

The Efficacy and Tolerability of Two Novel H₁/H₃ Receptor Antagonists in Seasonal Allergic Rhinitis

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Key Words

H₁/H₃ · H₃ antagonist · Seasonal allergic rhinitis · Allergen chamber

Abstract

Background: A therapeutic role for histamine H₃ receptor antagonism in allergic rhinitis has been proposed and may be complementary to the well-known benefits of H₁ receptor antagonism. Combined H₁/H₃ blockade has therefore been investigated as a novel therapeutic approach that may enhance symptom relief, particularly nasal blockage. **Methods:** Two novel H₁/H₃ dual receptor antagonists were investigated in phase I and II safety and efficacy studies. One molecule (GSK1004723) was designed for intranasal administration as a suspension or solution and the other molecule (GSK835726) for oral administration. In phase I and II studies, both molecules were compared with an active control and/or placebo in randomised studies. In phase II studies, efficacy was assessed in an environmental allergen challenge chamber (ECC). Subjects with seasonal allergic rhinitis were exposed to allergen to induce symptoms. Efficacy and safety was measured over 4, 7 and 20–24 h post-dose. The endpoints included total nasal symptom score and nasal blockage. **Results:** Intranasal suspension of GSK1004723 and oral GSK835726 were well tolerated. Single-dose intranasal suspensions of GSK1004723 (220, 1,100 µg) failed to demonstrate clinically significant attenuation of symptoms of aller-

gic rhinitis induced in the ECC. Single (10, 50, 100 mg) and 3-day repeat (10 mg) dose oral GSK835726 demonstrated clinically significant attenuation of symptoms in the ECC comparable to cetirizine 10 mg. Three-day repeat dosing of the intranasal solution GSK1004723 1,000 µg also demonstrated a statistically significant attenuation of nasal symptoms, but was less than seen with cetirizine and GSK835726 and caused initial nasal discomfort. **Conclusions:** Combined H₁/H₃ antagonism did not show differentiation from H₁ antagonism in reducing total nasal symptom score or nasal blockage.

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Introduction

Allergic rhinitis is an inflammatory disease of the nasal mucosa with increasing prevalence [1]. It is believed that the interaction of antigen with antigen-specific IgE bound to IgE receptors on the surface of nasal mast cells causes the release of mediators that generate the symptoms of the disease. The symptoms include nasal congestion, pruritus, sneezing and rhinorrhoea. Histamine is one of the mediators released from mast cells that may be responsible for the production of symptoms, and it is known that application of histamine to the nasal mucosa of non-allergic subjects mimics some of the symptoms of allergic rhinitis [2–4].

The actions of histamine on the nasal mucosa have been shown to be mediated largely by H_1 receptors [5, 6]. Histamine H_1 receptor antagonists are therefore widely used in the treatment of allergic rhinitis and many of the allergic effects of histamine are attenuated by first- and second-generation H_1 blockers [7]. While second-generation orally active H_1 -selective antihistamines such as cetirizine and fexofenadine provide rapid, effective relief for most of the nasal symptoms of allergic rhinitis, they are relatively ineffective for nasal congestion which is the most commonly reported symptom by allergic rhinitis patients [8]. Nasal patency is partly maintained by the activity of sympathetic nerves on vasoconstriction, mediated via the release of noradrenaline and its action at adrenergic receptors present on mucosal blood vessels. Antihistamines are therefore sometimes used in combination with α -adrenergic agonist decongestants to ease nasal congestion [9]. The use of α -agonists is limited, however, due to their potential to produce hypertensive and CNS-stimulant effects. The use of topical corticosteroids is also recommended in treatment guidelines for the treatment of nasal congestion [10].

Rationale for Combined H_1/H_3 Antagonism for the Treatment of Allergic Rhinitis

The anti-allergy efficacy of antihistamines against mast cell-mediated nasal congestion may be expanded by co-treatment with a histamine H_3 receptor antagonist [11]. H_3 receptors were first found in the brain [12], and the receptors have been considered autoreceptors in presynaptic terminals of histaminergic neurons that regulate histamine synthesis and release. These receptors also regulate the release of other chemical mediators such as acetylcholine, noradrenaline, dopamine, serotonin and substance P [13–15]. It has been demonstrated that H_3 receptors exist in human and animal peripheral tissues [13–16], and that H_3 receptors are localised on the epithelium and nerves in human nasal mucosa [17].

In the nose, after mast cell degranulation produced by an allergic reaction, it is proposed that released histamine acts on postsynaptic H_1 receptors to cause H_1 -mediated plasma extravasation, vasodilation and mucus secretion. In addition, histamine produces vasodilation by activating presynaptic H_3 receptors located on postganglionic sympathetic neurons producing a decrease in noradrenaline release.

In a murine model of allergic rhinitis, a potent histamine H_3 -receptor agonist demonstrated that H_3 receptors are involved in the aetiology of nasal allergy [18]. Repeated topical application of antigen caused an increase in sneez-

ing and nasal rubbing in sensitised mice. Oral administration of specific H_3 -receptor agonists resulted in an inhibition of nasal symptoms induced by an antigen similar to an H_1 -receptor antagonist, cetirizine. Furthermore, simultaneous use of H_3 -receptor agonists and an H_1 -receptor antagonist, cetirizine, caused a significant inhibitory effect on nasal symptoms at doses that showed no effect when used separately [18]. In addition, a combination of H_1 and H_3 receptor blockade was demonstrated to inhibit the increase in nasal resistance produced by nasal provocation in the cat [11, 19]. These data suggest that combined H_1/H_3 blockade may provide a novel approach for the treatment of allergic nasal congestion without the hypertensive liability of current α -adrenergic agonist decongestant therapies. This hypothesis was also tested in normal human nasal airways. Administration of histamine to the nose induced significant blockage of nasal airways in normal human subjects as measured by acoustic rhinometry. This was not completely blocked by an H_1 and H_2 antagonist indicating that non- H_1 and - H_2 mechanisms were operating. Thioperamide, an H_3 antagonist had no significant action on the nasal blockage induced by histamine when given alone, but in the presence of the H_1 antagonist cetirizine, thioperamide reduced the histamine-induced nasal blockage above that seen with cetirizine alone [20]. Administration of a specific H_3 agonist to the nasal airways also induced nasal blockage which was reversed by the addition of thioperamide, so there appears to be a contribution of H_3 receptors to histamine-induced nasal blockage in normal human subjects [20]. Activation of H_3 receptors in isolated human nasal turbinate mucosa was also shown to inhibit sympathetic vasoconstriction [21].

Two novel H_1/H_3 dual antagonists have been developed that both display H_1 as well as H_3 antagonist activity [22]. It was proposed that these novel H_1/H_3 antagonists, known as GSK1004723 and GSK835726, would offer a breakthrough in allergic rhinitis, since they would not only provide relief from the symptoms which are attenuated by H_1 receptor blockade such as rhinorrhoea, sneezing and itching, but would also provide relief from nasal congestion through H_3 receptor antagonism resulting in enhanced sympathetically mediated nasal vascular constriction [20, 21]. There is limited published clinical data for such compounds in allergic rhinitis, although data for one such compound has been published [23].

GSK1004723

GSK1004723 was designed for intranasal delivery, to have a long duration of action, low CNS penetration and to be suitable for once-daily administration [24].

Both a solution and suspension formulation were developed. GSK1004723 has a similar H_1 potency as azelastine. In vitro, GSK1004723 demonstrated a greater duration of action than azelastine on histamine-induced stimulation of human recombinant and native human bronchus H_1 receptors. In vivo following intranasal dosing, GSK1004723 was a potent inhibitor of histamine-induced nasal airway resistance in guinea pigs, with a significantly longer duration of action than azelastine. In addition, GSK1004723 was effective at a 10 times lower concentration than azelastine. GSK1004723 also blocked histamine H_3 receptor-mediated nasal secretion in pigs and inhibited the H_3 receptor agonist-induced inhibition of electrically stimulated guinea pig ileum preparation, where prejunctional inhibitory H_3 receptors on cholinergic nerve terminals caused inhibition of twitch contractions.

