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: VR1114693

Title : A two part study to investigate the pharmacokinetics and pharmacodynamics of SB705498, a TRPV1 antagonist, in cough. Part A: an open label study in healthy subjects to determine the exposure to SB705498. Part B: a randomised double-blind, placebo controlled, cross over study to investigate the effects of SB705498 on capsaicin-induced cough and 24 hour cough counts in patients with chronic cough

Rationale: It is anticipated that SB705498 will competitively antagonise capsaicin via the TRPV1 receptor resulting in a rightward shift of the C2/C5 curve in both healthy subjects and subjects with chronic cough. As chronic cough subjects were evaluated in Part B, it is hypothesised that an effect on cough counts may also be achieved

Phase: IIa

Study Period: 18th April 2011 – 19th January 2012

Study Design: Part A: an open label study in healthy subjects to determine the exposure to SB705498. Part B: a randomised double-blind, placebo controlled, cross over study.

Centres: 1
Medicines Evaluation Unit Southmoor Road The Langley Building Manchester M23 9QZ United Kingdom

Indication: Cough

Treatment: Part A investigated the systemic exposure of a single oral dose of 400 mg SB705498 in an open label design using healthy subjects. Part B involved a double blind, placebo controlled cross over study in subjects with chronic cough and a single oral dose of 600mg SB705498.

Objectives:

Part A

To determine the systemic exposure following a single oral dose of 400 mg SB-705498 (4 x 100 mg tablets).
To determine the capsaicin concentration required to achieve C5 following a single dose of SB705498.
To determine the capsaicin concentration required to achieve C2 following a single dose of SB705498.
To assess the safety tolerability of a single oral dose of SB705498.

Part B

To determine the capsaicin concentration required to achieve C5 following a single dose of SB705498 or placebo.
To assess the effect of SB705498 or placebo on 24 hour ambulatory cough counts.
To assess the effect of SB705498 or placebo on the Cough Quality of Life Questionnaire (CQLQ).
To determine the capsaicin concentration required to achieve C2 following a single dose of SB705498 or placebo.
To assess the effect of SB705498 or placebo on the urge to cough, following capsaicin challenge.
To determine the capsaicin concentration required to achieve C5, 24 hour post-dose, following a single dose of SB705498 or placebo.
To determine the capsaicin concentration required to achieve C2, 24 h post-dose, following a single dose of SB705498 or placebo.
To assess the safety tolerability of a single oral dose of SB705498.

Statistical Methods: For Part A, no formal hypothesis or sample size sensitivity was tested. For Part B a test for superiority was conducted. The null hypothesis for the treatment comparison was that there was no difference between SB705498 and placebo in capsaicin dose to elicit C5. The alternative hypothesis was that there is a 1-sided difference with the SB705498 capsaicin dose required being >the placebo capsaicin dose required. No sample size re-estimation was performed for either Part A or Part B.

The primary efficacy endpoint was the Capsaicin concentration required to achieve C5 following a single dose of SB-705498 at Tmax as compared to baseline (Day -1). The distributional properties were investigated. The difference between SB-705498 and placebo in log-transformed change from baseline was investigated using a mixed effects model with fixed effects terms for treatment and period. Subject was treated as a random effect in the model. The mean treatment difference and associated 95% confidence interval were back-transformed to provide a treatment ratio and 95% confidence interval for the ratio. Results were presented on log (base 2) scale. 24 hour cough count (rate/h) following single dose of SB-705498 as compared to placebo were analysed by first log transforming the cough counts taken on Day -1 and on Day 1 of each period in the 24 hours post dose. The time interval during which the challenge was conducted was excluded from the cough count. The counts rates (rate/h) were log(10) transformed. The

difference between SB-705498 and placebo in log-transformed count rates were investigated using a mixed effects model with fixed effects terms for Day -1, treatment and period. Subject was treated as a random effect in the model. The mean treatment difference and associated 95% confidence interval were back-transformed to provide a treatment ratio and 95% confidence interval for the ratio.

The secondary analysis involved measuring the Capsaicin concentration required to achieve C2 following a single dose of SB-705498 at Tmax compared to baseline. The C2 and C5 from the 24-hour post-dose challenge were analysed similarly to the analysis at Tmax. Urge to and severity of cough VAS following single dose of SB-705498 as compared to placebo were analyzed descriptively by treatment group. CQLQ results at 14 days post dose following single dose of SB-705498 as compared to placebo were analyzed descriptively by treatment group.
Relationships between the primary endpoint and secondary endpoints were explored by graphical means including log10(C5) and log10(C2) versus log10(cough rate) by treatment group.

Study Population:

Part A
Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination and laboratory tests, male or female between 30 to 75 years of age.

Part B
Chronic cough subjects who are otherwise healthy as determined by a responsible and experienced physician. Male or female18 to 75 (Part B) years of age.

Both parts of the study recruited subjects who were non-smokers for at least 6 months with a pack history ≤5pack years (Pack years=(No. of cigarettes smoked/day/20) x No. of years smoked). Body weight ≥ 50 kg and Body Mass Index (BMI) within the range 19 to 32.0 kg/m2.

