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TRPV1 inhibition does not prevent cold dry air-elicited symptoms in non-allergic rhinitis

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Key words

non-allergic rhinitis –
cold dry air challenge –
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chamber – intranasal –
SB-705498 – TRPV1-
antagonist – adults

Abstract. Background: The transient receptor potential vanilloid 1 (TRPV1)-expressing sensory C-fibers may play a role in the development of nasal hyper-responsiveness and symptoms of non-allergic rhinitis (NAR). Objective: To evaluate the effects of a TRPV1-antagonist, SB-705498, on cold dry air (CDA)-induced symptoms in patients with NAR. Methods: This randomized, double-blind, placebo-controlled, crossover study evaluated 14 days of once daily, topical intranasal SB-705498 12 mg in 40 patients with NAR using a CDA challenge experimental model in an environmental exposure chamber (EEC, Cetero Research, Mississauga, Ontario). The primary endpoint was total symptom score (TSS), expressed as weighted mean over 60 minutes (WM0-60) or maximum TSS at 1 hour and 24 hours post-dosing. Results: Treatment with SB-705498, relative to placebo, did not improve WM0-60 or maximum TSS at 1 hour and 24 hours post-dosing on days 1 or 14. Mean (95% CI) treatment differences (SB-705498 – placebo) on day 14 were, for WM0-60 at 1 hour: –0.12 (–0.60, 0.36); for maximum TSS at 1 hour: –0.03 (–0.58, 0.51). SB-705498 had no impact on any other efficacy parameters. SB-705498 was well tolerated and pharmacokinetics analysis supported the dosing regimen. Conclusion: SB-705498 12 mg for 14 days did not alleviate the CDA-induced symptoms of NAR. Despite engagement of the TRPV1 receptor, there was no translation to clinical efficacy, suggesting redundancy in symptom pathways.

mediated via an immunoglobulin E (IgE) mechanism or caused by infection. NAR is a heterogeneous disease, and several different phenotypes have been identified, including occupational, hormonal, NAR in the elderly, and NAR with eosinophilia syndrome [1, 3]. However, ~ 50% of patients have idiopathic NAR with no known associated etiology, although exposure to cold is perceived as a major trigger of symptoms in these patients [3]. Several pathological mechanisms in NAR have been postulated, and at present the two most plausible hypotheses have been reported as a localized non-IgE-mediated inflammatory response and an autonomic neural misbalance with involvement of non-myelinated sensory C-fibers [1, 2, 3, 4, 5].

The transient receptor potential vanilloid 1 (TRPV1) is a ligand gated ion channel expressed on sensory neurons, including C-fibers, and is activated by a range of physiological factors, including noxious temperature, protons (pH), osmotic stress, diverse lipid derivatives, and is sensitive to vanilloid molecules such as capsaicin [6, 7]. The activation of TRPV1-expressing sensory C-fibers is thought to play a role in the development of nasal hyper-responsiveness and associated symptoms of NAR through local release of neurotransmitters and by depolarization of nerve terminals, resulting in reflex parasympathetic secretory responses and sneeze as well as central sensory perception such as itch [8]. Blocking the nasal sensory nerve stimulation may therefore be expected to control nasal hyper-responsiveness and prevent the induction of rhinitis symptoms.

SB-705498 is a potent and selective TRPV1 antagonist [9, 10] that has been applied successfully in models of neuropathic and inflammatory pain [11]. Early oral dosing

Introduction

Rhinitis is a chronic nasal inflammatory condition characterized by symptoms of rhinorrhea, sneezing, nasal blockage, and/or nasal itching, affecting up to 30% of the Western population [1, 2]. In non-allergic rhinitis (NAR) patients, symptoms are not

