The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: HHI112864

Title: A randomised, double-blind, placebo-controlled, 4-period cross-over study to assess the efficacy and safety of repeat dose intranasal GSK1004723 (1000 mcg), oral GSK835726 (10 mg) and cetirizine (10 mg) in the environmental challenge chamber in subjects with seasonal allergic rhinitis.

Rationale: The aim of this study was to explore the effect of histamine H_1/H_3 receptor antagonism on symptoms of allergic rhinitis generated in the environmental challenge chamber (ECC). The ECC offered a controlled paradigm in which to reproducibly evaluate the effect of medication on allergic rhinitis. Cetirizine was used as a positive control.

Phase: II

Study Period: 15 JUN 2009 – 14 AUG 2009.

Study Design: A randomised, placebo-controlled, double-blind, triple-dummy, four-way crossover, repeat dose study.

Centres: One centre in Germany.

Indication: Seasonal allergic rhinitis.

Treatment: There were four treatment periods, each of 3 days, consisting of one of the following treatments once daily: intranasal GSK1004723 1000 mcg, oral GSK835726 10 mg, oral cetirizine 10 mg or placebo. Treatment periods were separated by a washout of ≥4 days.

Objectives: Investigate the effect of repeat intranasal doses of GSK1004723 vs. placebo on prevention of nasal symptoms of allergic rhinitis provoked by allergen and assessed during 6 h in the ECC (1 h post GSK1004723 dose). Investigate the effect of repeat oral doses of GSK835726 vs. placebo on prevention of nasal symptoms of allergic rhinitis provoked by allergen and assessed during 6 h in the ECC (1 h post GSK835726 dose).

Statistical Methods: The sample size of 54 subjects provided >90% power to detect a clinically relevant reduction of at least 1.0 in weighted mean total nasal symptom score (TNSS) (16 h) between active treatment and placebo using a two sided 95% confidence interval (CI), assuming a standard deviation of 1.20. Weighted mean (27 h post dose) and maximum (17 h post dose) were derived for TNSS and its individual components, sneeze, itch, rhinorrhoea and nasal blockage. Derived parameters were analysed using a mixed effects model. Differences in adjusted means for each treatment vs. placebo were presented. Weighted mean nasal congestion visual analogue scale (VAS) and nasal secretion (tissue wet weight) data were analysed in the same way as TNSS. No formal statistical analysis was performed on safety data. The 'All S ubjects population' was used for all analyses.

Study Population: Male and female non-smoking subjects aged 18 65 years, inclusive, with seasonal allergic rhinitis who were otherwise healthy (with the exception of mild asthma, which was permitted) were recruited. Subjects had a positive skin prick test (wheal ≥3 mm) for *Dactylis glomerata* and showed a moderate response in the ECC at Screening, defined as TNSS ≥6, and baseline forced expiratory volume in 1 second (FEV_1) ≥80% predicted. Subjects with nasal abnormalities or nasal polyposis, a history of nosebleeds, recent nasal surgery or upper respiratory tract infection were excluded. Subjects with perennial allergic rhinitis were also excluded.

Number of Subjects	**Total**
Planned, N	54
Randomised, N	54
All Subjects (Safety) Population, n (%)	54 (100)
Completed as Planned, n (%)	51 (94)
Total Number of Subjects Withdrawn, n (%)	3 (6)
Withdrawn due to Adverse Event, n (%)	2 (4)
Withdrawn at Investigator Discretion, n (%)	1 (2)

Demographics	Total
N (All Subjects)	54
Females: Males	15: 39
Mean Age in years (Standard Deviation)	37.9 (10.92)
Mean Weight in kg (Standard Deviation)	80.02 (12.059)
Mean Height in cm (Standard Deviation)	178.2 (7.82)
Mean Body Mass Index in kg/m^2 (Standard Deviation)	25.12 (2.949)
White, n (%)	54 (100)

Efficacy: Administration of GSK835726 10 mg and cetirizine 10 mg resulted in decreases in weighted mean TNSS (27% and 29% compared with placebo, respectively). The treatment difference for GSK835726 vs. placebo was statistically and clinically significant at -1.3 (95% CI: -1.8, -0.8). Weighted means of TNSS components showed significant decreases following GSK835726 10 mg, nasal blockage (13%), rhinorrhoea (27%), nasal itching (27%) and sneezing (38%). A significant reduction in weighted mean TNSS was observed with GSK1004723 1000 mcg (14%) relative to placebo, with a treatment difference of -0.7 (95% CI: -1.2, -0.1). The components rhinorrhoea, nasal itching and sneezing showed significant reductions of 13%, 18% and 50%, respectively, following GSK1004723 compared with placebo. However, no decrease in nasal blockage was observed with GSK1004723. Analyses of maximum TNSS showed results consistent with those for weighted mean. Decreases in nasal congestion VAS of 26% and 27% were observed, relative to placebo, with GSK835726 10 mg and cetirizine 10 mg respectively. No decrease in nasal congestion VAS was observed with GSK1004723 1000 mcg. Nasal secretion weights were lower following all active treatments than placebo. Adjusted mean results for weighted mean TNSS, individual TNSS components, nasal congestion VAS and nasal secretion weight are summarised below.

Weighted Mean (16 h post challenge)	**Estimate (95% Confidence Interval)**			
	Placebo	**GSK1004723 1000 mcg**	**GSK835726 10 mg**	**Cetirizine 10 mg**
TNSS score	4.9 (4.4, 5.4)	4.2 (3.7, 4.8)	3.6 (3.1, 4.1)	3.5 (3.0, 4.1)
Nasal blockage	1.5 (1.3, 1.7)	1.7 (1.5, 1.8)	1.3 (1.1, 1.4)	1.3 (1.1, 1.4)
Rhinorrhoea	1.5 (1.3, 1.7)	1.3 (1.1, 1.4)	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)
Nasal itching	1.1 (0.9, 1.3)	0.9 (0.7, 1.0)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)
Sneezing	0.8 (0.7, 0.9)	0.4 (0.3, 0.6)	0.5 (0.4, 0.6)	0.5 (0.3, 0.6)
Nasal Congestion VAS (cm)	3.97 (3.36, 4.57)	4.29 (3.69, 4.89)	2.92 (2.32, 3.52)	2.90 (2.29, 3.51)
Nasal Secretion (g)	6.251 (5.198, 7.304)	5.210 (4.167, 6.254)	4.491 (3.446, 5.336)	3.459 (2.406, 4.512)

16 h post challenge was 27 h post dose.

Safety results: Adverse event and serious adverse event (SAE) data were recorded from the start of the 2-h challenge at screening and until follow-up.

Adverse Events:	**Placebo**	**GSK100472 3 1000 mcg IN**	**GSK835726 10 mg PO**	**Cetirizine 10 mg PO**
N (All Subjects)	52	54	53	52
No. subjects with AEs n (%)	15 (29)	53 (98)	13 (25)	17 (33)
Most Frequent AEs (at least 5% of subjects with any treatment)				
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)
Lacrimation increased	0	5 (9)	0	0
IN = intranasal; PO = oral.				
Serious Adverse Events: No SAEs were reported.				