Number of Subjects:	**Part A**	**Part B**
Planned N	12	24
Dosed N	13	21
Completed n (%)	13(100)	19 (90)
Total Number Subjects Withdrawn N (%)	0 (0)	2 (10)
Withdrawn due to Adverse Events n (%)	0 (0)	2 (10)
Withdrawn due to Lack of Efficacy n (%)	NA	NA
Withdrawn for Other Reasons n (%)	0 (0)	0 (0)
Demographics	**Part A**	**Part B**
N (ITT)	13	21
Females: Males	8:5	15:6
Mean Age in Years	48.2	53
Mean Weight in Kg	77.62	75.37
White n (%)	12 (92)	21 (100)
African American/African Heritage	1 (8)	0

Pharmacokinetics (PK)
Part A

Following oral administration of 400 mg SB705498 (administered as 4 x 100 mg tablets), the systemic exposure was comparable to those seen in other studies with this molecule where 100 mg tablets have been administered, but was notably lower than those studies where 16 x 25 mg tablets have been administered. In addition, the variability in the exposure was increased compared to other studies, with a 6- fold range in AUC(0-tlast) and a 7- fold range in Cmax. Three subjects appeared to have higher exposures than the other subjects in this dose group. Since this appeared to artificially raise the average exposures following dosing at 400 mg, it was decided to use 600 mg as the dose in Part B of the study.

Part B

Following oral administration of 600 mg SB705498 (administered as 6 x 100 mg tablets), the systemic exposure was higher than observed with 400 mg (Part A), with the magnitude of increase in AUC(0-4h) and Cmax being proportional to the increase in dose. The variability in the exposure was similar to that seen previously, with a 7- fold range in AUC(0-tlast) and a 10- fold range in Cmax.

Dose (mg)		AUC(0-4) (ng.h/mL)	AUClast (ng.h/mL)	Cmax (ng/mL)	C24 (ng/mL)	Tmax (h)
400	N	13	13	13	-	13
	Mean	2466	4661	984	-	
	Sd	1634	2905	641	-	
	Min	995	2091	341	-	0.75
	median	1812	3560	760	-	1.50
	Max	6827	11454	2444	-	4.00
	geomean	2116	3999	829	-	
	L95%	1524	2858	577	-	
	U95%	2939	5595	1189	-	
	SDLogs	0.544	0.556	0.598	-	-
	%CVb [1]	58.7	60.2	65.6		-
600	N	19	19	19	19	19
	Mean	3107	13826	1254	389	
	Sd	1185	6344	586	162	
	Min	747	3372	257	151	1.00
	median	3313	13536	1260	342	1.50
	Max	4777	24414	2472	633	3.00
	geomean	2815	12231	1094	354	
	L95%	2206	9410	823	283	
	U95%	3592	15897	1453	443	
	SDLogs	0.506	0.544	0.589	0.464	-
	%CVb [1]	54.0	58.7	64.4	49.0	-

[1] CVb (%)= 100 x sqrt (exp(SDLogs^2)-1)

Pharmacodynamics (PD):

In Part A, no formal PK/PD analysis was undertaken.

In Part B the change from baseline doubling dose of Capsaicin required to induce C2 and C5 following administration of 600 mg SB705498 compared to placebo which showed there was a statistically significant ($p<0.05$) 1.16- [95% CI: 0.33– to 1.99] doubling dose difference in C5 2h post SB705498 treatment. For C2 at both 2h and 24h, and C5 at 24h, the doubling doses were less than 1, and for C2 the 95% CI spanned zero. Receptor occupancy was also measured and found to be 45% 2 hours after dosing dropping to 25% at 24 hours post dose.

When dosing with SB705498 was compared to placebo there were no significant changes detected in cough counts nor were changes detected in the Cough Quality of Life Questionnaire (CQLQ) or the VAS score.

Safety results:

Dosing with SB705498 had no significant effect on blood pressures or heart rate compared to placebo. Antagonism of the TRPV1 receptor is hypothesized to have an effect of increasing the sense of being cold and may be accompanied by thermogenesis. There were no significant increases in reported body temperature whilst receiving SB705498 compared to placebo.

Adverse events (AE) and serious adverse event (SAE) were collected from the start of Investigational Product and until the follow-up contact. No drug related adverse events were reported in Part A. In Part B six non-serious adverse events suspected as related to the investigational product were reported. Two counts of headache were observed whilst taking placebo and one count whilst receiving SB705498. In addition three other non-serious adverse events of

mouth ulceration, chest pain and myalgia occurred whilst receiving SB705498. All of these were of mild to moderate in intensity, of short duration and with the exception of chest pain resolved in 1-2 days of onset. Two subjects were withdrawn due to AE in Part B after a single dose of placebo. Both events leading to withdrawal were not considered serious and were followed up to resolution. No clinically significant ECG or laboratory results were observed.

Adverse Events:	**Part A**	**Part B**
N (ITT)	13	21
No. subjects with AEs n (%)	3 (23)	15 (71)

Adverse Event	**Part A SB705498 400mg**	**Part B SB705498 600mg**	**Part B Placebo**
Any Event n (%)	3 (23)	7 (37)	10 (48)
Nausea	1 (8)	0	0
Seasonal Allergy	1 (8)	0	0
Oral Herpes	1 (8)	0	0
Headache	1 (8)	2 (11)	3 (14)
Oropharyngeal pain	1 (8)	0	0
Dizziness	0	0	2 (10)
Nasopharyngitis	0	0	2 (10)
Lower RTI	0	0	1 (5)
Sinusitis	0	0	1 (5)
Back pain	0	0	1 (5)
Myalgia	0	1 (5)	0
Pain in extremity	0	1 (5)	0
Diarrhoea	0	1 (5)	0
Mouth Ulceration	0	1 (5)	0
Vomiting	0	1 (5)	0
Chest Pain	0	1 (5)	0
Arthropod bite	0	1 (5)	0
Allergy to arthropod bite	0	0	1 (5)

Serious Adverse Events, n (%)

No SAEs were reported.