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studies have been completed in neuropathic pain [11], dental pain (NCT00281684), migraine (NCT00269022) as well as cough [12] and have demonstrated no clinically meaningful response. The hyperthermia associated with many of the oral TRPV1 antagonists led to termination of numerous early agents [11]. In a single-dose, cross-over placebo-controlled study evaluating oral doses of 600 mg SB-705498 in patients with chronic cough, TRPV1 receptor occupancy derived from plasma levels and factoring a plasma/lung ratio of 1 was ~ 45% at 2 hours and 25% at 24 hours [12]. This translated to a 4-fold shift in capsaicin dose – response on SB705498 administration and was maintained over the 24-hour period. An intranasal formulation has been developed for treatment of NAR. It was anticipated that a 12 mg intranasal dose would result in high levels of local receptor occupancy and a higher level of receptor engagement than observed with oral doses in the cough study. In a pre-clinical rhinitis guinea pig model where nasal parasympathetic fluid secretory responses were measured by MRI, intranasal SB-705498 was shown to block both capsaicin-induced and hypertonic saline-induced contralateral reflex fluid secretory responses [13]. In the first clinical study in patients with NAR, single doses of 12 mg SB-705498 resulted in a marked reduction in nasal symptoms following capsaicin challenge, compared with placebo [14]. The dose was well tolerated but represented the maximum dose possible based on the physio-chemical properties and viscosity of the suspension.

The aim of this study was to evaluate the effects of 14 days treatment with intranasal SB-705498 on nasal symptoms induced by cold dry air (CDA) in patients with NAR, utilizing a challenge chamber as well as exploring the impact of “wild type” exposure i.e., following natural exposure to common environmental stimuli.

Materials and methods

Patient population

Male or females aged 18 – 65 years with a diagnosis of NAR were eligible. NAR was defined as a > 1 year history of perennial rhinitis symptoms for several months per year

that were triggered by environmental provocateurs (e.g., weather changes, irritants, air pollution) but were not attributed to allergy, infections, or nasal abnormalities. A symptomatic response to CDA challenge (total symptom score ≥ 4 out of a total of 9) was required to be shown at two screening visits. All patients had normal levels of total serum IgE and negative skin prick or radioallergosorbent tests to common allergens. Patients with nasal polyps, nasal septal perforation, 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; 48 hours: nasal antihistamines; 7 days: oral antihistamines, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, methylxanthines; 4 weeks: nasal or inhaled corticosteroids; 12 weeks: oral corticosteroids.

All patients gave their written informed consent prior to participation, and the study was approved by the Ontario IRB Services Ethics Committee

Study design

This was a randomized, double blind, placebo-controlled, two-way crossover study conducted over the winter and spring months in a single center in Ontario, Canada (study number VR1114974; NCT01424514). Randomized patients were scheduled to receive 2 weeks treatment with SB-705498 12 mg or placebo with a 4-week washout period in between each treatment. Treatment was administered via intranasal spray, 4 actuations per nostril once daily. The primary endpoint was the effect of 14 days treatment on total symptom scores elicited by a 1 hour CDA challenge at 1 hour and 24 hours post-dosing.

Cold dry air (CDA) challenge

The CDA challenge was performed using an experimental model in an environmental exposure chamber (EEC, Cetero Research, Mississauga, Ontario). The EEC is a specific facility designed to create controlled environ-

ments ideal for the study of NAR, in which factors of relative humidity, temperature, and air flow can be accurately controlled [15]. A maximum of four patients could be challenged at one time, with patients sitting in the front row of the chamber in the direct air stream for ~ 60 minutes. Patients were exposed to CDA at 14 °C ($\pm$ 5 °C), less than 15% relative humidity, and with air velocity at ~ 5 feet/second ($\pm$ 3 feet/second) directed at the patients' faces.

One to 5 weeks prior to the first treatment period, patients were screened and underwent two CDA challenges to ensure eligibility based on induced nasal symptoms. During the treatment periods, CDA challenge was performed on day 1 at 1 hour post-dosing and day 14 at 1 hour and 24 hours post-dosing (i.e., day 15).

Study outcomes

Symptom scores

Symptoms were assessed using patient-completed symptom score diary cards. The total symptom score (TSS) comprised the three components of nasal congestion, rhinorrhea, and post nasal drip. Each was scored on a four point scale from 0 to 3 (where 0 = absent symptoms, 3 = severe symptoms), giving a TSS range from 0 to 9. Sneezing was measured separately on the same 0 – 3 rating scale.

Total Ocular Symptom Score (TOSS) was based on the assessments of red, itchy, and tearing eyes, also assessed on a four point scale of 0 – 3, giving a maximum TOSS of 9 averaged for both eyes.

