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The effects of a TRPV1 antagonist, SB-705498, in the treatment of seasonal allergic rhinitis

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Key words

seasonal allergic rhinitis
– intranasal SB-705498
– TRPV1-antagonist

Abstract. Background: Current pharmacotherapy for allergic rhinitis (AR) does not totally ameliorate all symptoms for all patients. Residual symptoms could be due to nasal neuronal hyperresponsiveness caused by stimulation of the ion channel transient receptor potential vanilloid 1 (TRPV1). SB-705498 is a TRPV1 antagonist that has been developed in an intranasal formulation for treatment of AR. Methods: This randomized, double-blind, 3-way incomplete block crossover study evaluated the effects of 8 days treatment with SB-705498 12 mg alone, SB-705498 12 mg plus fluticasone propionate 200 µg (FP), FP 200 µg alone or placebo on allergen-induced symptoms in 70 patients with AR. The primary endpoint was total nasal symptom score (TNSS), expressed as mean over 4 hours or maximum TNSS during allergen challenge in the Vienna Challenge Chamber on 8th day of treatment. Results: At the end of treatment, there were no differences in allergen-induced mean TNSS between SB-705498 alone and placebo or between SB-705498 plus FP and FP alone. Treatment with FP and SB-705498 plus FP resulted in a significant decrease in TNSS vs. placebo. Mean (90% CI) treatment differences in TNSS over 0 – 4 hours were: SB-705498 – placebo: –0.2 (–0.9, 0.4); SB-705498 plus FP – FP: 0.7 (0.2, 1.2); FP – placebo: –2.9 (–3.4, –2.5); SB-705498 plus FP – placebo: –2.3 (–2.8, –1.8). SB-705498 had no impact on diary card symptoms, nasal airflow or Rhinoconjunctivitis Quality of Life Questionnaire scores. SB-705498 was well tolerated and pharmacokinetics exposure results supported the dosing regimen. Conclusion: SB-705498 12 mg for 8 days did not alleviate the allergen-induced symptoms of AR, or provide additional relief of symptoms when in combination with FP. Despite engagement of the TRPV1 receptor there was no translation to clinical efficacy, suggesting redundancy in symptom pathways.

Introduction

Allergic rhinitis (AR) represents a global health problem affecting 10 – 20% of the population [1], and is associated with a considerable social and economic burden, impacting on quality of life and affecting performance at work and school [2, 3, 4, 5, 6]. Depending on the severity of disease, the mainstay treatments for AR are oral or topical H1-antihistamines and intranasal corticosteroids (INS), with INS reported to be the most efficacious currently available treatment [7, 8]. Despite treatment, many patients may still suffer some residual symptoms [9, 10], and it has been reported that up to 1 in 5 patients with AR remain symptomatic when treated with the best available pharmacotherapy [11].

In AR, an immunoglobulin E (IgE)-mediated immediate response to an inciting inhaled allergen, involving mast cell and basophil degranulation and mediator release, leads to acute clinical symptoms [12]. A subsequent late-phase response involves the recruitment and activation of inflammatory cells including eosinophils, resulting in chronic obstruction and nasal hyperresponsiveness. Neuronal hyperreactivity is a known factor in the symptoms of AR and allergic mediators affect directly the sensory nasal nerves and reduce their threshold potential for activation [12, 13, 14]. The transient receptor potential vanilloid 1 (TRPV1) is a ligand gated ion channel expressed on sensory nerve terminals, and its activation is thought to play a role in the development of rhinitis symptoms through local release of neurotransmitters and by depolarization

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of nerve terminals, resulting in reflex parasympathetic secretory responses and sneeze, as well as central sensory perception such as itch [15]. TRPV1 is sensitive to vanilloid molecules such as capsaicin and is activated by a range of physiological stimuli including endogenous inflammatory mediators, such as histamine, prostaglandins and lipoxygenases [16]. AR patients have been shown to demonstrate an increased sensitivity to capsaicin in the pollen season [17] and an increased itch response to TRPV1 agonists in the pollen season [18]. The TRPV1 mechanism may be responsible for some of the residual, post-pharmacotherapy symptoms of AR and blocking this pathway could be expected to contribute to the control of nasal hyperresponsiveness and the associated symptoms of rhinitis.

SB-705498 is a potent and selective TRPV1 antagonist and has been developed in an intranasal formulation for the treatment of AR and non-allergic rhinitis. In a pre-clinical rhinitis guinea pig model, intranasal SB-705498 was shown to block capsaicin driven contralateral reflex fluid secretory responses [19]. In a clinical study in patients with non-allergic rhinitis, single doses of 12 mg SB-705498 resulted in a marked reduction in nasal symptoms following capsaicin challenge, compared with placebo [20].

