Study No: VR1111924

Title : A randomized, double-blind, placebo controlled, incomplete block, 3 way cross over study in subjects with allergic rhinitis to assess the effect of intranasal repeat doses of SB-705498 when administered alone or in conjunction with intranasal fluticasone propionate on the symptoms of rhinitis in the Vienna allergen challenge chamber

Rationale: The purpose of this study was to assess the pharmacodynamic effects (total nasal symptom score (TNSS) and its individual components: rhinorrhoea, nasal congestion, nasal itch, sneeze) of intranasal, repeat dose SB-705498 in subjects with allergic rhinitis, elicited by an allergen chamber challenge.

Phase: IIa

Study Period: 14 APR 2011 to 07 JUL 2011

Study Design: A randomized, double-blind, placebo controlled, incomplete block, 3 way cross over study

Centres: Vienna Challenge Chamber, Vienna, Austria

Indication: None

Treatment: Each subject was to participate in 3 treatment periods with incomplete allocation of 4 treatments. The following treatments were administered:

- Repeat intranasal doses of placebo twice daily (morning and evening)
- Repeat intranasal doses of FP (200µg) once daily (evening), along with intranasal placebo (morning)
- Repeat intranasal doses of SB-705498 (12mg) once daily (morning), along with intranasal placebo (evening)
- Repeat intranasal doses of SB-705498 once daily (morning) along with intranasal FP (evening).

The 3 treatment periods were separated by a washout of 14-20 days. Subjects attended the unit on D8 for assessment of symptoms following an allergen chamber challenge after repeat dosing.

Objectives: Effect of 8-day treatment with intranasal SB-705498 on nasal symptoms elicited by an allergen chamber challenge in subjects with allergic rhinitis (AR) when co administered with fluticasone propionate (FP), compared to FP alone. Effect of 8-day treatment with intranasal SB-705498 on nasal symptoms elicited by an allergen chamber challenge in subjects with AR compared to placebo.

Statistical Methods: Seventy subjects were randomised to ensure 54 subjects completed the study. With 54 completed subjects, it was estimated that the study would have at least 90% power to detect a difference of at least 1 point between SB-705498+FP and FP alone using a one-sided 5% significance level, assuming a within subject SD of 1.454 and between subject SD of 2.081. The power for the comparison of SB-705498 and placebo was 91%, and between FP and placebo was >99%, assuming a clinically relevant difference of 1.3 points and using a one-sided 5% significance level. No formal interim analyses were planned or performed. For all treatment comparisons, two sided 90% confidence intervals were calculated as appropriate for one-sided hypothesis testing at the 5% significance level. The weighted mean (WM) and maximum TNSS 0-4 hrs post start of the challenge on day 8 were derived and analysed separately using mixed effects models, including period, treatment and covariates for pre-dose day 1 TNSS score as fixed effects and subject as a random effect. The mean TNSS from day 4 to day 8 recorded on the daily diary card was computed and analysed using a mixed effects model including period, treatment and covariates for pre-dose day 1 TNSS score as fixed effects and subject as a random effect. The weighted mean Total Nasal Airflow as measured by active anterior rhinomanometry 0-4 hrs post start of the challenge on day 8 was derived and analysed using a mixed effects model, including period and treatment as fixed effects and subject as a random effect. Pharmacokinetic and safety data were summarised and listed by treatment group. An exploratory analysis of log transformed $AUC_{(0-t)}$ and Cmax was performed.
The 'All Subjects' population was defined as all subjects who received at least one dose of study medication. All 70 randomised subjects were included in this population. This population was used to summarise all PD and safety data
The 'Pharmacokinetic' population, defined as all subjects for whom a pharmacokinetic sample was obtained and analysed, comprised 69 subjects, and was used to summarise pharmacokinetic data.

Study Population: Male and female subjects aged 18-65 years, inclusive, with a diagnosis of allergic rhinitis for more than 1 year and with body mass index within the range 19-29.9 kg/m^2 (inclusive). Subjects had a positive skin prick test (wheal ≥ 4mm) and a positive RAST test for seasonal pollen at or within the 12 months preceding the screening visit. Subjects demonstrated TNSS greater than or equal to 4 (on a twelve-point scale) at the screening visit following the allergen chamber challenge.

Number of Subjects:	**Total**
Planned N	up to 72
Dosed N	70
Completed n (%)	69 (99)
Total Number of Subjects Withdrawn N (%)	1 (1)
Withdrawn due to Adverse Events n (%)	0

Withdrawn for other reasons n (%)	1 (1)
Demographics	
N (all subjects)	70
Females: Males	33:37
Mean Age in Years (sd)	28.1 (6.86)
Mean Weight in Kg (sd)	71.5 (12.48)
White-White Caucasian/European Heritage n (%)	67 (96)

Pharmacodynamics (PD):

Treatment differences for SB705498 + FP compared to FP alone are summarised below

	n		Adjusted Mean Treatment Difference (vs. FP alone)	
Endpoint	**SB705498+FP**	**FP**	**Estimate**	**90% CI**
WM TNSS 0-4 hours	46	70	0.66	(0.16, 1.16)
Maximum TNSS 0-4 hours	46	70	1.1	(0.5, 1.7)
Diary Data Mean TNSS Day 4 - 8	47	70	0.16	(-0.30, 0.61)
WM Total Nasal Airflow 0-4 hours	46	70	-8.95	(-33.10, 15.22)

Treatment differences for SB705498 alone compared to Placebo are summarised below

	n		Adjusted Mean Treatment Difference (vs. Placebo)	
Endpoint	**SB705498**	**Placebo**	**Estimate**	**90% CI**
WM TNSS 0-4 hours	23	69	-0.23	(-0.90, 0.44)
Maximum TNSS 0-4 hours	23	69	-0.40	(-1.20, 0.40)
Diary Data Mean TNSS Day 4 - 8	23	69	-0.44	(-1.04, 0.16)
WM Total Nasal Airflow 0-4 hours	23	69	-7.31	(-39.70, 25.05)

Pharmacokinetics (PK):

Following 8 days repeated intra nasal administration of 12 mg SB-705498, the mean treatment ratio for SB-705498+FP compared to SB-705498 alone was 1.05 (90% CI 0.8, 1.38) for AUC(0-t) and 1.07 (90% CI 0.82, 1.4) for Cmax). Tmax was around 5 hours post dose on Day 8 for both treatment regimens.

Safety Results:

Adverse event and serious adverse event (SAE) data were collected and recorded on the eCRF from the start of study treatment until the follow-up contact. In addition, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests or change in existing therapy) or related to a GSK concomitant medication were to be recorded from the time a subject consented to participate in the study up to and including any follow-up contact. The most frequently reported AEs are summarised below.

Adverse Events:	**Placebo**	**FP**	**SB-705498**	**SB-705498 + FP**	**Total**
N (All Subjects)	68	69	23	47	70
No. subjects with AEs n (%)	24(35)	28(41)	13(57)	19(40)	46(66)
Most Frequent AEs (greater than or equal to 2% subjects)					
Hypersensitivity	12(18)	11(16)	7(30)	10(21)	27(39)
Headache	9(13)	11(16)	5(22)	5(11)	22(31)
Nasal discomfort	3(4)	2(3)	0	0	5(7)
Cough	1(1)	0	0	1(1)	2(3)
Nasaopharyngitis	1(1)	1(1)	1(4)	1(2)	4(6)
Influenza	0	2(3)	0	1(2)	3(4)
Pyrexia	0	1(1)	1(4)	0	2(3)
Toothache	1(1)	1(1)	0	0	2(3)

Serious Adverse Events n(%): No SAEs were reported.