Synopsis

Identifier: HM2007/00628/00 **Study Number:** VRA105345

Title: A multi-centre, randomised, single blind, placebo controlled, parallel group study to examine the effect of single doses of SB-705498, a TRPV1 receptor antagonist, on pain following third molar tooth extraction

Investigators:
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Publications: None at the time of this report.

Study period:

Initiation Date: 07 December 2005

Completion Date: 11 October 2007

Phase of development: II

Objectives:

Primary

- To evaluate the analgesic efficacy of SB-705498 following dental surgery.

Secondary

- To further evaluate the safety and tolerability of SB-705498.
- To evaluate the duration of analgesic effect for SB-705498.
- To evaluate the pharmacokinetic and pharmacodynamic relationship between drug exposure and analgesic effect of SB-705498.
- To compare the analgesic efficacy of SB-705498 when dosed adjunctively with ibuprofen to the analgesic efficacy of ibuprofen alone.

Methodology:

SB-705498 is a transient receptor potential vanilloid 1 (TRPV1) antagonist that has demonstrated antihyperalgesic activity in both animal and human models of inflammatory pain. The dental pain model of tooth extraction is a recognised and validated tool for assessment of clinical efficacy for inflammatory pain. The type of physiological reaction that results from tooth extraction is likely to activate the TRPV1 receptor, e.g. local acidification of tissue and the release of inflammatory mediators such as bradykinin and prostanoid E2. Hence it was considered reasonable to postulate that the TRPV1 receptor is involved in the pain and discomfort following tooth extraction.

SB-705498 is under development for the treatment of painful conditions and has demonstrated efficacy in a healthy volunteer model of inflammatory pain (ultraviolet B irradiation) whilst proving to be safe and well tolerated at the starting dose level used in this study (400mg). The protocol allowed for the dose of SB-705498 to be increased in the second half of the study to 1000mg, providing the 400mg dose was found to be safe and well tolerated.

This clinical trial was a multi-centre, randomised, single-blind, parallel group, placebo-controlled, single oral dose study with a positive control arm. Subjects previously scheduled for 3rd molar tooth extraction, who were otherwise healthy, were recruited. As soon as possible after completion of surgery, subjects were randomised to treatment and dosed with the study medication. All subjects remained in the clinical unit until the following morning. This was a two-part study that included the option to add a second higher dose if SB-705498 was well tolerated in Part 1. Following a safety review after an initial 52 subjects were dosed, a dose of 1000mg was included in the second part of the study. Ibuprofen was provided as rescue medication if needed.

Number of subjects:
Planned: 50 subjects in the first group and 90 subjects in the second group.
Actual: 52 subjects in the first group (21 subjects treated with SB-705498 400mg, 15 subjects treated with placebo and 16 subjects treated with co-codamol) and 93 subjects in the second group (15 subjects treated with SB-705498 400mg, 34 subjects treated with

SB-705498 1000mg, 22 subjects treated with placebo and 22 subjects treated with co-codamol).

Subject Disposition and Demographics:

