holter ECG or 12-lead ECG measurements. No clinically significant laboratory values were reported.

The subject was withdrawn from the study due to a protocol violation of a positive drugs of abuse test result, in which she tested positive for cocaine. She was tested positive at screening on [redacted] but the Investigator considered that this was not drug abuse because she was not a habitual user of cocaine. She was accepted into the study after her repeat screening test for drugs of abuse on [redacted] was negative. Her pre-dose drugs of abuse test on [redacted] was positive and she was dosed with placebo the following day. She completed one treatment period which was placebo. GlaxoSmithKline were notified of the positive drugs of abuse test result during routine clinical monitoring. After discussion between the GlaxoSmithKline study team and the Investigator the subject was withdrawn because this subject's intermittent use of cocaine could interfere with the efficacy endpoints.

Concomitant medications: The subject received co-fluampicil and penicillin V to treat paronychia in the left big toe. Co-fluampicil (250 mg) was taken 2 days before the screening took place and was an on-going treatment. Penicillin V (250 mg) was taken for a total of 6 days starting 3 days before dosing with placebo. The subject also received co-codamol (see above).

Pharmacokinetics/Pharmacodynamics: There were no pharmacokinetic or pharmacodynamic results reported due to subject withdrawal and termination of the study.

Conclusions:

The objectives of this study were not met due to the early termination of the study. Only one subject was recruited, but, due to a protocol violation, this subject was withdrawn from the study. This subject completed one treatment period which was placebo. The study was terminated due to difficulties with recruitment.

Date of Report: April 2008