GSK835726

GSK835726 is an oral, selective and specific dual H_1/H_3 receptor antagonist in vitro with approximately similar affinity for both receptor subtypes. The H_1 antagonist potency of GSK835726 is similar to that of the gold standard second-generation H_1 antagonists, fexofenadine and cetirizine. GSK835726 specifically inhibited histamine-induced activation of the human recombinant H_1 and H_3 receptors with pA_2 values of 8.1 and 7.8, respectively [25]. GSK835726 is also an effective antagonist of histamine H_1 receptor-mediated responses in vivo. Thus, GSK835726 blocked histamine-induced nasal secretions in pigs and histamine-induced skin wheal and flare responses in guinea pigs, with a similar potency as gold standard H_1 receptor antagonists. GSK835726 also inhibited H_3 receptor-mediated inhibition of sympathetic tone in pig nasal turbinates [25].

Objectives of the H_1/H_3 Receptor Antagonist Clinical Programme in Allergic Rhinitis

The objectives of the clinical programme were to establish the safety and tolerability of GSK1004723 and GSK835726, and to test whether they were efficacious in patients with seasonal allergic rhinitis. Intranasal and oral formulations were developed as it is unclear which route of administration would be most beneficial in reducing nasal congestion. The criteria chosen to establish efficacy were a reduction in total nasal symptom score (TNSS) >1 and a reduction in nasal congestion versus placebo.

This review summarises data from two phase I and three phase IIa studies.

Material and Methods

Phase I Clinical Studies

Study 1 (protocol number HHI110157) was conducted to investigate the safety, tolerability and pharmacokinetics (PK) of GSK1004723. It was the first-time-in-man (FTIM) study for the intranasal formulation in which a napadisylate suspension formulation of GSK1004723 was used. It was a double-blind, placebo-controlled, randomised single-dose escalation study, followed by a double-blind, placebo-controlled, randomised parallel group 14-day once daily repeat-dose study in healthy male subjects. The single-dose escalating phase of the study consisted of two cohorts of a total of 19 healthy male subjects; subjects in cohort 1 received 55 μ g (n = 8), 110 μ g (n = 8) and placebo (n = 8). Subjects in cohort 2 received 110 μ g (n = 10), 220 μ g (n = 9), 550 μ g (n = 10), 1,100 μ g (n = 10) and placebo (n = 8). There was an overlapping dose between cohort 1 and 2 (110 μ g, total n = 18). A total of 30 healthy male volunteers were randomised to receive 220 μ g (n = 10), 1,100 μ g (n = 10) or placebo (n = 10) in the parallel group repeat-dose phase of the study. Serial blood samples for PK analyses of plasma GSK1004723 were collected at pre-dose and regular intervals over 24 h post-dose (15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h). Blood samples were analysed for GSK1004723 using a validated analytical method.

Study 2 (protocol number HH3110161) was conducted to investigate the safety, tolerability and PK of oral GSK835726. It was the FTIM study for the oral formulation. It was a double-blind, placebo-controlled, randomised single-dose escalation study, followed by a double-blind, placebo-controlled, randomised parallel group 7-day once daily repeat-dose study in healthy male subjects. The single-dose escalating phase of the study consisted of two cohorts consisting of a total of 17 healthy male subjects. Subjects in cohort 1 received 10 mg (n = 7), 20 mg (n = 8), 50 mg (n = 8) and placebo (n = 8). Subjects in cohort 2 received 50 mg (n = 8), 100 mg (n = 8) and placebo (n = 8). There was an overlapping dose between cohort 1 and 2 (110 μ g; total n = 16). A total of 12 healthy male volunteers were randomised to receive 50 mg (n = 8) or placebo (n = 4) in the parallel group repeat-dose phase of the study. Serial blood samples for PK analyses of plasma GSK835726 were collected at pre-dose and regular intervals over 24 h post-dose (as per study 1). Blood samples were analysed for GSK835726 using a validated analytical method based on protein precipitation followed by high-performance liquid chromatography/mass spectrometry/mass spectrometry analysis. The PK was assessed by non-compartmental methods. In this study, histamine-induced wheal and flare measurements were taken pre-dose and at 1, 2, 3, 6, 12 and 24 h post-dose. All injections of histamine (30 μ l of 0.1 mg/ml) were given intradermally at separate sites on the subject's back at least 4 cm apart. Physiological saline was injected intradermally as a negative control at baseline. At baseline (pre-dose on day 1) there was 1 saline injection and two histamine injections with the average result of the two histamine assessments used as a control. The wheal surface area (swelling) and the flare surface area (red area) were measured using a planimeter after 15 min. Both the wheal area and the flare area are recorded as mm^2 .

Phase II Clinical Studies

Study 3 (protocol number HHI110159) was a randomised, double-blind, placebo-controlled three-period crossover trial of two single intranasal doses (220 and 1,100 μ g) of GSK1004723 and

matching placebo in an environmental allergen challenge chamber (ECC) in male subjects with seasonal allergic rhinitis. Fifty-four subjects were randomised into the study to receive placebo or GSK1004723. A napadisylate suspension formulation of GSK1004723 was used in this study which was the intranasal proof-of-concept study (POC).

The primary objective of the study was to investigate the effect of single doses of intranasal GSK1004723 suspension on nasal symptoms of allergic rhinitis following 4 h in the ECC post-dose on day 1. The secondary objectives were to investigate the effect of GSK1004723 suspension on nasal airflow resistance and weight of nasal secretions following 4 h in the ECC post-dose on day 1 and nasal symptoms 20–24 h post-dose on day 1.

Study 4 (protocol number HH3110161) was a randomised, double-blind, placebo- and positive-controlled, 4-period crossover, incomplete block study of three single oral doses of GSK835726 (100, 50, 10 mg), cetirizine (10 mg) and matching placebo in an ECC in male subjects with seasonal allergic rhinitis. Up to 54 subjects were randomised to receive 4 out of the 5 treatments. The objectives of the study were the same as for study 3. This was the oral POC study.

Study 5 (protocol number HHI112864) was a randomised, double-blind, placebo-controlled triple-dummy repeat-dose 4-period crossover study of intranasal GSK1004723 solution, oral GSK835726, cetirizine and matching placebos dosed prior to entering an ECC in male and female subjects with seasonal allergic rhinitis. Up to 54 subjects were randomised to the study. A dihydrochloride solution formulation of GSK1004723 was used in this study. This was a repeat-dose study.

The primary objective of the study was to investigate the effect of repeat intranasal doses of GSK1004723 solution and repeat oral doses of GSK835726 versus placebo on the prevention of nasal symptoms of allergic rhinitis provoked by allergen and assessed during 6 h in the ECC (1 h post-study drug dose).

Methods

Subjects

Study 1. Healthy male subjects aged between 18 and 50 years, with a body weight within the range of 50–100 kg and body mass index within the range 19–29.9. The subjects were non-smokers for at least 12 months. Subjects enrolled in the study had a normal nasal examination as per ear, nose and throat assessment.

Study 2. Healthy male subjects aged between 18 and 50 years, with a body weight within the range of 55–100 kg and body mass index within the range 19–29. The subjects were non-smokers for at least 12 months. Subjects participating in the single-dose escalation part of the study had negative skin prick test reactivity to the saline control and positive skin prick test reactivity to histamine of 3-mm wheal greater than saline control and some associated surrounding erythema.

Study 3. Male subjects aged between 18 and 65 years, with a known history of seasonal allergic rhinitis, a body weight ≥ 50 kg, with body mass index within the range 19–32 and relevant positive skin prick test (wheal ≥ 3 mm) for *Dactylis glomerata* (at or within 12 months preceding the screening visit) were included in the study. The subjects were non-smokers for at least 12 months with a pack history <10 pack-years with $FEV_1 \geq 80\%$ predicted prior to each nasal allergen challenge. All subjects exhibited a moderate response to 4,000 grass pollen grains/m³ within 2 h in the environmental chamber which is defined as a TNSS ≥ 6 at

screening. Subjects with a history of any structural nasal abnormalities, nasal polypsis, frequent nosebleeds and recent nasal surgery, were excluded from the study. Subjects with recent (within 3 weeks) or ongoing upper respiratory tract infection and/or exacerbation of asthma within 3 weeks before the screening were also not considered.

Study 4. As for study 3 except that the upper age limit was 60 years.

Study 5. As for study 3 except that female subjects were also recruited.

