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: HH3110163
Title: A randomised, double-blind, placebo-controlled, 4-period incomplete block crossover study of single oral dose GSK835726 (100 mg, 50 mg, 10 mg), Cetirizine (10 mg) and placebo to evaluate the efficacy and safety using an Environmental challenge chamber in male subjects with seasonal allergic rhinitis (SAR).
Rationale: GSK835726 is a novel oral dual histamine H1/H3 receptor antagonist which is anticipated to display greater efficacy against congestion than the second generation antihistamines which selectively block H1 receptors. The aim of the study was to evaluate the efficacy and safety of GSK835726 in subjects with seasonal allergic rhinitis using an Environmental challenge chamber (ECC). The doses were selected based on safety data from the first time in human (FTIH) study, the estimated H1 and H3 receptor occupancy from the pharmacokinetic (PK) data and the histamine wheal and flare response data from the FTIH study. Cetirizine was chosen as a positive control due to its well established effectiveness and wide use in the treatment of allergic rhinitis.
Phase: IIA
Study Period: 16 SEP 2008 - 27 NOV 2008
Study Design: Randomised, double-blind, double dummy, placebo-controlled, four-period incomplete block crossover study.
Centres: One centre in Hannover Niedersachsen, Germany.
Indication: Seasonal allergic rhinitis.
Treatment: Each subject received at least 4 of the following 5 treatments: GSK835726 10 mg, GSK835726 50 mg, GSK835726 100 mg, Cetirizine 10 mg and Placebo. At each dosing period, the subjects received 2 tablets and 1 capsule in a double-dummy design. All doses were administered to subjects two hours after entering the environmental challenge chamber (ECC) on each treatment day.
Objectives: The primary objective of the study was to investigate the effect of single doses of oral GSK835726 on nasal symptoms of allergic rhinitis following 4 hours (h) in the Allergen Challenge Chamber post-dose on Day 1.
Statistical Methods: Fifty-four subjects were randomised into this study, to achieve forty-nine 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 in weighted mean TNSS (0-4 h) between GSK835726 and placebo using a two sided 95% confidence interval, assuming a standard deviation of 1.23. Weighted Mean (0-4 hour) and Weighted Mean (20-24 hour) were derived for TNSS and for the individual symptom scores (Nasal Blockage, Rhinorrhoea, Nasal Itching, Sneezing). The derived parameters were statistically analysed using a mixed effects model. Adjusted means for each treatment and differences in adjusted means for comparisons of each active treatment dose vs. placebo were estimated. The weighted means of the individual symptom scores of TNSS were analysed and presented as for TNSS. Comparisons between GSK835726 with placebo on Day 1 at each time-point over the 4-hours post-dose in the allergen chamber were also investigated. A repeated measures analysis was performed on the serial time-points relative to start of study medication administration. Adjusted means for each active treatment and differences in adjusted means for comparisons of each active treatment vs. 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 for the endpoints; Nasal airflow, visual analogue scale (VAS) score (congestion) and nasal secretion were derived and analysed in the same way as weighted mean TNSS. No formal statistical analysis was performed on safety data.
Study Population: Male subjects aged between 18 and 60 years with a known history of SAR,

body weight ≥50 kg with body mass index (BMI) within the range 19 to 32 kg/m^2 and relevant positive skin prick test (wheal ≥3 mm) for Dactylis glomerata were included in this study.

Number of Subjects:	**Total**
Planned N	54(100)
Dosed N	54(100)
Completed n (%)	49(91)
Total number subjects withdrawn N (%)	5(9)
Withdrawn due to adverse events (AEs) n (%)	3(6)
Withdrawn for other reasons n[1] (%)	2(4)

1. Other reasons for subject withdrawal included investigator's discretion

Demographics	
N	54
Females: Males	0:54
Mean age in years (sd)	34.0(9.04)
Mean weight in kg (sd)	81.6(10.97)
White n (%)	53(98)

Pharmacodynamics (PD) Endpoints: A summary of statistical analyses of the weighted mean TNSS, is presented in the following table.