Chamber challenge assessment

On the clinic study days (days 1, 14, and 15), patients completed symptom score diary cards pre-dose and during the CDA challenge post-dose at 10-minute intervals for the first 1/2 hour and at 15-minute intervals during the second 1/2 hour.

“Wild type” assessment

On days 7 – 13, patients completed symptom diary cards at home in the evening, rep-

resenting a reflective rating of the patients' symptoms over the preceding 12 hours. Trigger days were noted as days when the subject went outside and the temperature was below 14 °C. Outside air temperature in the location of the Research Unit was also recorded.

Other efficacy endpoints

On clinic study days 1, 14, and 15, nasal cavity geometry (minimal cross-sectional area) was measured using acoustic rhinometry at pre-dose (days 1 and 14) and at the end of the 1 hour CDA challenge. All measurements were completed by trained operators, and every effort was made to use the same equipment consistently for each patient.

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 [16]. The RQLQ was self-completed by patients in the clinic at pre-dose on days 1 and 14 and after the CDA challenge on day 15 (25 hours after last dose of study medication).

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 first screening visit and pre-dose on study days 1 and 14 of treatment. Routine hematology, blood chemistry and urinalysis assessments, and single 12-lead electrocardiograms (ECGs) were assessed at screening and pre-dose on study day 14 of treatment. Patients with QTcB > 500 msec or uncorrected QT > 600 msec were required to be withdrawn from the study.

Pharmacokinetic assessments

Blood samples for the determination of plasma concentrations of SB-705498 were collected on study days 1 (pre-dose, and 1, 2, and 3 hours post-dose) and 14 (pre-dose, and 1, 2, 3, and 24 hours post-dose) of treatment. Samples were analyzed using a validated analytical method based on protein

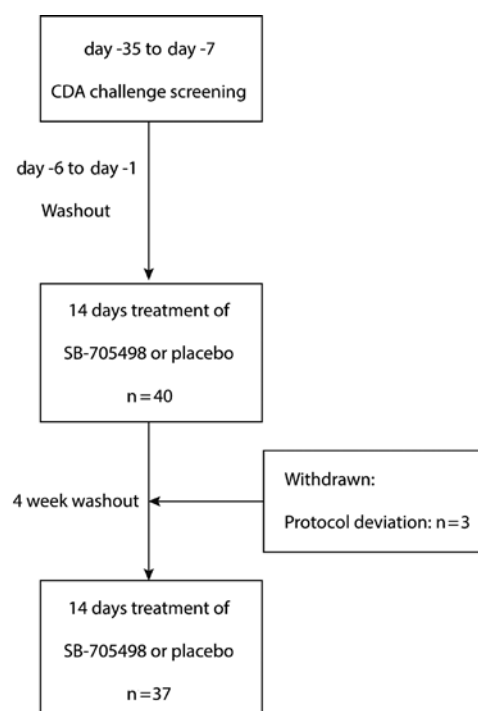


Figure 1 Flow of patients through study. CDA: cold dry air; SB-705498: intranasal SB-705498 12 mg once daily.

Table 1. Demography characteristics of the total population.

Randomized, n	40
Age in years, mean (range)	41 (22 – 61)
Male, n (%)	20 (50)
Body mass index in kg/m ² , mean (range)	25.26 (20.0 – 29.4)
Race, n (%)	
White Caucasian	29 (73)
African American/African Heritage	3 (8)
Asian Heritage	4 (10)
Other	4 (10)

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.

Statistical analysis

A sample size of 36 patients was estimated to give > 98% chance of correctly declaring a positive study if the true effect size (SB-705498 – placebo) was 1 point (the target effect size), and a 5% chance of incorrectly declaring a positive study if the true effect size was zero, based on the primary endpoint TSS and assuming a standard deviation of 1.168.

The weighted mean TSS over 0 – 60 minutes (WM 0 – 60) and the maximum TSS at 1 hour post-dosing on day 1, and at 1 hour and 24 hours post-dosing on day 14 were derived and analyzed separately using mixed effects models, including period and treatment as fixed effects and subject as a random effect. Individual symptom scores, TOSS, TSS recorded in home diary cards on days 7 – 13 of treatment, and minimum cross sectional nasal area assessed by acoustic rhinometry were also analyzed using this model. Covariates for pre-dose (day 1) measurements were also included in the analysis of minimum cross sectional nasal area assessed by acoustic rhinometry.