Number of Subjects	Placebo	SB-705498 400mg	SB-705498 1000mg	Co-codamol
Number of subjects planned, N	35	35	35	35
Number of subjects randomised, N	37	36	34	38
Number of subjects included in All subjects (safety) population, n (%)	37 (100%)	36 (100%)	34 (100%)	38 (100%)
Number of subjects included in ITT population, n (%)	37 (100%)	34 (94%)	33 (97%)	38 (100%)
Number of subjects completed as planned, n (%)	36 (97%)	36 (100%)	33 (97%)	38 (100%)
Number of subjects withdrawn (any reason), n (%)	1 (3%)	0	1 (3%)	0
Number of subjects withdrawn for SAE, n (%)	0	0	0	0
Number of subjects withdrawn for AE, n (%)	0	0	0	0
Reasons for subject withdrawal, n (%)				
Lost to follow-up	0	0	1 (3%)	0
Subject decision	1 (3%)	0	0	0
Demographics				
Age in Years, Mean (SD)	27.5 (7.4)	27.0 (6.5)	26.0 (7.3)	27.0 (6.4)
Range	18–48	18–44	18–43	19–48
Sex, n (%)				
Female	19 (51%)	18 (50%)	20 (59%)	19 (50%)
Male	18 (49%)	18 (50%)	14 (41%)	19 (50%)
BMI (kg/m^2), Mean (SD)	24.2 (3.6)	24.6 (5.1)	22.3 (2.7)	24.5 (4.6)
Range	18.9–32.8	17.7–39.2	17.6–27.8	18.0–43.3
Height (cm), Mean (SD)	169.8 (7.8)	169.7 (10.4)	168.8 (9.6)	169.7 (9.8)
Range	152–182	152–188	155–197	153–188
Weight (kg), Mean (SD)	69.9 (12.6)	71.3 (18.1)	63.8 (11.4)	70.9 (14.5)
Range	49.0–96.0	49.5–121.4	45.1–88.2	42.2–112.1
Ethnicity, n (%)				
Hispanic or Latino	2 (5%)	2 (6%)	3 (9%)	3 (8%)
Not Hispanic or Latino	35 (95%)	34 (94%)	31 (91%)	35 (92%)
Race, n (%)				
African American/African Heritage	1 (3%)	1 (3%)	1 (3%)	2 (5%)
Asian – Central/South Asian Heritage	0	0	0	3 (8%)
Asian – East Asian Heritage	8 (22%)	5 (14%)	13 (38%)	8 (21%)
Asian – Japanese Heritage	0	0	2 (6%)	0
Asian – South East Asian Heritage	3 (8%)	0	0	1 (3%)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (3%)
White – Arabic/North African Heritage	0	1 (3%)	0	0
White – White/Caucasian/European Heritage	25 (68%)	28 (78%)	18 (53%)	23 (61%)
Other	0	1 (3%)	0	0

Source Data: Table 9.1, Table 9.2, Table 9.6, Table 9.7

Diagnosis and main criteria for inclusion:

Male and female subjects, 18 to 50 years old, who were scheduled for out-patient surgical removal of up to four 3rd molar teeth under local anaesthesia were recruited into the study. At least one 3rd molar tooth had to be fully or partially impacted in the mandible, requiring bone removal. Subjects had to be healthy and females of child-bearing potential had to use an effective method of contraception. All subjects had to agree not to take analgesics other than protocol defined rescue analgesics during treatment (up to 24 hours post-dose).

Treatment administration:

The initial group of subjects were dosed according to a 4:3:3 ratio (SB-705498 400mg: placebo: co-codamol) and then the safety of SB-705498 was reviewed. The safety data showed the 400mg dose was well tolerated so a higher dose group of SB-705498 1000mg was introduced and a second group of subjects were randomised using a 3:7:4:4 treatment allocation (SB-705498 400mg: SB-705498 1000mg: placebo: co-codamol). All subjects received a single dose of their allocated treatment as soon as reasonably possible after completion of the tooth extraction operation (but within 1 hour). Rescue medication (ibuprofen 400mg) was allowed from 3 hours post-dose.

Batch numbers: SB-705498 200mg capsules: 051108614; SB-705498 300mg capsules: 061128358; placebo capsules: 051108594; co-codamol capsules: 051108595

Criteria for evaluation:

Efficacy

A 100mm Visual Analogue Scale (VAS) and a 4-point Verbal Rating Scale (VRS) were used to quantify pain intensity over 10 hours post-dose. Time to rescue medication use and the proportion of subjects requiring rescue medication were also assessed.

Safety

The safety and tolerability of SB-705498 were assessed by monitoring subjects for changes in 12-lead electrocardiogram (ECG), 24-hour Holter tape, vital signs, body temperature, biochemistry, haematology, plasma and serum hormone levels as well as recording adverse events (AEs).