Study Design and Treatment Schedule

Study 1. Subjects underwent screening within 21 days prior to first dosing occasion. In the two single-dose ascending cohorts, a total of 5 dose levels and placebo were examined. In cohort 1 there were three single-dose treatment periods and in cohort 2 five single-dose treatment periods. These periods were separated by at least 7 days. In the repeat-dose cohorts, subjects participated in one treatment period and received GSK1004723 or placebo. Each subject taking part in the study underwent a follow-up visit within 14–21 days of their last dose. The total duration of the study for each subject recruited into cohort 1 was approximately 9 weeks and 11 weeks for subjects recruited into cohort 2. The total duration of the study for each subject recruited into cohort 3 and 4 was 8 weeks.

Study 2. Subjects underwent screening within 21 days prior to the first dosing occasion. In the two single-dose ascending cohorts, a total of 4 dose levels and placebo were examined. In cohort 1 there were four single-dose treatment periods and in cohort 2 three single-dose treatment periods. These periods were separated by at least 7 days. In the repeat-dose cohort, subjects participated in one treatment period and received GSK835726 or placebo. Each subject taking part in the study underwent a follow-up visit within 14–21 days of their last dose. The total duration of the study for subjects recruited into the single-dose cohorts was up to 8 weeks. The total duration of the study for each subject recruited into the repeat-dose cohort was 7 weeks.

Study 3. Subjects underwent screening 7–28 days prior to study start. During screening they underwent an allergen challenge session to check that they had an adequate allergen response in the ECC. There was a minimum 7-day wash-out period between the screening allergen challenge session and the start of treatment. There were three dosing periods, each lasting approximately 2 days. Subjects received a single dose of either GSK1004723 suspension or matching placebo at each dosing period. On day 1, subjects entered the ECC for a 6-hour period. Subjects were dosed with GSK1004723 or placebo 2 h following allergen exposure. A second allergen challenge took place on day 2, 20–24 h after dosing with GSK1004723 or placebo, starting 22 h after the subjects entered the chamber on day 1. The washout period between doses was no less than 7 days. Each subject underwent a follow-up visit within 7 days of their last visit to the ECC. The total duration of the study per subject was not more than 10 weeks.

Study 4. As for study 3, except that there were four dosing periods, each lasting approximately 2 days. Subjects received a single dose of either oral GSK835726 or matching placebo or cetirizine at each dosing period.

Study 5. As for study 3, except there were four treatment periods each lasting 3 days. Subjects received either intranasal GSK1004723 solution 1,000 μ g, oral GSK835726 10 mg, oral cetirizine 10 mg or placebo once daily. On the third dosing day, sub-

jects entered the ECC for a duration of 6 h, 1 h after receiving their third dose. Time 0 h was the time of entering the ECC. Subjects did not receive any drug whilst in the chamber. Treatment periods were separated by a washout of at least 4 days, and there were at least 7 days between ECC days.

Assessment of Efficacy and Safety

The main efficacy assessment criteria were the TNSS and the individual symptom scores of TNSS (nasal blockage, rhinorrhoea, nasal itching, sneezing), nasal air flow, nasal symptom visual analogue scale (VAS) and nasal secretion. Safety and tolerability were also assessed by monitoring adverse events (AE), vital signs and spirometry.

Assessment Measurements

Nasal symptoms (nasal blockage, itch, sneeze and rhinorrhoea) were scored by each subject on a categorical scale from 0 to 3. For each subject and time point, TNSS was calculated as the sum of the response for nasal blockage, nasal itch, sneeze and rhinorrhoea. Nasal airflow resistance was measured using active anterior rhinomanometry (study 3 and 4), nasal secretion was assessed by measuring wet tissue weight and a VAS (scale 0–10 cm) was used by each subject to record nasal congestion. Twelve-lead ECGs were obtained using an ECG machine that automatically calculated the heart rate and measured PR, QRS, QT and QTc intervals.

Subjects were pre-screened in order to ensure they demonstrated threshold symptoms in response to a fixed allergen load. The ECC accommodated up to 18 subjects in one sitting, all of whom were under constant supervision by medical staff outside the chamber. Communication was possible through clear glass windows and via an intercom system. The chamber was charged with indoor air, which was cleaned, cooled, dried and then loaded with a qualitatively and quantitatively determined allergen load. Dactylis glomerata was constantly dispensed into the air of the pollen chamber to create a stable concentration of 4,000 airborne pollen per cubic metre. Allergen concentration, temperature and humidity were continuously monitored, allowing for a constant humidity ($40 \pm 10\%$), temperature ($21 \pm 2^\circ\text{C}$) and allergen load (approximately 4,000 grains per cubic metre) to be maintained throughout the exposure period. These conditions were selected to simulate those found outdoors on a typical warm summer's day near a meadow.

Statistical Analysis

Study 1. This was primarily a safety and tolerability study and formal statistical analysis was not undertaken.

Study 2. This was primarily a safety and tolerability study and formal statistical analysis was undertaken but the planned sample size arose primarily from study conduct feasibility. To assess the PK of single oral doses of GSK835726, plasma concentration data-derived PK parameters were calculated and dose proportionality was assessed using the power model and analysis of variance (ANOVA) method.

To characterise the dose response of a single oral dose of GSK835726 on the weighted mean (0–24 h) wheal or the weighted mean flare response, a non-linear mixed model was fitted. Predicted values for each treatment based on the estimated dose-response model were calculated and ratios between each active dose and placebo were investigated. The dose-response relationship was also investigated by fitting a linear mixed model for the weighted mean (0–24 h) wheal or flare endpoint with compari-

sons between each oral GSK835726 dose and placebo. Data for both endpoints was log transformed prior to analysis.

Study 3. Fifty-four subjects were randomised into this study, to achieve 48 completed subjects. Subjects who withdrew from the study were not replaced. This sample size provided more than 90% power to detect a reduction of at least 1.0 in TNSS (0 to 4 h post-dose) between GSK1004723 and placebo using a two-sided 95% confidence interval (CI), assuming a standard deviation of 1.8. The primary analysis was the comparison of GSK1004723 with placebo on day 1 at each time-point over the 4 h post-dose in the allergen chamber. The onset of action of GSK1004723 was defined as the first time-point at which a statistically significant difference in TNSS was observed from placebo, and was maintained from this time-point onwards (for up to 3 consecutive time-points) during the allergen chamber exposure. A repeated measures analysis was carried out on the serial time-points relative to the start of study medication administration. Baseline was derived as the maximum value of the three readings taken prior to study medication administration. Assumptions of normality and homoscedasticity were examined using residual plots. Where necessary, an appropriate transformation of the response variable was used and the analysis performed on the transformed scale.

Adjusted means for each treatment and differences in adjusted means for comparisons of each dose versus placebo were presented for each time-point. The individual symptom scores of TNSS were analysed and presented in a similar manner to TNSS.

Weighted means (0 to 4 h and 20 to 24 h) were derived for TNSS and for the individual components. The derived parameters were statistically analysed using a similar mixed-effects model. Nasal airflow, VAS (congestion) and nasal secretion were analysed in the same way as TNSS. No formal statistical analysis was performed on safety data.

Study 4. Statistical analysis was performed as for study 3. Fifty-four subjects were randomised into this study, to achieve 49 completed subjects. Subjects who withdrew from the study were not replaced. This sample size provided more than 90% power to detect a clinically relevant reduction of at least 1.0 in weighted mean TNSS (0–4 h) between GSK835726 and placebo using a two-sided 95% CI assuming a standard deviation of 1.23. Nasal congestion was a key secondary endpoint of this study. Based on an observed estimate for the within-subject standard deviation for weighted mean nasal blockage component of the TNSS score (0–4 h post-dose) of 0.43, 49 completed subjects provided more than 90% power to detect a clinically relevant difference of 0.5 in weighted mean (0–4 h) nasal blockage component of the TNSS score between GSK835726 and placebo using a two-sided 95% CI.

Study 5. Fifty-four subjects were randomised into this study, to achieve 48 completed subjects. Subjects who withdrew from the study were not replaced. This sample size provided more than 90% power to detect a clinically relevant reduction of at least 1.0 in weighted mean TNSS (1–6 h) between active treatment and placebo using a two-sided 95% CI, assuming a standard deviation of 1.20. Weighted mean (2–7 h post-dose) and maximum (1–7 h post-dose) were derived for TNSS and for the individual components. Statistical analysis of the derived parameters was performed as for study 3.