Weighted Mean TNSS

Challenge	**Comparison**	**Adjusted Mean**		**Treatment Differences**	
		Estimate	**SE**	**Difference**	**95%CI**
0-4 h post-dose	Placebo	5.96	0.214		
	GSK835726 10 mg vs. Placebo	4.55	0.214	-1.42	(-1.90, -0.94)
	GSK835726 50 mg vs. Placebo	4.83	0.213	-1.13	(-1.61, -0.66)
	GSK835726 100 mg vs. Placebo	4.90	0.212	-1.06	(-1.53, -0.59)
	Cetirizine 10 mg vs. Placebo	4.98	0.208	-0.98	(-1.45, -0.52)
20-24 h post-dose	Placebo	6.55	0.216		
	GSK835726 10 mg vs. Placebo	5.77	0.214	-0.78	(-1.26, -0.30)
	GSK835726 50 mg vs. Placebo	5.03	0.212	-1.53	(-2.01, -1.05)
	GSK835726 100 mg vs. Placebo	5.07	0.212	-1.48	(-1.95, -1.01)
	Cetirizine 10 mg vs. Placebo	4.61	0.208	-1.94	(-2.41, -1.47)

Summary of the statistical analysis of weighted mean nasal airflow is presented in the following table.

Weighted Mean Nasal Airflow

Treatment Group	**N**	**Challenge**	**Adjusted Mean (95% CI)**	**Treatment Difference (95% CI) (Relative to Placebo)**

Placebo	40	Day 1 (0-4 h)	189.41 (153.89, 224.93)	-
		Day 1 (20-24 h)	177.07 (133.81, 220.34)	-
GSK835726 10 mg	40	Day 1 (0-4 h)	203.77 (168.42, 239.12)	14.36 (-26.64, 55.36)
		Day 1 (20-24 h)	216.34 (173.72, 258.96)	39.27 (-14.24, 92.78)
GSK835726 50 mg	41	Day 1 (0-4 h)	211.38 (176.19, 246.56)	21.97 (-19.12, 63.05)
		Day 1 (20-24 h)	220.71 (178.31, 263.11)	43.64 (-10.03, 97.30)
GSK835726 100 mg	42	Day 1 (0-4 h)	215.24 (180.52, 249.96)	25.83 (-14.55, 66.21)
		Day 1 (20-24 h)	204.03 (162.26, 245.80)	26.96 (-25.89, 79.81)
Cetirizine 10 mg	43	Day 1 (0-4 h)	204.47 (170.01, 238.94)	15.07 (-24.94, 55.07)
		Day 1 (20-24 h)	208.00 (166.57, 249.43)	30.93 (-21.38, 83.24)

Safety results: Adverse events (AEs) were collected from the start of first allergen challenge until the follow-up visit. A total of 43 AEs were reported by 23 subjects in this study. Out of these, 4 subjects experienced a total of 4 pre-treatment AEs. The most common AE across all treatment groups was headache**.** Three subjects were withdrawn from the study due to AEs which were moderate in intensity. One subject experienced an AE of somnolence of moderate intensity following dosing with placebo, which was considered possibly related to the investigational product by the investigator. However, the subject was not withdrawn from the study. A summary of all AEs is presented in the following table.

Adverse Events:	**Placebo**	**GSK835726**			**Cetirizine**
		10 mg	**50 mg**	**100 mg**	**10 mg**
N	40	40	41	42	43
No. subjects with AEs n (%)	5(13)	7(18)	9(22)	6(14)	8(19)
Most Frequent AEs					
Headache	2(5)	5(13)	4(10)	4(10)	4(9)
Somnolence	1(3)	0	2(5)	0	1(2)
Nasopharyngitis	1(3)	0	0	1(2)	0
Oral herpes	0	0	0	1(2)	0
Paronychia	0	0	1(2)	0	0
Upper respiratory tract infection	0	0	1(2)	0	0
Eye injury	0	0	0	1(2)	0
Joint sprain	1(3)	0	0	0	0
Cough	0	0	0	0	1(2)
Epistaxis	0	0	1(2)	0	0
Oropharyngeal pain	0	0	0	0	1(2)
Arthralgia	0	2(5)	0	0	0
Vertigo	0	0	1(2)	0	0
Eye pruritus	0	1(3)	0	0	0
Stomatitis	0	0	0	0	1(2)
Hyperhidrosis	0	0	0	0	1(2)

Serious Adverse Events: There were no deaths or serious adverse events reported in this study.

Publications: None