Pharmacokinetic-Pharmacodynamic

Subject exposure to SB-705498 and the paracetamol component of co-codamol was assessed by serial pharmacokinetic blood sampling. If appropriate the relationship between measures of exposure to SB-705498 and efficacy or safety outcomes were investigated.

Statistical methods:

Sample size considerations and justification

Based on a standard deviation of 25mm, and assuming a similar distribution for the response at early dosing as for dosing at moderate to severe pain, it was estimated that a sample size of 34 subjects per group would be needed to detect a difference of 20mm with 90% power and a 5% significance level. The planned number of subjects per group was 35.

Interim Analyses

No interim analyses were performed. However, safety data were reviewed once the first 52 subjects completed dosing, before increasing the dose to 1000mg.

Efficacy Analyses

The weighted mean change from baseline over 10 hours for pain intensity based on the VAS was analysed using analysis of covariance (ANCOVA), adjusting for age, sex, baseline VAS and country, for both last observation carried forward (LOCF) and observed case (OC) datasets. Descriptive summary statistics were also produced for the change in VAS and weighted mean change over 10 hours. Exploratory figures of weighted mean change over 10 hours were also produced.

Similar analyses were produced for pain intensity based on the VRS.

Time to first dose of rescue medication was summarised by time and presented graphically in a Kaplan-Meier plot. Time to first rescue medication use and time to second rescue medication use were compared using the log rank test.

Descriptive statistics were provided for the Subject Global Evaluation and dental surgery details.

Safety Analyses

No formal statistical analysis of safety data was conducted for this study. Summaries (exposure, AEs, laboratory parameters, ECGs, vital signs, body temperature) by treatment and individual subject listings were produced. Descriptive summaries of temperature over time were presented graphically.

Pharmacokinetic Analyses

Pharmacokinetic analyses of plasma SB-705498 concentration-time data were conducted using a non-compartmental model, with actual elapsed time from dosing used to estimate all individual plasma PK parameters for evaluable subjects. No formal PK analyses were conducted on plasma paracetamol and ibuprofen concentrations. Values for the following PK parameters were estimated:

- The time prior to the first measurable SB-705498 concentration (tlag).
- The maximum observed plasma SB-705498 concentration (Cmax) and the first time to reach Cmax (tmax) based on actual observed values.

- The area under the plasma SB-705498 concentration-time curve from time zero to 10 hours post-dose (AUC(0-10)).

Paracetamol concentrations were compared to published values to assess whether levels were as expected. Plasma SB-705498 parameter estimates were listed by subject and treatment. Plasma SB-705498 PK parameter values were summarized by treatment. The relationship between SB-705498 systemic exposure and VAS pain scores were investigated.

An exploratory examination of changes from baseline in core body temperature across subjects on placebo, co-codamol and 1000mg SB-705498 was undertaken. The analysis examined changes at 2, 4, 6, 8 and 10 hours post-dose.

Summary:

Efficacy:

Detailed statistical analyses to assess the weighted mean for the pain intensity VAS over 10 hours for the LOCF dataset showed no notable difference between either of the SB-705498 groups and placebo, however, there was a difference seen between the co-codamol group and placebo, consistent with an analgesic effect of co-codamol (point estimate -9.40, 95% confidence intervals [CIs]: -19.8, 1.00), although this did not achieve statistical significance.