An exploratory analysis for weighted mean 3–7 h post-dose TNSS (and individual components) was carried out. The time points were selected based on the time most nasal AEs had resolved following nasal administration. This analysis was per-

Table 1. Summary of GSK835726 PK parameters after single and repeat dosing in study 2 (FTIM oral study)

Treatment GSK835726	n	AUC (0–∞) μg·h/ml	AUC (0–τ) μg·h/ml	CL/F l/h	C _{max} μg/ml	t _{1/2} h	t _{max} h
Single							
10 mg	7	15.8 (14.9)	10.1 (11.6)	0.632 (14.9)	0.747 (19.1)	15.5 (19.4)	1.00 (0.53–6.02)
20 mg	8	28.0 (18.9)	18.3 (10.9)	0.715 (18.9)	1.32 (16.5)	14.9 (19.6)	1.01 (1.00–2.00)
50 mg	16	62.0 (20.3)	56.7 (25.2)	0.806 (20.3)	2.94 (12.8)	17.1 (19.2)	1.00 (0.75–6.00)
100 mg	8	116 (18.2)	113 (16.4)	0.861 (18.2)	4.72 (11.9)	16.9 (19.7)	2.00 (1.00–2.00)
Multiple							
Day 1, 50 mg	8	57.6 (18.9)	36.7 (12.4)	0.868 (18.9)	2.56 (15.1)	15.4 (16.4)	2.05 (1.00–4.02)
Day 7, 50 mg	8	NA	81.5 (20.9)	0.931 (16.3)	3.76 (15.0)	17.6 (17.1)	1.00 (0.75–2.00)

PK results presented as geometric mean (with CV% in parentheses), except for t_{max} median (with ranges in parentheses). NA = Not applicable.

Table 2. Summary of subject disposition and demographic characteristics for the phase II studies

Number of subjects	Total (study 3)	Total (study 4)	Total (study 5)
Number of subjects randomised	54	54	54
Mean age, years	34.4 (19–61)	34.0 (18–55)	37.9 (22–62)
Males	54 (100%)	54 (100%)	39 (72%)
Mean BMI	25.77 (20.9–31.4)	24.96 (20.5–31.1)	25.12 (20.0–31.4)
Mean height, cm	180.3 (163–195)	180.7 (163–193)	178.2 (157–193)
Mean weight, kg	84.0 (59–112)	81.6 (66–103)	80.02 (53.0–105.0)

Figures in parentheses are ranges, unless indicated otherwise.

formed to evaluate the difference in response reported by the subjects once the nasal AEs had resolved. Nasal congestion VAS and nasal secretion and the derived weighted means were analysed in the same way as TNSS.

No formal statistical analysis was performed on safety data.

Results

Study 1 (FTIM Intranasal Study)

GSK1004723 suspension was well tolerated following single and repeat dosing in healthy male subjects. All AEs were mild to moderate in intensity and one subject was withdrawn due to a non-drug-related AE in the single-dose phase of the study. There was very low systemic exposure at all doses following single and 14-day repeat dosing, with the majority of GSK1004723 suspension plasma concentrations being non-quantifiable (<22 pg/ml). There was some evidence that the current dosage regimen of once-daily dosing lead to higher exposure after 14-day repeat dosing of GSK1004723 suspension

1,100 μg. The maximum individual AUC(0–t) was 32.9 pg·h/ml for day 1 and 946.7 pg·h/ml for day 14 (median, NC and 185.8 pg·h/ml, respectively). The maximum individual C_{max} was 51.4 pg/ml for day 1 and 68.6 pg/ml for day 14 (median NC and 31.95 pg/ml, respectively), with the median t_{max} approximately 2 h.

Study 2 (FTIM Oral Study)

GSK835726 was well tolerated following single and repeat dosing in healthy male subjects. All AEs were mild to moderate in intensity and the most common AE experienced in all treatment groups was headache. GSK835726 was rapidly absorbed into plasma with peak concentrations observed around 1 h after single and once-daily repeat dosing. Following single dose administration of GSK835726, dose-proportional increases in AUC (0–∞) were observed up to 50 mg, but these increases became less than dose proportional as the dose level increased up to 100 mg. Similarly dose-proportional increases were seen up to 20 mg for C_{max} but not as the dose level increased. The range of values for GSK835726 terminal

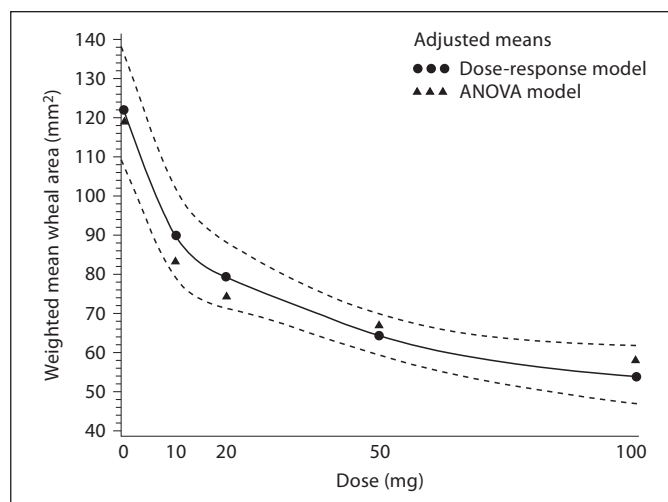


Fig. 1. Plot of predicted weighted mean wheal area (0–24 h) (95% CIs) vs. dose (dose-response model) in study 2 (FTIM oral study).

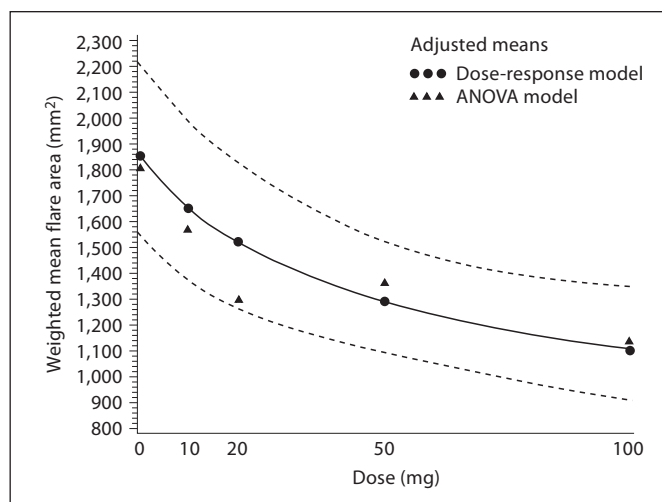


Fig. 2. Plot of predicted weighted mean flare area (0–24 h) (95% CIs) vs. dose (dose-response model) in study 2 (FTIM oral study).

elimination half life ($t_{1/2}$) was similar for all doses, ranging from 15 h to 17 h. Observed accumulation of GSK835726 was approximately 1.5 [AUC (0– τ) and C_{max}] and was consistent with the $t_{1/2}$ of 15 h to 17 h, while the steady state ratio indicated a small and not clinically relevant decrease in systemic exposure over 7 days dosing. Visual assessment of the median trough concentration data suggested that steady state was achieved following 5 to 7 days of once-daily dosing with GSK835726 50 mg. A summary of the PK parameters following single administration and repeat administration is shown in table 1.

Figure 1 illustrates the dose-response relationship for weighted mean (0–24 h) wheal area and suggests evidence of a decrease in WM(0–24 h) wheal area with increasing dose of GSK835726. A similar dose-response relationship was observed for WM(0–24 h) flare and is presented in figure 2.

Study 3 (Intranasal POC)

Study Population

Fifty-four male subjects with seasonal allergic rhinitis were randomised to treatment, with 51 subjects completing all three treatment periods (placebo $n = 52$; 220 μg $n = 51$; 1,100 μg $n = 53$). The demographic characteristics are shown in table 2.