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 from zero to 3 hours post-dose (AUC (0–3)) and from zero to 24 hours post-dose (AUC (0–24)).

Data for adverse events and other safety parameters were summarized.

Results

Study population

40 patients were randomly assigned to study treatment in a cross-over design (Figure 1). Three patients were withdrawn during the study due to deviations from the protocol and did not receive the second 14 days of treatment.

The mean age of the group was 41 years, the proportion of males and females was even, and most patients were white (73%) (Table 1).

Study outcomes

Symptom scores – chamber challenge

Treatment with SB-705498, relative to placebo, did not result in any improvements in CDA-induced symptoms either in WM 0 – 60 or maximum TSS at 1 hour and 24 hours post-dosing after 1 or 14 days of treatment (Figure 2). Mean (95% CI) treatment differences (SB-705498 – placebo) on day 14 were, for WM 0 – 60 at 1 hour: –0.12

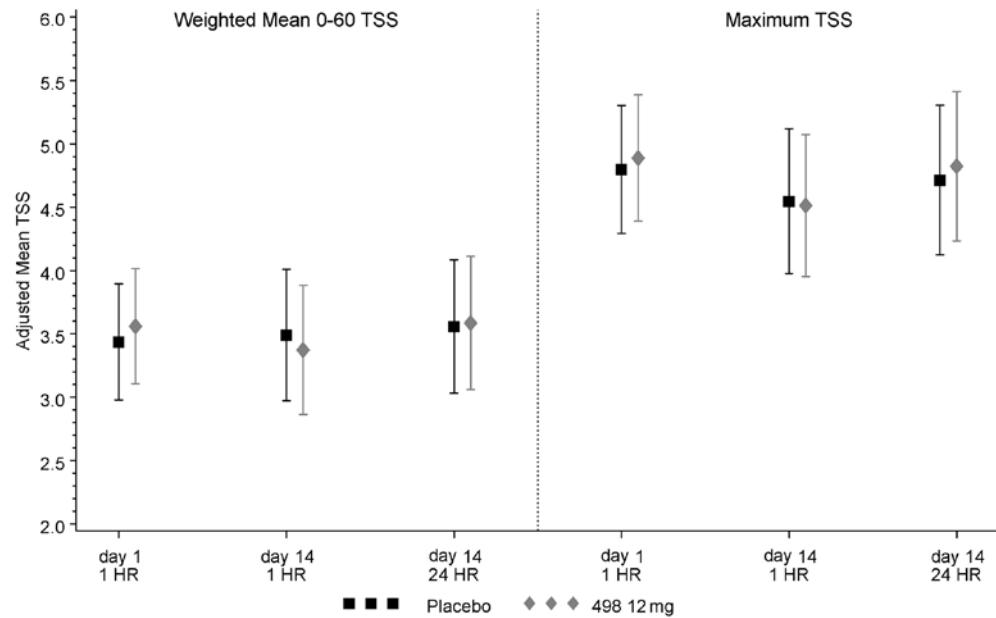


Figure 2. TSS weighted mean and maximum score during CDA challenge on days 1 and 14 of treatment. TSS = total symptom score; CDA = cold dry air; 498 12 mg: intranasal SB-705498 12 mg once daily.