Summary of Analysis of Weighted Mean for the Pain Intensity VAS Over 10 Hours – LOCF Dataset

	Test LS Mean	Placebo LS Mean	Point Estimate	95% CI
SB705498 400mg - Placebo	35.91	36.27	-0.37	(-11.0, 10.23)
SB705498 1000mg -Placebo	38.10	36.27	1.83	(-9.08, 12.73)
Co-codamol - Placebo	26.87	36.27	-9.40	(-19.8, 1.00)

Baseline VAS score and country were significant predictors of the weighted mean change in VAS at the 5% level, after adjusting for sex, age and treatment. Further investigation identified subjects with baseline VAS scores >20mm as having large negative weighted mean changes in VAS. Country effects showed that weighted mean changes in VAS were generally higher and less variable in Italy, with subjects in Korea having the most variable changes in VAS, although it is unclear whether this is a true country effect or an artefact of many confounding factors. Number of teeth extracted was not a significant predictor of weighted mean change in VAS after adjusting for sex, age, baseline VAS, country and treatment. The results over the first 6 hours reflected those seen over 10 hours.

Post-hoc analysis of weighted mean change over 6 hours in VAS for subjects receiving placebo and co-codamol showed a trend for co-codamol to be more effective than placebo, with this difference reaching statistical significance at the 6-hour timepoint.

The analyses of pain intensity using VRS showed no notable difference between the SB-705498 groups and placebo, but a trend in favour of co-codamol was seen in the comparison between the co-codamol and placebo groups, although again the difference did not reach statistical significance.

Only 18% of subjects in the co-codamol group needed rescue medication before their 3-hour assessment compared to 32% of subjects in the placebo group, 47% in the SB-705498 400mg group and 48% in the SB-705498 1000mg group. By 6 hours post-surgery at least 50% of subjects in each treatment group had taken their first dose of rescue medication. Kaplan-Meier analysis indicated that subjects receiving co-codamol required rescue medication later than subjects treated with placebo during the first 6 hours post-surgery, while subjects treated with SB-705498 required rescue medication earlier than subjects treated with placebo.

Very little difference was seen between the treatment groups in the Subject Global Evaluation.

Safety:

In all treatment groups study medication was generally well tolerated.

The overall incidence of AEs was similar between the treatment groups, with the exception of pyrexia, which was seen to occur in the SB-705498 treatment groups with a higher frequency compared to the placebo and co-codamol groups. The most common AE was headache, with the incidence of headache in the SB-705498 1000mg group being similar to that in the placebo group.

Summary of Adverse Events

Preferred Term, n (%)	Placebo (N=37)	SB-705498 400mg (N=36)	SB-705498 1000mg (N=34)	Co-codamol (N=38)
Subjects with Any AE	16 (43%)	10 (28%)	14 (41%)	14 (37%)
Headache	5 (14%)	1 (3%)	5 (15%)	4 (11%)
Nausea	1 (3%)	1 (3%)	0	3 (8%)
Dizziness	1 (3%)	0	0	3 (8%)
Feeling hot	2 (5%)	0	2 (6%)	0
Pyrexia	0	1 (3%)	2 (6%)	0
Vomiting	2 (5%)	0	0	0

The majority of AEs in each treatment group were considered mild. The only AE reported as severe was one case of nausea in a subject in the placebo group.

The overall incidence of drug-related AEs was similar between most of the treatment groups, although the SB-705498 400mg group had a notably lower incidence of drug-related AEs. The most common drug-related AE was headache, with the incidence of drug-related headache being highest in the placebo group.

No non-fatal or fatal SAEs were reported during the study and no subjects had an AE that led to withdrawal from the study. There was one SAE recorded after the study had completed. This was a spontaneous abortion that occurred 56 days after dosing with 400mg SB-705498 in a subject who was noted to have a positive pregnancy test at the follow-up visit.

Small changes in laboratory values were seen in all treatment groups but there were no clear differences between the groups or trends to suggest a drug effect. There were no differences of note in ECGs or vital signs between the treatment groups.

Interpretation of the temperature change data from this study is complicated, as small increases in mean temperature were seen in all treatment groups, including placebo, and are probably related, in part at least, to tissue inflammation due to the surgical procedure. As would be predicted from its antipyretic effects, the increases in temperature appear to be smallest in the co-codamol group. Exploratory PK/PD analyses examining the effect on SB-705498 on core body temperature suggested that there was a slight trend for higher core body temperature at 2 hours post-dose in the SB-705498 treated subjects. However, caution should be used when interpreting the temperature data given its limited nature and the use of rescue medication after 2 hours.