The aim of this study was to evaluate the effects of 8 days treatment with intranasal SB-705498, given alone or co-administered with the intranasal corticosteroid fluticasone propionate (FP), on nasal symptoms elicited by allergen challenge in patients with allergic rhinitis.

Materials and methods

Patients

Male or female patients aged 18 – 65 years, with a history of seasonal allergic rhinitis for more than 1 year, defined as rhinitis symptoms that lasted for several months per year and that were not attributed to infections or nasal abnormalities, were eligible for inclusion. Patients were required to demonstrate a positive skin prick test (wheal ≥ 4 mm) and a positive radioallergen sorbent test (RAST, $\geq$ Class 2) for grass allergen

at the screening visit or within the previous 12 months. A symptomatic response to grass pollen challenge (total nasal symptom score (TNSS) ≥ 4 out of total of 12) was required to be shown at the screening visit. A pre-challenge forced expiratory volume in 1 second (FEV₁) of $\geq 80\%$ of predicted and a FEV₁/forced vital capacity (FVC) ratio of $\geq 70\%$ was also required. Patients with frequent nosebleeds, or symptoms due to upper respiratory tract infection that had not been completely resolved for at least 3 weeks prior to inclusion were not eligible.

Patients were not permitted the following medications in the time frame specified prior to each visit: 24 hours: nasal and oral decongestants or nasal corticosteroids; 72 hours: nasal or oral antihistamines; 7 days: inhaled corticosteroids, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, methylxanthines; 12 weeks: oral corticosteroids.

All patients gave their written informed consent prior to participation and the study was approved by the Ethics Committee of Österreichische ARGE für klinische Pharmakologie und Therapie (The Austrian Working Group for Clinical Pharmacology and Therapeutics) and the private hospital, Institut für Hypertoniker (Institute for Hypertension) (study number VR1111924; NCT01424397).

Study design

This was a randomized, double blind, placebo-controlled, three-way incomplete block crossover study conducted during the pollen season over the spring/summer months in a single center in Vienna, Austria. Randomized patients were scheduled to receive 3 out of the following 4 study treatments, each for 8 days with a 14 – 20 day washout in between treatments: SB-705498 12 mg alone, SB-705498 12 mg plus FP 200 µg, FP 200 µg alone or placebo. All patients received the placebo and FP arms, and then either SB-705498 12 mg plus FP 200 µg or SB-705498 12 mg alone (in a 2 : 1 ratio in order to increase the power of the SB-705498 plus FP vs. FP alone analysis).

Regardless of treatment arm, patients received SB-705498 in the morning and FP in the evening. To maintain the study blind, each patient was given two intranasal spray

devices to be administered as 4 actuations per nostril each morning and evening.

The primary endpoint was the effect of 8 days treatment on weighted mean TNSS elicited by an allergen challenge over 1–5 hours post-dosing.

Allergen challenge in the Vienna challenge chamber

Allergen challenge was conducted in the Vienna Challenge Chamber (VCC), using a previously validated method [21, 22, 23]. During the process, the chamber was charged with 100% fresh air, which was cleaned, cooled, dried and then loaded with a qualitatively and quantitatively determined allergen load. Allergen concentration, temperature and humidity were continuously monitored, allowing for a constant humidity (~40%), temperature (~24 °C) and allergen load (~1,500 grains per cubic meter) which were maintained throughout the exposure period. These conditions simulated those found outdoors on a typical, warm summer's day in Vienna. The VCC could accommodate up to 20 patients in one sitting, all of whom were under constant supervision by medical staff outside the chamber.

In the period 2 days to 5 weeks prior to the first treatment period, patients were screened and underwent an allergen challenge to ensure eligibility based on induced nasal symptoms. During the treatment periods, allergen challenge was performed on Day 8 of treatment, starting at 1 hour post-dosing and lasting ~4 hours.

Study outcomes

Symptom scores

The total nasal symptom score (TNSS) comprised the four components of nasal congestion, rhinorrhea, nasal itch and sneeze. Each was scored on a 4-point scale from 0 to 3 (where 0 = absent symptoms, 3 = severe symptoms) giving a TNSS range from 0 to 12. On the clinic study days (Day 8 of each treatment period), patients completed the TNSS assessment 1 hour post-dose and immediately prior to entering the chamber,

and at 15-minute intervals during the 4-hours allergen challenge.