TNSS

During the first 2 h of allergen exposure, mean TNSS values increased comparably in all three treatment groups. After administration of study medication, the

magnitude of the decrease in mean TNSS was similar for both doses of GSK1004723 and was only slightly less for the placebo group. The effect of GSK1004723 on TNSS was not consistent over the 4 h post-dose. The greatest reduction in mean TNSS score compared to placebo was 0.73 (95% CI: –1.32, –0.15) at 1 h 20 min after administration of GSK1004723 220 μg . The effect of GSK1004723 1,100 μg was greatest 2 h following study medication administration (0.61; 95% CI: –1.22, –0.01). Although the definition of onset for GSK1004723 1,100 μg was met within 1 h the treatment effect observed was small and showed only borderline significance from placebo. In addition, the treatment effect was not sustained over the 4 h following study medication administration. Therefore, the data does not support a clinically meaningful improvement in TNSS symptoms over the 4 h in the ECC, following administration of GSK1004723.

Generally, the results from the analysis of the weighted mean TNSS support the findings from the repeated measure analyses. There was some suggestion of a small reduction in TNSS weighted mean (0 to 4 h) relative to placebo for both doses of GSK1004723, although no difference in the magnitude of reduction was observed. Data from the second allergen challenge also indicated a similar difference in TNSS weighted mean (20 to 24 h) between GSK1004723 and placebo. Neither of the weighted mean (0 to 4 h) or (20 to 24 h) point estimates showed a reduction in weighted mean TNSS of greater than 0.5 from placebo, and none of the lower limits of the 95% CI reached –1.

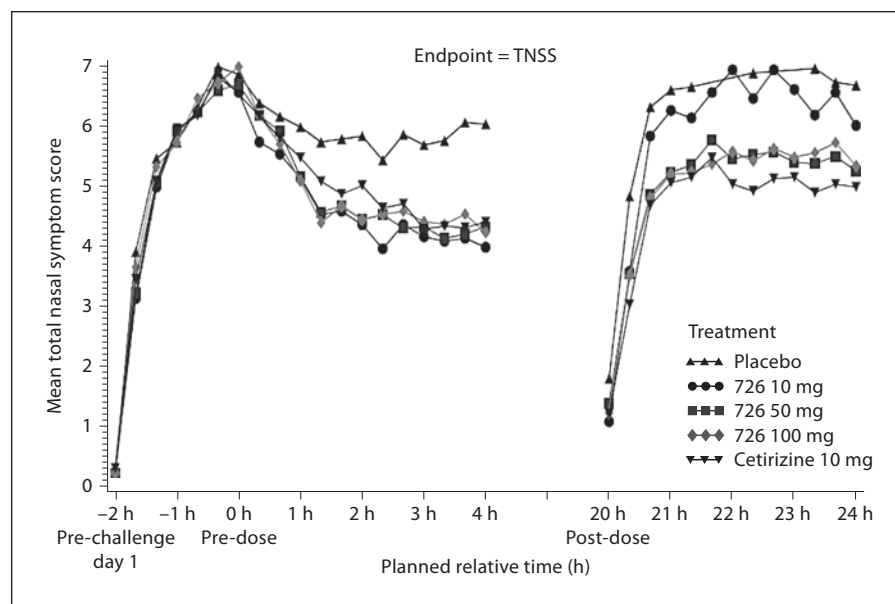


Fig. 3. Mean profile plot for TNSS for study 4 (oral POC study).

Individual Symptoms of the TNSS

The results from the analysis of the individual symptoms of the TNSS followed a similar pattern to the overall TNSS.

Nasal Airflow, VAS and Secretion

Results from analysis of the secondary endpoints supported the data from the primary analysis.

Safety

There were no deaths or serious AEs reported in this study. Three subjects were withdrawn from the study due to AEs; two following administration of GSK1004723 1,100 µg due to productive cough and bronchitis and one following administration of placebo due to nasopharyngitis. The three events were not considered related to treatment.

Nineteen subjects experienced a total of 26 treatment-emergent AEs; 6 (12%) subjects following dosing with placebo, 8 (16%) subjects following dosing with GSK1004723 220 µg and 9 (17%) subjects following dosing with GSK1004723 1,100 µg. Headache was the most common AE experienced in all the treatment groups, with four subjects (8%) experiencing headache in the placebo and 1,100 µg groups and six subjects (12%) in the 220 µg group.

There were no 12-lead ECG abnormalities that were considered to be of clinical significance by the investigator, no clinically significant abnormalities in vital signs and no haematology abnormalities of potential clinical

concern were reported. One subject had an increase in alanine aminotransferase levels at follow-up, and this was recorded as an AE by the investigator.

Study 4 (Oral POC)

Study Population

Fifty-four male subjects with seasonal allergic rhinitis were randomised to receive 4 out of the 5 treatments (placebo $n = 40$; 10 mg $n = 40$; 50 mg $n = 41$; 100 mg $n = 42$; cetirizine $n = 43$). Five subjects withdrew from the study prematurely. The demographic characteristics are shown in table 2.

TNSS

During the first 2 h of allergen exposure, mean TNSS values increased comparably in all five treatment groups (fig. 3). There was evidence of a statistically significant reduction in TNSS weighted mean (0–4 h) for all active doses of GSK835726 compared to placebo. The greatest reduction was observed following administration of 10 mg GSK835726, with a reduction of 1.42 (95% CI –1.90, –0.94) in TNSS score compared to placebo. The effect of cetirizine relative to placebo was similar to that seen for GSK835726 50 and 100 mg (table 3).

Following the second challenge (20–24 h post-dose), there was evidence of a statistically significant reduction in TNSS weighted mean (20–24 h) for all active doses of GSK835726 compared to placebo (table 3; fig. 4). The difference in the magnitude of TNSS reduction compared to placebo was similar for GSK835726 50 and 100 mg doses.

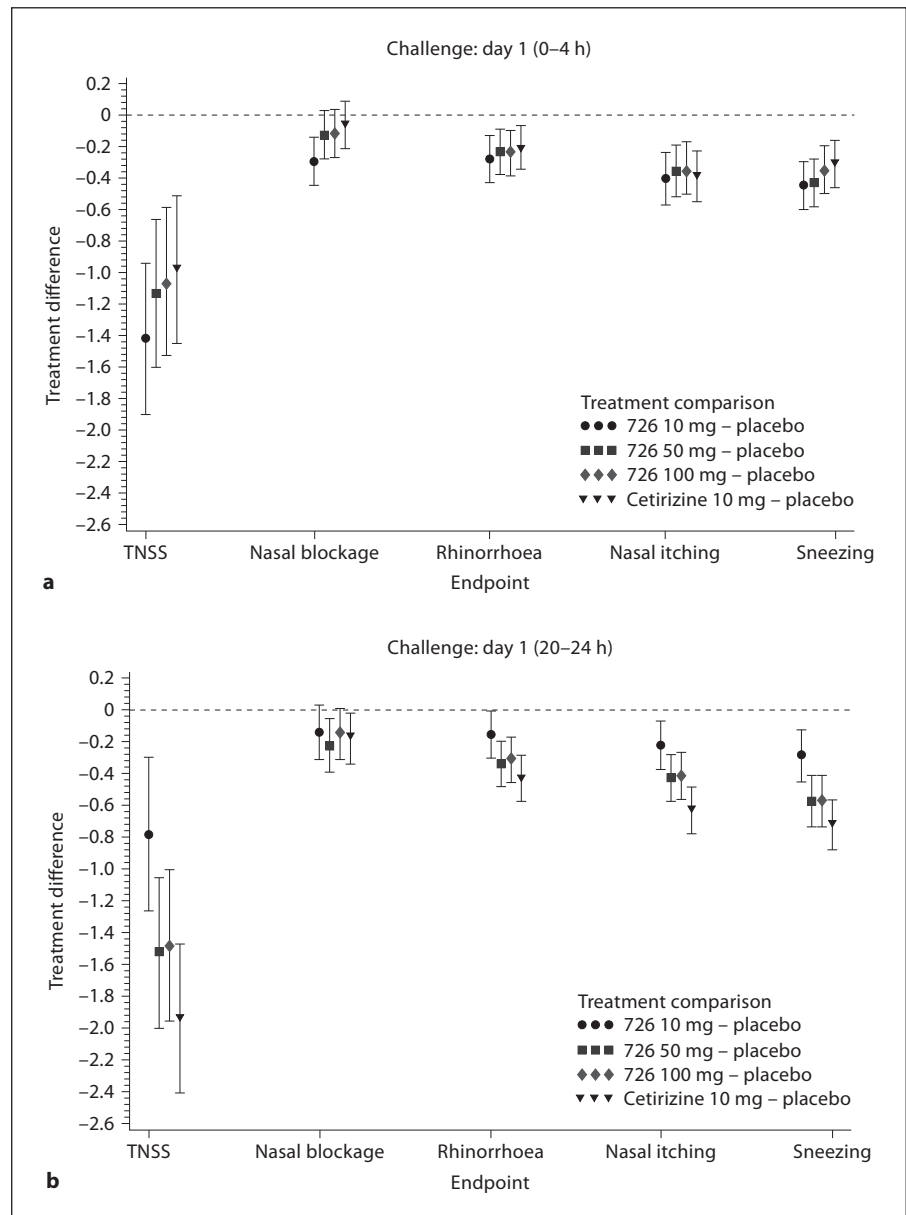


Fig. 4. Plot of treatment differences for weighted mean TNSS and individual symptom scores (95% CI) for study 4 at 0–4 h (a) and 20–24 h (b) (oral POC study).