Pharmacokinetics:

A summary of plasma SB-705498 pharmacokinetic parameters is displayed in the Table below:

Summary (Geometric mean (CV_b%) of Plasma SB-705498 Pharmacokinetic Parameters

SB-705498 Dose	n	Tmax (h)[1]	Cmax (ug/mL)	AUC(0-10) (ug.h/mL)
400mg	32	1.5 (1.00 - 8.15)	0.586 (43.1)	3.15 (51.8)
1000mg	33	1.5 (1.00 - 10.15)	0.890 (41.8)	4.83 (37.6)

1. median (range)

Following oral administration of SB-705498, absorption of SB-705498 was rapid with systemic concentrations of SB-705498 generally detected 20-40 minutes after dosing and peak concentrations generally observed 1-2 hours post-dose. Increases in SB-705498 Cmax and AUC at 400mg and 1000mg were not proportional to dose. For the 2.5-fold increase in dose, an approximate 1.5 fold increase in Cmax and AUC was observed.

Plasma paracetamol concentrations were consistent with published literature values following a single oral dose of 1000mg paracetamol.

The relationship between SB-705498 systemic exposure and VAS pain scores was investigated but there appeared to be no clear evidence of a relationship between SB-705498 systemic exposure (Cavg) and changes from baseline in VAS pain scores. Further analyses that examined changes from baseline in VAS pain scores based on three levels of average SB-705498 concentrations: <0.35ug/mL, 0.35-0.5ug/mL and >0.5ug/mL, versus subjects on co-codamol and placebo, confirmed that there was no clear evidence of a relationship between SB-705498 systemic exposure and changes from

baseline in VAS pain scores.

Conclusions:

- For the primary efficacy parameter of weighted mean change from baseline over 10 hours for pain intensity based on the VAS, no notable difference was seen between either of the SB-705498 groups and placebo, however, there was a difference seen between the co-codamol group and placebo, consistent with an analgesic effect of co-codamol, although this did not achieve statistical significance.
- The analyses of pain intensity using VRS showed no notable difference between the SB-705498 groups and placebo, but again a trend in favour of co-codamol was seen in the comparison between the co-codamol and placebo groups, although this did not reach statistical significance.
- Subjects receiving co-codamol required rescue medication later than subjects treated with placebo during the first 6 hours post-surgery, while subjects treated with SB-705498 required rescue medication earlier than subjects treated with placebo.
- Very little difference was seen between the treatment groups in the Subject Global Evaluation.
- SB-705498 systemic exposure at a dose of 400mg was approximately 50% lower than expected. Increases in SB-705498 dose to 1000mg resulted in limited increases in systemic exposure, such that for the 2.5-fold increase in dose, an approximate 1.5 fold increase in Cmax and AUC was observed.
- No clear relationship between SB-705498 plasma concentrations and changes in VAS pain scores was observed.
- Study medication in all treatment groups was generally well tolerated. One SAE (spontaneous abortion) was recorded after the study had completed. The incidence of AEs was generally similar in all of the treatment groups, although pyrexia was only reported in the SB-705498 treatment groups. The most common AE overall was headache. There were no clear differences between the groups or trends to suggest a drug effect on heart rate, blood pressure, ECG or clinical laboratory values.
- Exploratory PK/PD analyses examining the effect on SB-705498 on core body temperature suggested that there was a slight trend for higher core body temperature at 2 hours post-dose in the SB-705498 treated subjects, where subjects had not been administered the rescue medication ibuprofen. However, interpretation of the temperature data is difficult as increases in mean temperature were seen in all treatment groups and were probably related to tissue inflammation due to the surgical procedure.

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