On Days 4–7 of treatment, patients completed symptom diary cards at home in the evening, representing a reflective TNSS rating of the patients' symptoms over the preceding 12 hours.

Other efficacy endpoints

On clinic study days, nasal flow was measured using active anterior rhinomanometry immediately prior to entering the chamber and at 30-minute intervals during the challenge. Patients were instructed to breathe through one nostril while a sensor in the other nostril measured the difference in pre-nasal and choanal pressure. Nasal flow and nasal resistance were observed at pressure levels of 75, 150 and 300 Pa. The defined measuring range for the flow was $\pm 1,000$ ml/s.

Quality of life was assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) which covers 7 domains: activities limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function [24]. The minimal important difference (MID) in RQLQ has been shown to be 0.5 [25]. The RQLQ was self-completed by patients in the clinic at the screening visit and immediately after leaving the challenge chamber on Day 8 of each treatment.

Safety assessments

Adverse events and serious adverse events were recorded throughout the study starting from Day 1 of the first treatment period. Heart rate, blood pressure and oral temperature were assessed at the screening visit, then at pre-dose and immediately after leaving the challenge chamber on each clinic study day. Routine hematology, blood chemistry and urinalysis assessments, and single 12-lead electrocardiograms (ECGs) were assessed at screening and pre-dose on each clinic study day. Patients with QTcB > 500 msec or uncorrected QT > 600 msec were required to be withdrawn from the study. FEV₁ was measured on allergen challenge study days, pre-challenge and every hour during the challenge procedure.

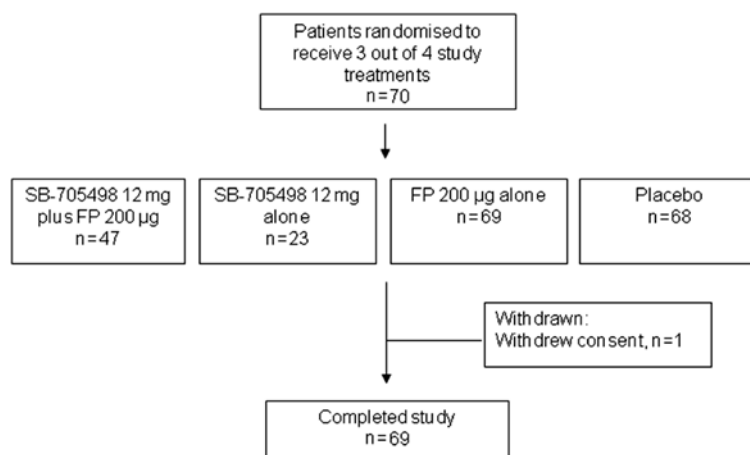


Figure 1. Flow of patients through study.

Table 1. Demography characteristics of the total population.

Randomized, n	70
Age in years, mean (range)	28 (19 – 51)
Male, n (%)	37 (53)
Body mass index in kg/m ² , mean (range)	23.8 (19.1–29.8)
Race, n (%)	
White, Caucasian	67 (96)
White, Arabic/North African Heritage	1 (1)
Asian Heritage	1 (1)
Mixed race	1 (1)

Pharmacokinetic assessments

Blood samples for the determination of plasma concentrations of SB-705498 were collected on Study Day 8 of each treatment, at 1 hour and 5 hours post-dose administration, i.e., pre- and post-allergen challenge. For treatment Periods 2 and 3, an additional sample was taken on Day 1 of treatment to ensure that there were no carry-over effects between treatments. Additional details may be found in the Supplement section.

Statistical analysis

A sample size of 54 was estimated to provide at least 90% power to detect a minimum difference of 1 in TNSS between SB-705498 plus FP relative to FP alone using a one-sided 95% confidence interval, assuming a within subject standard deviation (SD) of 1.45 and between subject SD of 2.08. The power required to detect a difference of 1.3 between SB-705498 and placebo, and between FP and placebo, was estimated to be 91%, and > 99% respectively. 70 subjects were randomized to ensure 54 subjects completed the study.

The weighted mean TNSS and maximum TNSS during the 4-hour allergen challenge period on Day 8 of treatment were derived and analyzed separately using mixed effects models, including period, treatment and co-variables for pre-dose Day 1 TNSS score as fixed effects and subject as a random effect. TNSS recorded in home diary cards on Days 4 to 7 of treatment and weighted mean total nasal airflow assessed by Active anterior rhinomanometry, were also analyzed using this model.