The magnitude of the reduction in weighted mean TNSS (20–24 h) was greatest following cetirizine, as compared with placebo (table 3).

A summary of the statistical analysis of TNSS by time-point indicated an improvement in TNSS symptoms over the 4 h in the ECC following administration of GSK835726. The greatest reduction in TNSS was observed 4 h following GSK835726 10 mg administration (–2.20; 95% CI –3.00, –1.40). There was no apparent difference in the magnitude of reduction in TNSS score, compared to placebo, between the two higher GSK835726 doses (50 and 100 mg). TNSS symptoms were also ob-

served to decrease over the 4 h following dosing with cetirizine 10 mg.

Individual Symptoms of the TNSS

The results from the analysis of the individual symptoms of the TNSS followed a similar pattern to the overall TNSS (table 3).

Nasal Airflow, Nasal Congestion VAS and Secretion

No apparent difference in WM(0–4 h) nasal airflow was observed following administration of single-dose GSK835726 or cetirizine as compared with placebo.

Table 3. Statistical analysis of weighted mean total nasal symptom score and individual components (1–4 h and 20–24 h post challenge start) in study 4 (oral POC study)

Parameter	Comparison	N	Adjusted mean (0–4 h after challenge)			Adjusted mean (20–24 h after challenge)		
			n	estimate	95% CI	n	estimate	95% CI
TNSS	placebo	40	40	5.96	5.54, 6.39	39	6.55	6.13, 6.98
	GSK835726 10 mg	40	40	4.55	4.12, 4.97	40	5.77	5.35, 6.20
	GSK835726 50 mg	41	41	4.83	4.41, 5.25	41	5.03	4.61, 5.44
	GSK835726 100 mg	42	42	4.90	4.49, 5.32	42	5.07	4.65, 5.49
	cetirizine 10 mg	43	43	4.98	4.57, 5.39	43	4.61	4.20, 5.02
Nasal blockage	placebo	40	40	1.86	1.72, 2.00	39	1.91	1.76, 2.05
	GSK835726 10 mg	40	40	1.57	1.43, 1.70	40	1.77	1.63, 1.91
	GSK835726 50 mg	41	41	1.73	1.60, 1.87	41	1.68	1.54, 1.83
	GSK835726 100 mg	42	42	1.75	1.61, 1.88	42	1.76	1.62, 1.90
	cetirizine 10 mg	43	43	1.80	1.67, 1.87	43	1.73	1.59, 1.87
Rhinorrhoea	placebo	40	40	1.59	1.46, 1.72	39	1.72	1.59, 1.86
	GSK835726 10 mg	40	40	1.32	1.18, 1.45	40	1.57	1.44, 1.70
	GSK835726 50 mg	41	41	1.36	1.23, 1.49	41	1.39	1.26, 1.52
	GSK835726 100 mg	42	42	1.35	1.23, 1.48	42	1.42	1.28, 1.55
	cetirizine 10 mg	43	43	1.38	1.25, 1.51	43	1.29	1.16, 1.42
Nasal itching	placebo	40	40	1.42	1.27, 1.57	39	1.58	1.44, 1.72
	GSK835726 10 mg	40	40	1.02	0.87, 1.17	40	1.36	1.22, 1.50
	GSK835726 50 mg	41	41	1.06	0.92, 1.21	41	1.15	1.02, 1.29
	GSK835726 100 mg	42	42	1.09	0.94, 1.23	42	1.17	1.03, 1.30
	cetirizine 10 mg	43	43	1.03	0.89, 1.18	43	0.95	0.81, 1.08
Sneezing	placebo	40	40	1.08	0.95, 1.22	39	1.35	1.21, 1.49
	GSK835726 10 mg	40	40	0.64	0.51, 0.77	40	1.07	0.93, 1.20
	GSK835726 50 mg	41	41	0.66	0.52, 0.79	41	0.78	0.64, 0.91
	GSK835726 100 mg	42	42	0.74	0.61, 0.87	42	0.78	0.64, 0.92
	cetirizine 10 mg	43	43	0.77	0.65, 0.90	43	0.63	0.50, 0.77

On average there was a 0.83-cm (95% CI –1.30, –0.36) reduction in WM(0–4 h) VAS nasal congestion score, relative to placebo, following single-dose GSK835726 10 mg. This reduction was not sustained in the second allergen challenge visit (20–24 h post-dose). No difference in average VAS nasal congestion score was observed within the first 4 h of dosing with GSK835726 50 mg and 100 mg relative to placebo. Conversely, estimates indicated that dosing with GSK835726 50 mg and 100 mg caused a greater reduction in VAS score 20–24 h post-dose. Results for cetirizine relative to placebo were consistent with the findings for the higher doses of GSK835726.

Data suggests a reduction in nasal secretion weight following administration with GSK835726, relative to placebo. The greatest reduction observed was following GSK835726 100 mg, on average there was a 1.99-g (95% CI –2.69, –1.29) reduction in nasal secretion weight relative to placebo. There was also an indication that the

reduction in nasal secretion for GSK835726 (50 mg and 100 mg) was sustained over the 20–24 h period post-dose. Results for cetirizine relative to placebo were consistent with the findings for the higher doses of GSK835726, on average there was a 1.49-g (95% CI –2.19, –0.79) reduction in WM(0–4 h) nasal secretion weight relative to placebo.

Safety

There were no deaths or serious AEs reported in this study. Three subjects were withdrawn from the study due to AEs which were not considered related to treatment; one following administration of GSK835726 100 mg due to nasopharyngitis, one following administration of placebo due to nasopharyngitis and one following administration of GSK835726 50 mg due to an upper respiratory tract infection.

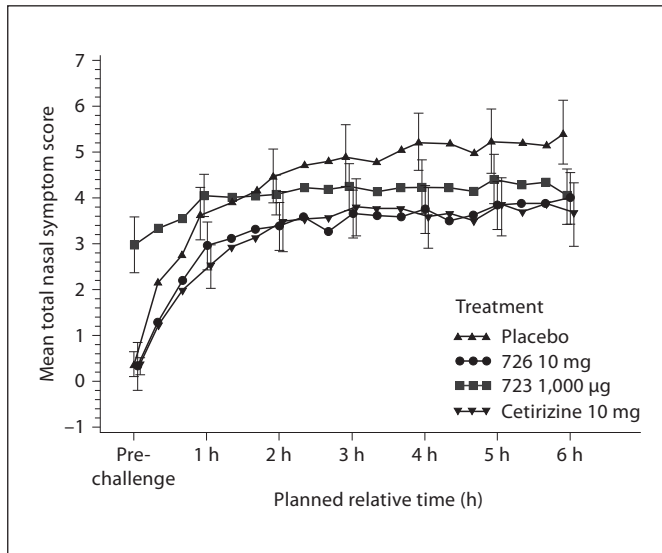


Fig. 5. Mean (95% CI) profile plot for total nasal symptom score for study 5 (repeat-dose study).