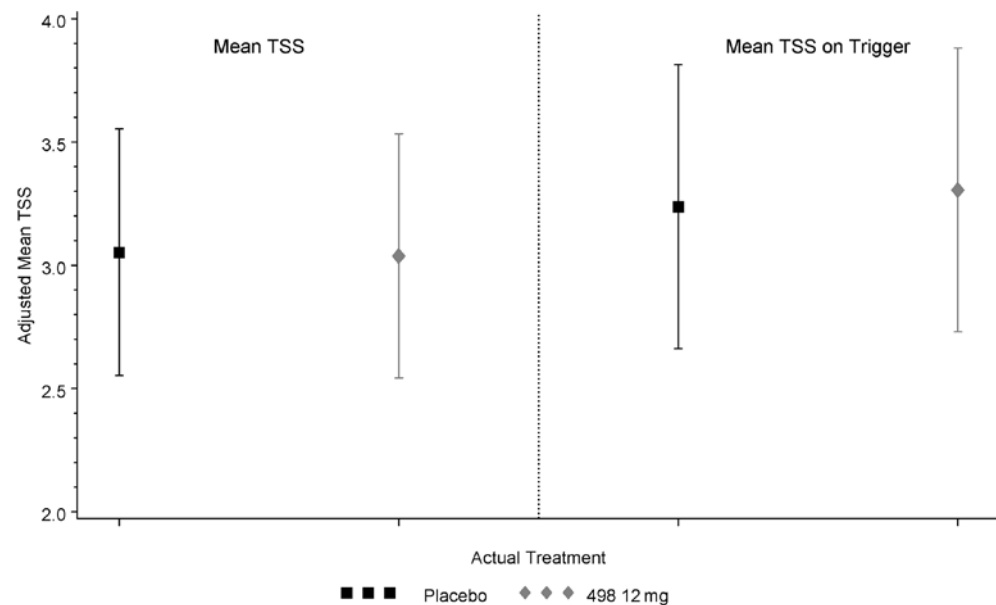


Figure 3. Diary card mean TSS over days 7 to 14 of treatment. Mean TSS: mean for all days from day 7 to 14; mean TSS on trigger: mean of days when the patient went outside and the temperature was below 14 °C. TSS = total symptom score; 498 12 mg: intranasal SB-705498 12 mg once daily.

(−0.60, 0.36), at 24 hours: 0.03 (−0.45, 0.51); for maximum TSS at 1 hour: −0.03 (−0.58, 0.51), at 24 hours: 0.11 (−0.51, 0.72).

Symptom scores – “wild type” environmental exposure

There were no differences between treatments in diary card mean TSS over 7 to 14 days, either overall (treatment difference: −0.01 (95% CI −0.51, 0.48)) or on trigger

days (treatment difference: 0.07 (95% CI −0.56, 0.69)) (Figure 3).

Repeat dosing with SB-705498 also had no impact on sneezing scores or ocular symptoms (data not shown).

Other efficacy endpoints

There was no significant increase of nasal cavity area after SB-705498 treatment relative to placebo. The treatment difference in

Table 2. Summary of all on-treatment adverse events.

Adverse event, n (%)	Placebo (n = 38)	SB-705498 (n = 39)
Any event	8 (21)	9 (23)
URTI	1 (3)	3 (8)
Cough	0	2 (5)
Dizziness	1 (3)	1 (3)
Nasal congestion	1 (3)	1 (3)
Erythema	0	1 (3)
Hematoma	1 (3)	0
Headache	0	1 (3)
Nasal discomfort	1 (3)	0
Oropharyngeal pain	0	1 (3)
Paresthesia	1 (3)	0
Pruritis	0	1 (3)
Rib fracture	1 (3)	0
Sneezing	1 (3)	0
Tonsillitis	1 (3)	0

URTI = upper respiratory tract infection; SB-705498 = intranasal SB-705498 12 mg once daily.

the sum of the minimum cross sectional area for the left and right nostril after 14 days treatment was -0.08 cm^2 (95% CI $-0.13, -0.02$).

There was also no effect of treatment on quality of life; change from baseline mean RQLQ scores (treatment difference on day 14: -0.05 (95% CI $-0.36, 0.26$).

Safety

The proportion of patients reporting adverse events was similar in the placebo and SB-705498 treatment periods (21% and 23%, respectively) (Table 2). The most common event was upper respiratory tract infection, reported by 1 (3%) and 3 (8%) of patients during placebo and SB-705498 treatment, respectively. Drug-related events were reported for 2 (5%) patients in the pla-

cebo group, one due to dizziness and one due to nasal discomfort/paraesthesia; and for 1 (3%) patient in the SB-705498 group, due to nasal congestion. There were no serious adverse events.

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

Pharmacokinetic assessments

Results for SB-705498 pharmacokinetic (PK) analysis showed that the systemic exposure was similar to those seen previously with this dosing regimen and supported once daily dosing, showing an ~ 2 -fold accumulation over the dosing period (Table 3). Over 14 days, there was an increase in geometric means for $C_{\max}$ of 1.65-fold and for AUC (0–3) of 2.25-fold. Systemic exposure to SB-705498 was not affected by the order in which the treatments were received. The 4 weeks between sessions ensured complete washout of drug.