Pharmacokinetic parameters determined from the plasma concentration-time data for SB-705498 were: maximum observed concentration ($C_{\max}$); time at which $C_{\max}$ was observed ($t_{\max}$); area under the SB-705498 concentration-time curve (AUC) Data for adverse events and other safety parameters were summarized.

Results

Patients

70 patients were randomly assigned to receive 3 out of 4 study treatments in a cross-over design (Figure 1). One patient withdrew consent for the study following completion of treatment Period 2 and was withdrawn. In addition, due to a treatment administration error during treatment Period 3, 2 patients had the wrong treatments given so that one ended up having two periods of placebo and no FP treatment, whilst the other received two periods of FP treatment and no placebo. This was discovered after the subjects had completed the follow-up visits and all data for these subjects were reported according to the actual treatment received. Neither subject reported any adverse events relating to study treatment.

The mean age of the group was 28 years, there were approximately even numbers of males and females, and most patients were Caucasian (96%) (Table 1).

Study outcomes

Symptom scores

At the end of 8 days treatment, there were no treatment differences between SB-705498

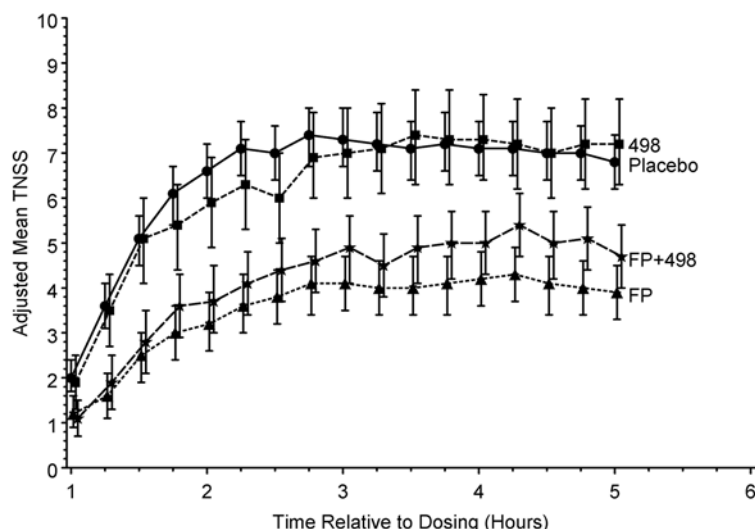


Figure 2. Mean TNSS time profile during 4-hour allergen challenge on Day 8 of treatment. Means adjusted for covariates in the statistical model. 498 = SB-705498 12 mg; FP = Fluticasone propionate 200 µg; TNSS = total nasal symptom score.

Table 2. Summary of on-treatment adverse events with incidence $\geq 2\%$ in any treatment group.

Adverse event, n (%)	SB-705498 + FP n = 47	SB-705498 n = 23	FP n = 69	Placebo n = 68
Any event	19 (40)	13 (57)	28 (41)	24 (35)
Hypersensitivity ¹	10 (21)	7 (30)	11 (16)	12 (18)
Headache	5 (11)	5 (22)	11 (16)	9 (13)
Nasal discomfort	0	0	2 (3)	3 (4)
Cough	1 (2)	0	0	1 (1)
Nasopharyngitis	1 (2)	1 (4)	1 (1)	1 (1)
Influenza	1 (2)	0	2 (3)	0
Pyrexia	0	1 (4)	1 (1)	0

¹Symptoms due to allergic rhinitis.

alone and placebo or between SB-705498 plus FP and FP alone, in mean TNSS over the 4-hour challenge period (Figure 2). Treatment with FP alone or SB-705498 plus FP, vs. placebo, resulted in significant reductions in mean TNSS over the 4-hour challenge period. Compared with placebo, the mean score reduction during FP treatment was at least 1.9 at all time points, and during SB-705498 plus FP was at least 1.6 at all time points, both representing a clinically meaningful reduction in symptoms. Mean (90% CI) treatment differences in TNSS over 0–4 hours: SB-705498 – placebo: weighted mean (WM): -0.2 ($-0.9, 0.4$), maximum score (Max): -0.4 ($-1.2, 0.4$); SB-705498 plus FP – FP: WM: 0.7 ($0.2, 1.2$), Max: 1.1 ($0.5, 1.7$); FP – placebo: WM: -2.9 ($-3.4, -2.5$),

Max: -3.2 ($-3.8, -2.7$); SB-705498 plus FP – placebo: WM: -2.3 ($-2.8, -1.8$), Max: -2.1 ($-2.8, -1.5$)

Mean TNSS data recorded in diary cards at home on Days 4 to 7 of treatment showed a similar pattern of results. Mean (90% CI) treatment differences were: SB-705498 – placebo: -0.4 ($-1.0, 0.2$); SB-705498 plus FP – FP: 0.2 ($-0.3, 0.6$); FP – placebo: -1.4 ($-1.8, -1.0$); SB-705498 plus FP – placebo: -1.2 ($-1.7, -0.8$).