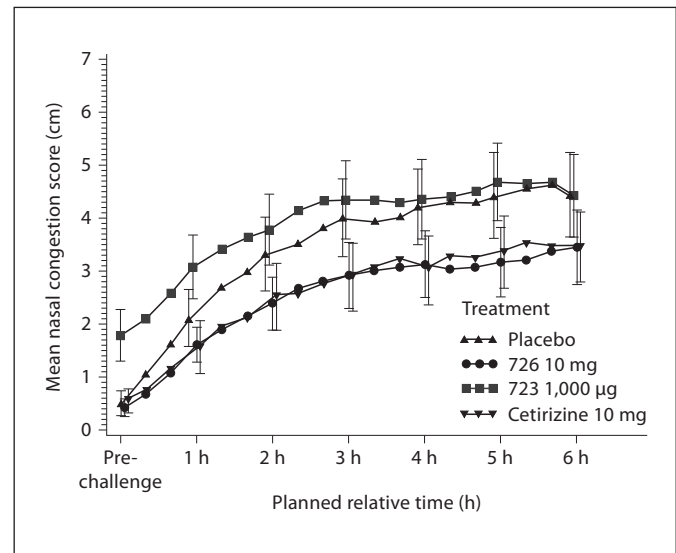


Fig. 6. Mean (95% CI) profile plot for nasal congestion VAS score for study 5 (repeat-dose study).

Twenty-three subjects experienced a total of 43 treatment-emergent AEs. Headache was the most common AE experienced in all the treatment groups. Two subjects (5%) in the placebo group, 5 subjects (13%) in the GSK835726 10 mg group and 4 subjects (10%) in all the other treatment groups experienced headache. No other AE was reported by greater than one subject in any treatment group.

There were no 12-lead ECG abnormalities that were considered to be of clinical significance by the investigator, no clinically significant abnormalities in vital signs and no haematology or clinical chemistry abnormalities of potential clinical concern were reported.

Study 5 (Repeat-Dose Study)

Study Population

Fifty-four subjects with seasonal allergic rhinitis were randomised to treatment, with 51 subjects completing all four treatment periods (placebo $n = 52$; GSK1004723 1,000 μg $n = 54$; 10 mg GSK835726 10 mg $n = 53$; cetirizine 10 mg $n = 52$). The demographic characteristics are shown in table 2.

TNSS

Pre-challenge TNSS scores (and individual components) recorded following treatment with GSK1004723 1,000 μg were on average higher than those reported following the other treatment groups. Pre-challenge

scores for placebo, cetirizine 10 mg and GSK835726 10 mg were comparable. Similar reductions in weighted mean TNSS (1–6 h post-challenge) were evident for cetirizine 10 mg (1.3 score reduction; 95% CI: $-1.8, -0.8$) and GSK835726 10 mg (1.4 score reduction; 95% CI: $-1.9, -0.8$) versus placebo (fig. 5). For GSK1004723 1,000 μg , a reduction of 0.7 (95% CI: $-1.2, -0.1$) versus placebo was observed. The results of the statistical analysis are shown in table 4.

Individual Symptoms of the TNSS

The results from the analysis of the individual symptoms of the TNSS followed a similar pattern to the overall TNSS (table 4).

Nasal Congestion VAS and Nasal Secretion

Pre-challenge nasal congestion as measured using VAS recorded following treatment with GSK1004723 1,000 μg was on average higher than that reported following the other treatments (fig. 6). Pre-challenge scores for placebo, cetirizine 10 mg and GSK835726 10 mg were comparable. Similar reductions in weighted mean VAS (1–6 h post-challenge) were evident for cetirizine 10 mg (1.07 score reduction; 95% CI: $-1.68, -0.46$) and GSK835726 10 mg (1.05 score reduction; 95% CI: $-1.65, -0.45$) versus placebo. For GSK1004723 1,000 μg , an increase in nasal congestion of 0.32 (95% CI: $-0.28, 0.93$) versus placebo was observed.

Table 4. Statistical analysis of weighted mean total nasal symptom score and individual components (1–6 h after challenge start) in study 5 (repeat-dose study)

Parameter	Comparison	N	Adjusted mean		
			n	estimate	95% CI
TNSS (1–6 h after challenge)	Placebo	52	51	4.9	4.4, 5.4
	GSK1004723 1,000 µg	54	53	4.2	3.7, 4.8
	GSK835726 10 mg	53	53	3.6	3.1, 4.1
	Cetirizine 10 mg	52	51	3.5	3.0, 4.1
Nasal blockage (1–6 h after challenge)	Placebo	52	51	1.5	1.3, 1.7
	GSK1004723 1,000 µg	54	53	1.7	1.5, 1.8
	GSK835726 10 mg	53	53	1.3	1.1, 1.4
	Cetirizine 10 mg	52	51	1.3	1.1, 1.4
Rhinorrhoea (1–6 h after challenge)	Placebo	52	51	1.5	1.3, 1.7
	GSK1004723 1,000 µg	54	53	1.3	1.1, 1.4
	GSK835726 10 mg	53	53	1.1	0.9, 1.3
	Cetirizine 10 mg	52	51	1.0	0.9, 1.2
Nasal itching (1–6 h after challenge)	Placebo	52	51	1.1	0.9, 1.3
	GSK1004723 1,000 µg	54	53	0.9	0.7, 1.0
	GSK835726 10 mg	53	53	0.8	0.6, 1.0
	Cetirizine 10 mg	52	51	0.8	0.6, 1.0
Sneezing (1–6 h after challenge)	Placebo	52	51	0.8	0.7, 0.9
	GSK1004723 1,000 µg	54	53	0.4	0.3, 0.6
	GSK835726 10 mg	53	53	0.5	0.4, 0.6
	Cetirizine 10 mg	52	51	0.5	0.3, 0.6

Results of the statistical analysis of the adjusted geometric means showed that nasal secretion weights were lower following all active treatments compared with placebo. Cetirizine 10 mg showed the greatest mean reduction in nasal secretion weight.

Safety

GSK1004723 1,000-µg intranasal solution was poorly tolerated: the majority of subjects (87%) experienced nasal discomfort, described by subjects as a sensation of burning, irritation or itching. The onset of this AE was generally within 5 min post-dose (range: 1–36 min). The reported duration of nasal discomfort was between 11 min and 1 day. Thirty-three subjects (61%) reported nasal discomfort on all three dosing days. In approximately one-third of these subjects, the duration of the AE appeared to decrease on repeat dosing. However, there was no apparent pattern of increase or decrease in reported severity over the 3 days.

On day 3 (day of entry into challenge chamber) 36 subjects reported nasal discomfort following dosing with GSK1004723 1,000 µg. The onset ranged from 1 to 21

min, (median 2 min), and duration ranged from 11 min to 3 h 45 min with a median of 56 min. Nasal discomfort following GSK1004723 1,000 µg was classed as severe in three subjects, with onset 1 to 4 min post-dose on day 1 and a duration of approximately 1 to 2 h. One of these subjects was withdrawn due to several AEs, including the nasal discomfort and another AE of (severe) increased lacrimation. The other two subjects went on to have mild or moderate nasal discomfort on day 2 or 3.

The AE profile for GSK1004723 1,000 µg included nasal dryness, nasal congestion, rhinorrhoea, sneezing and increased lacrimation in up to 9% of subjects in addition to the nasal discomfort. Despite this, these AEs following GSK1004723 did not require concomitant medication and the majority of subjects (96%) received all planned doses of GSK1004723 intranasal solution.

The most frequently reported AE other than nasal discomfort was headache, which occurred in similar proportions of subjects following each of the four treatments (table 5). The majority of AEs following all treatments were considered by the investigator to be of mild or moderate intensity.

Table 5. Summary of AEs occurring in greater than or equal to 5% of subjects with any treatment in study 5 (repeat-dose study)

AE (preferred term)	Placebo (n = 52)	GSK1004723 1,000 µg (n = 54)	GSK835726 10 mg (n = 53)	Cetirizine 10 mg (n = 52)
Any adverse event	15 (29)	53 (98)	13 (25)	17 (33)
Nasal discomfort	1 (2)	47 (87)	1 (2)	1 (2)
Nasal congestion	1 (2)	4 (7)	0	1 (2)
Nasal dryness	2 (4)	4 (7)	0	0
Rhinorrhoea	1 (2)	3 (6)	0	0
Sneezing	0	3 (6)	0	0
Headache	8 (15)	7 (13)	6 (11)	11 (21)
Fatigue	2 (4)	4 (7)	3 (6)	4 (8)
Increased lacrimation	0	5 (9)	0	0

Figures in parentheses are percentages.

There were no clinically significant safety laboratory findings in any subject. One subject had a clinically significant decrease in FEV₁ during the allergen challenge, after placebo dosing, which was not considered related to the investigational product.