Discussion

This study showed that, compared with placebo, 14 days treatment with intranasal SB-705498 did not alleviate the symptoms of NAR triggered by cold in an environmental challenge chamber (ECC) or in a wild type setting. Results were consistent across all efficacy endpoints, including symptom scores, nasal cavity geometry, and RQLQ scores. The PK results supported the once daily regimen and were consistent with other

Table 3. Plasma pharmacokinetics for SB-705498 12 mg following single and 14 days of dosing.

	AUC (0–3 h) (ng·h/mL)		AUC (0–24 h) (ng·h/mL)		$C_{\max}$ (ng/mL)		$t_{\max}$ (h)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Mean	107	204	NC	1422	66.9	104	–	–
SD	87.2	166	NC	1236	50.0	87.7	–	–
Minimum	NC	24.5	NC	76.8	2.85	10.6	0.98	0.98
Median	88.6	168	NC	909	64.4	75.3	2.00	2.98
Maximum	351	735	NC	4815	191	399	3.03	3.08
Geometric mean	64.0	144	NC	950	44.0	72.8	–	–
95% CI	42.5–96.3	109–192	NC	694–1,302	30.9–62.8	54.4–97.4	–	–

AUC = area under the SB-705498 concentration-time curve from 0 to 3 hours post-dose (AUC (0–3)) and from 0 to 24 hours post-dose (AUC (0–24)); $C_{\max}$ = maximum observed concentration; $t_{\max}$ = time to maximum observed plasma concentration; NC = not calculated; SD = standard deviation; CI = confidence interval.

studies, showing an ~ 2-fold accumulation over the dosing period [13], and therefore insufficient plasma concentrations cannot account for the lack of efficacy shown. Earlier studies with this compound were positive in both a pre-clinical guinea pig rhinitis model [13] and in a single dose evaluation in patients with NAR [14], both showing a reduction in capsaicin-induced nasal secretions and symptoms. Although the previous studies used a capsaicin challenge model, compared with the CDA model used in this study, cold air-induced symptoms are the result of mucosal drying and increased osmolarity of surface lining fluid, which activates the same TRPV1 receptor as capsaicin [17, 18], thus the different phenotypes would not be expected to respond differently. A recent study of SB-705498 12 mg for 8 days also showed no effects on the allergen-induced symptoms of seasonal allergic rhinitis, or provided additional relief of symptoms when in combination with fluticasone propionate [19]. A similar study by Alenmyr using low doses in an unformulated vehicle showed comparable effects [20].

Although intranasal SB-705498 is a highly potent and selective topical drug, demonstrating 85% receptor occupancy following intranasal administration, this was not reflected in the clinical efficacy endpoints in this study. In parallel studies in cough, oral dosing of 600 mg resulted in 45% receptor occupancy at peak plasma concentrations, which was sufficient to shift the dose response to capsaicin by 4-fold [12]. This 4-fold shift also did not translate to a clinical effect in cough symptoms. The collective evidence for the intranasal formulation in NAR indicates that, despite engagement of the mechanism via antagonism of the TRPV1 receptor, the lack of translation to clinical efficacy suggests a redundancy in symptom pathways.

Data for the primary endpoint for this study were collected in a controlled setting using an ECC model, which has previously been shown to provide a consistent and reliable method for measuring CDA-induced symptoms in patients with NAR [15]. Although this paper did not report on the validation of the model in healthy volunteers (HVT), 10 HVTs were included in the initial validation and showed no response to chal-

lenge in objective (rhinometry) or subjective measures (AM Salapatek; personal communication). Other studies have also reported CDA challenge as a robust method for measuring nasal reactivity in patients with NAR, demonstrating good specificity and sensitivity [21, 22]. The advantage of a challenge model is that the environmental conditions can be exactly reproduced at all challenge time-points so that the results are not confounded by any external factors. Although our study employed different CDA stimuli (14 °C and < 15% relative humidity) to previous studies (–10 °C and < 10% RH) [20, 21], all patients underwent a screening challenge to ensure nasal symptoms were induced under these conditions, and the symptom scores demonstrated in the placebo arm showed that these data were reproducible.