Other efficacy endpoints

Treatment with SB-705498 alone or SB-705498 plus FP had no effect on mean nasal airflow or mean RQLQ scores (data not shown). Compared with placebo, treatment with SB-705498 plus FP or with FP alone resulted in significant increases in nasal airflow (Mean (90% CI) treatment differences were: SB-705498 plus FP – placebo: 72.4 ($48.3, 96.5$) ml/s; FP – placebo: 81.4 ($60.5, 102.2$) ml/s). Treatment with SB-705498 plus FP or with FP alone also resulted in significant improvements in mean global RQLQ scores; the mean differences from placebo both exceeded the MID (Mean (90% CI) treatment differences were: SB-705498 plus FP – placebo: -0.52 ($-0.74, -0.31$); FP – placebo: -0.68 ($-0.87, -0.49$)).

Safety

The proportion of patients reporting adverse events during each treatment was: SB-705498: 57%; SB-705498 plus FP: 40%; FP: 41%; placebo: 35% (Table 2). The most common events reported in all groups were allergic rhinitis symptoms, categorized as hypersensitivity, followed by headache. Very few patients reported events that were attributed to study medication: SB-705498: 0; SB-705498 plus FP: 1 patient reported throat irritation; FP: 1 patient reported nasal discomfort and 1 reported nasal discomfort and headache; placebo: 1 report of nasal discomfort with sneezing, 1 of nasal discomfort, 1 of headache).

Routine laboratory parameters, heart rate, blood pressure, oral temperature and ECG values showed no clinically significant changes during any treatment.

Pharmacokinetic assessments

Results for SB-705498 pharmacokinetic (PK) analysis showed the systemic exposure was similar to those seen previously with this dosing regimen. (See Supplement section).

Discussion

This study showed that 8 days treatment with SB-705498 was not effective in alleviating the symptoms of AR, or in providing additional relief of symptoms to treatment with FP, in either a validated challenge chamber setting or in symptoms induced in the wild-type setting. The results were consistent across the other efficacy endpoints of nasal flow and RQLQ scores. FP alone was very effective in treating the symptoms of AR and in improving RQLQ scores, consistent with previous studies [26, 27, 28, 29]. The systemic exposure to SB-705498 showed no marked differences in exposure when SB-705498 was administered alone or in combination with FP. SB-705498 is a highly potent and selective topical drug, demonstrating 85% receptor occupancy following intranasal administration, and earlier studies showed it to be effective in reducing capsaicin-induced nasal secretions in both a pre-clinical model and in a single dose study in patients with non-allergic rhinitis [19, 20]. Despite the evidence for engagement of the TRPV1 receptor, a translation in to clinical efficacy was not demonstrated in this study. It is interesting to speculate that TRPV1 should exhibit an impact on the pruritic component of the TNSS score i.e., itch, however there was no impact on this domain.

Treatments with SB-705498 and FP were administered separately in the morning and evening which excluded any possibility that one treatment had any washout effect on the other. In addition, the pronounced treatment effects observed with FP treatment, together with the homogeneity of response in VCC-derived TNSS scores clearly indicate that this was a well-designed and adequately powered study. The VCC is a robust and well established methodology that has been used previously in AR studies, showing reproducible effects on TNSS scores [21, 22, 23]. An in-depth review of the role of allergen challenge chambers in evaluating anti-allergic

medications in allergic rhinitis concluded that they provide important supportive data to, and have some advantages over, studies in wild-type disease [21]. Most chamber studies are conducted out of season but this study was conducted in grass pollen season and confirmed the utility of chamber studies at any time of year. Patients' symptoms upon entering the chamber were minimal, suggesting that despite being primed, the transfer from home to car to unit and protocol processing time allowed for any overt symptoms to subdue. Although chamber studies cannot provide information on the long-term effects of medications in the wild-type environment, the advantage of challenge chambers is that they provide a controlled environment which can eliminate some of the confounding factors encountered in traditional outdoor studies. These include variability in outdoor pollen counts over the course of a study and variability in pollen exposures due to patients' daily routines. In addition, the effects of allergen on TNSS have been reported to be similar when generated in a challenge chamber compared with natural conditions [21, 30]. This was also the experience in the current study as diary card data collected at home during the pollen season supported the results for the primary endpoint data generated in the chamber.