Additional Analysis for GSK1004723

Pre-challenge TNSS scores (and individual components) recorded following treatment with GSK1004723 1,000 µg were on average higher than those reported following the other treatment groups, suggesting that the nasal AEs were influencing the subject rating of their TNSS scores. In the event of a short-lived nasal discomfort effect of the nasal spray (resolved 2 h following dosing), an exploratory analysis investigating weighted means derived from 3–7 h post-dose (2–6 h post challenge start) was performed. Results were consistent with the findings for weighted mean (1–6 h post challenge start).

Discussion

A therapeutic role for histamine H₃ receptor antagonism in allergic rhinitis has been proposed and may be complimentary to the well-known benefits of H₁ receptor antagonism [21, 26]. Combined H₁/H₃ blockade has therefore been investigated as a novel therapeutic approach that may enhance symptom relief, particularly nasal blockage. GSK1004723 and GSK835726 are novel dual histamine H₁/H₃ receptor antagonists, which were developed as potential treatments for allergic rhinitis. One molecule was designed for oral administration

(GSK835726) and the other for intranasal administration (GSK1004723), as it is unclear which route of administration has the greatest potential to maximise relief of nasal congestion. The doses chosen in our studies were expected to be active at both the H₁ and H₃ receptors based on preclinical pharmacology data [22, 24, 25].

For our studies we have induced symptoms of seasonal allergic rhinitis by allergen challenge in the Hannover environmental chamber. The environmental chamber offers a controlled paradigm in which to reproducibly evaluate the effect of medication on allergic rhinitis and is widely used [27, 28]. Single doses of topical GSK1004723 failed to significantly attenuate the symptoms of seasonal allergic rhinitis elicited by an allergen challenge in the Hannover environmental chamber, compared to placebo. The reduction in TNSS compared with placebo was never greater than 1 point score as would be expected after active anti-allergic treatment. We expected the onset of action to be within 15–20 min, similar to cetirizine. Although the definition of onset for GSK1004723 1,100 µg was met, the observed treatment effect was small and showed only borderline significance from placebo. The data were consistent across all time points and endpoints and there were no clinically significant differences in responses between the two GSK1004723 doses used in the study.

In the oral POC study, GSK835726 showed excellent H₁ antagonist activity comparable to cetirizine. At all doses of GSK835726, there was a statistically and clinically significant attenuation of TNSS of allergic rhinitis, as induced by allergen challenge, at all dose levels over 0–4 h. The effects on nasal blockage seen with GSK835726 in the oral POC study showed no evidence of a dose-response relationship. The data suggest that for the first 4 h after dosing all three dosages of GSK835726 were approximately equivalently effective in action to 10 mg of cetirizine and persisted as long as that of cetirizine over the ensuing 24 h, except for the 10 mg dose. It may have been true that a lower dose might have been equally effective, but a lower dose of 5 mg of GSK835726 was not expected to have a 24-hour duration. We were aware that these doses of GSK835726 were close to their maximal H₁ antagonist effect, but we wanted to investigate their potential as a H₃ antagonist.

The safety profile for GSK1004723 nasal spray suspension showed that all doses were well tolerated and the pharmacokinetic profile showed there was minimal systemic exposure. GSK835726 was also well tolerated with pharmacokinetic data showing high bioavailability and an elimination half-life suitable for once-daily dosing.

This was supported by data from the wheal and flare response which showed dose-related suppression at 24 h suggesting once-daily dosing was possible.

The GSK1004723 nasal spray suspension results were unexpected given that the *in vitro* potency of GSK1004723 at the H₁ receptor was comparable to cetirizine, fexofenadine and azelastine [25]. One hypothesis for the failure of GSK1004723 nasal spray suspension to attenuate symptoms of allergic rhinitis is that the low solubility of the GSK1004723 napadisylate salt in the suspension formulation may have resulted in a low biological availability of the active drug. This hypothesis could not be tested as nasal concentrations of GSK1004723 were not determined during clinical investigation as their collection would interfere with nasal tolerability assessment. The treatment effect of GSK1004723 was expected to be derived from the local effect in the nasal mucosa and was given at a dose expected to achieve an appropriate local nasal concentration.

The methodology used to determine the onset of action for a single dose of GSK1004723 and GSK835726 in the ECC is widely used [27, 28]. The drugs are administered after the allergen challenge to determine the onset of reduction in induced symptoms of rhinitis. However, these studies are perhaps not long enough in duration to test the effects of the drugs on nasal congestion. To optimise the opportunity for GSK835726 to demonstrate efficacy, another study was performed in which subjects received drug once daily for 3 days (repeat-dose study). In this study, GSK1004723 was also given as a dihydrochloride salt which has greater aqueous solubility than the napadisylate salt. It was hypothesised that a larger concentration of drug would be available for uptake by the nasal mucosa and subsequent binding to H₁ and H₃ receptors by delivery of GSK1004723 as the dihydrochloride nasal spray solution. Published data for fluticasone propionate has shown that a solution formulation achieves greater pharmacokinetic exposure than suspension formulations [29]. A limitation of this study was, however, that pharmacokinetic blood samples were not obtained to test the hypothesis because the allergen chamber did not allow for the collection of blood within a relevant time window for investigation.

Results from the repeat-dose study showed that administration of GSK1004723 solution, oral GSK835726 and cetirizine 1 h before the start of the allergen challenge alleviated the symptoms of allergic rhinitis. The observed effect of GSK835726 on TNSS and nasal congestion VAS appeared similar to that of cetirizine. However, an increase in the nasal blockage component of TNSS and an

increase in nasal congestion VAS were observed following GSK1004723 administration. GSK1004723 induced nasal symptoms, as evidenced by increased baseline TNSS and individual nasal symptom scores. The pre-challenge TNSS scores (and individual components) recorded following treatment with GSK1004723 1,000 µg were on average higher than those reported following the other treatment groups, suggesting that the nasal AEs were influencing the subject rating of their TNSS scores. The majority of subjects experienced nasal discomfort described by subjects as a sensation of burning, irritation or itching, which was classed as severe in three cases. In the event that the nasal discomfort effect of the nasal spray was resolved 2 h following dosing, an exploratory analysis investigating TNSS weighted means derived from 3–7 h post-dose was performed as for the majority of subjects the AEs resolved within 2 h. Only one outlier had an AE with a duration of 1 day. Results were, however, consistent with the findings for weighted mean 1–6 h post challenge start. The combination of histamine H₁ and H₃ receptor antagonism was expected to reduce nasal blockage to a greater extent than H₁ antagonism alone. However, although the study was not set up to directly compare the two treatments, no obvious differentiation could be made between GSK835726 and cetirizine in terms of observed efficacy.

Overall low doses of GSK835726 appeared to be more effective than higher doses at early time points, whereas higher doses were more effective at later time points. That finding coupled with the observation that a high dose of GSK1004723 appeared to show a trend towards more severe congestion suggests a non-linear dose-response curve. However, a range of doses (10–100 mg), single and repeat dosing, dosing during and prior to allergen challenge and various end-points up to 24 h post-dose have been tested. Even if there were a non-linear dose response the optimum degree of H₃ receptor occupancy for reducing nasal congestion should have been identified. The PK data and wheal and flare data for GSK835726 show that the drug has significant *in vivo* pharmacodynamic activity but despite this no convincing effect on nasal congestion was seen.

Our data are consistent with data published from another novel H₃ receptor antagonist [23]. The effect of two doses of the potent oral H₃ receptor antagonist PF-03654746 was investigated on subjective (symptoms) and objective (acoustic rhinometry) responses to nasal allergen challenge. For both PF-03654746 and GSK835726 there was a significant effect on subjective nasal congestion at one dose, which was not seen with other doses, and there was no effect on objective measures of congestion.

This suggests that if H₃ antagonism does have an impact on nasal congestion, the effects are not large enough to be clinically relevant.

In conclusion, GSK835726 appears to behave in man like an excellent H₁ antagonist, is well tolerated and has a profile similar to cetirizine. Unfortunately, the nasal discomfort reported with the GSK1004723 solution makes it

difficult to fully interpret the results for GSK1004723. Although there was some evidence for an additional benefit in reducing nasal congestion with combined H₁/H₃ receptor antagonism, there was insufficient differentiation from H₁ receptor antagonism in reducing TNSS or nasal congestion even when administered at high doses or prophylactically.

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