It could be hypothesized that if CDA is activating TRPV1 via osmotic stress mechanisms then hot dry air should be a more potent stimulus. The Chamber validation study [15] demonstrated an increase in TNSS when patients were exposed to warm dry air (35 °C 20% RH) with mild to moderate congestion as the main symptom but also included rhinorrhea, and further increased the overall TNSS when the temperature was switched to 15 °C 15% RH. This is in part supported by the findings of Togias et al. [23] where hot dry air increased general rhinitis symptoms. However, with most patients complaining of CDA as the provocation agent causing symptoms, the CDA paradigm was deemed optimal. This view is supported by Van Gerven, where short-term exposure to CDA is seen as a reliable diagnostic tool with high sensitivity and specificity [22].

Having defined the response in the chamber, “Wild type” NAR symptoms were also evaluated during treatment through collection in daily diary cards, specifically on days when the temperature was the same or below that in the ECC. The study was conducted during the winter and spring, and so the wild type exposure monitoring would have been influenced by external cold and other environmental provocation agents. However, results for the diary card symptoms were highly concordant with results generated in the ECC, providing good cross-validation data between natural exposure conditions and the ECC model.

Currently, the two most plausible hypotheses for pathological mechanisms in NAR are reported to be localized non-IgE-mediated inflammatory response and autonomic neural misbalance with involvement of non-myelinated sensory C-fibers [1, 2, 3, 4, 5]. Further exploration of the parasympathetic nervous system could have utilized a muscarinic antagonist. To our knowledge, this has not been performed in a Chamber setting, but a close paradigm is the successful use of ipratropium bromide in cold induced rhinitis in alpine skiers where the prevalence of rhinorrhea was 48%, with 96% reporting severe symptoms [24]. National guidelines recommend anti-muscarinic agents for symptoms of “watery rhinorrhea” but not for the other symptoms within the TNSS [25]. A selective TRPV1 antagonist should impact all domains of the TNSS. Blockade of the TRPV1-expressing sensory C-fibers was predicted to result in reduction of nasal hyper-responsiveness and associated symptoms of NAR. Increased concentrations of neuropeptides in the nasal mucosa of symptomatic patients with NAR have been reported [26], and prolonged treatment with capsaicin, resulting in the desensitization of C-fibers, has been shown to be therapeutically effective in NAR [27, 28, 29]. Cruz et al. [30] reported that nasal mucosal epithelial shedding was associated with clinical symptoms in CDA sensitive patients, suggesting a defect in mucosal water homeostasis. They hypothesized that this could be attributable to the activation of capsaicin-sensitive nerve endings due to the hypertonicity itself. How this links to TRPV1 activation has been explored in rodent systems; in rat isolated trigeminal ganglion cells, changes in osmolarity have been shown to augment capsaicin-induced currents and cell surface expression of TRPV1 [17]. In addition, the finding that SB-705498 inhibits hypertonic saline induced parasympathetic nasal fluid responses in the guinea pig also suggest that tonicity changes involve TRPV1 dependent pathways [13]. An alternative mechanism based on physical trauma to nasal mucosa resulting in nociceptor exposure and development of symptoms has also been proposed. Treatment with the antihistamine azelastine has been shown to reduce total

rhinitis symptom scores in patients with vasomotor, non-allergic rhinitis [31]. Powe et al. [32] demonstrated increased mucosal mast cells and IgE cells, and increased eosinophilia in the superficial submucosa of patients with idiopathic rhinitis compared with non-rhinitis controls. However, such findings have not been confirmed by other groups [33, 34]. Our data suggest that the blockade of a single receptor such as TRPV1 is unlikely to be an effective treatment in NAR. The lack of clinical efficacy demonstrated in this study highlights the problems of developing new treatments for a heterogeneous disease with many phenotypes and for which the pathophysiological mechanisms are not fully understood [2, 4]. Future strategies may lead to the development of selective TRPV1/A1/V4 antagonists or combination therapies to minimize the impact of diverse physiological triggers or other neuronal targeted therapy.

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, indicating that this class of compound would not be an effective treatment in NAR.

Conflict of interest

This study was funded by GlaxoSmithKline. RDM, PB, JD, AN, JB, and KS, are GSK employees and hold shares in GSK. KY was an employee of GSK at the time of study conduct. DP's institute at the time of study conduct, Cetero Research, received an Investigator Grant from GSK for conducting this study.

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