The neural mechanisms involved in AR are less well understood than the well-described immunological, IgE-mediated mechanism, but studies have shown that in AR, inflammatory mediators stimulate afferent sensory nerve endings resulting in mucosal hyperinnervation and an increased expression of neurotrophins and neuropeptides [31, 32]. TRPV1 is expressed on sensory neurons including those innervating the nasal mucosa, and an increased number of sensory nerve fibers have also been reported in patients with AR compared with controls [33]. The rationale for treating AR with a TRPV1 antagonist was based on the reasoned hypothesis that the residual symptoms of AR after standard pharmacotherapy may be the result of nasal neuronal hyper-responsiveness. Our results suggest that any such symptoms are not mediated via the TRPV1 pathway. In a study, evaluating 7 days treatment with a low dose of SB-705498 in patients with AR, SB-705498 inhibited low-

grade pain and heat sensation elicited by a 5 μ M capsaicin spray but was ineffective in attenuating the symptoms induced by allergen challenge [34]. Although this study was limited by the fact that the formulation of SB-705498 used was not optimized with regard to its solubility, vehicle, particle size and pharmacokinetic properties, these results concur with the findings of our study. A study in patients with non-allergic rhinitis also showed a lack of efficacy on cold dry air challenge-induced symptoms following 14 days treatment with SB-705498, despite engagement of the TRPV1 mechanism [35].

In conclusion, although SB-705498 is a highly selective, potent topical therapy, and an effective antagonist of the TRPV1 receptor, this did not translate to clinical efficacy in a robust clinical model of allergic rhinitis, suggesting a redundancy in symptom pathways. These results indicate that this class of compound would not be an effective treatment in allergic rhinitis.

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Conflict of interest

PB, RDM, JD, JB and KS are GSK employees and hold shares in GSK. KY was an employee of GSK at the time of study conduct. PZ, RZ, PL and FH are employees of the Vienna Challenge Chamber, Allergy Centre in Vienna which received an Investigator Grant from GSK for conducting this study.

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Supplement

Pharmacokinetic assessments

Methods

Blood samples for the determination of plasma concentrations of SB-705498 were collected on Study Day 8 of each treatment, at 1 hour and 5 hours post-dose administration i.e. pre- and post-allergen challenge. For treatment periods 2 and 3, an additional sample was taken on Day 1 of treatment to ensure that there were no carry-over effects between treatments. Samples were analysed using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography/tandem mass spectrometry analysis. The lower limit of quantification was 2.5 ng/ml using a 50 µl aliquot of EDTA plasma. The higher limit of quantification was 2,000 ng/ml.

Results

Results for SB-705498 pharmacokinetic (PK) analysis showed the systemic exposure was similar to those seen previously with this dosing regimen (Table 1S). Exposure to SB-705498 on Day 8 was similar when taken in combination with FP compared with SB-705498 alone (mean treatment ratio: 1.05 (90% CI 0.8, 1.38) for AUC and 1.07 (90% CI 0.82, 1.4) for C_{max}). t_{max} was also similar between the two regimens, being ~ 5 hours post dose (range: 0 – 5.23 h) on Day 8.

Table 1S. Plasma pharmacokinetics for SB-705498 12 mg following 8 days of dosing

	AUC _{0-t} (ng×h/ml)		C _{max} (ng/ml)		t _{max} (h)	
	SB-705498 12 mg	SB-705498 12 mg + FP	SB-705498 12 mg	SB-705498 12 mg + FP	SB-705498 12 mg	SB-705498 12 mg + FP
Mean	698	744	171	185	3.64	3.42
SD	385	477	90.6	111	2.05	2.07
Minimum	115	135	32.3	31.5	0.00	0.00
Median	604	640	149	153.9	5.03	4.93
Maximum	1475	2300	345	482.7	5.22	5.23
Geometric mean	588	609	146	154	–	–
95% CI	446 – 776	500 – 741	111 – 191	128 – 186	–	–

AUC_{0-t} = area under the SB-705498 concentration-time curve from 0 to last time point; C_{max} = maximum observed concentration; t_{max} = time to maximum observed plasma concentration; SD = standard deviation

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