Synopsis

Identifier: GM2007/00511/00 **Study Number:** IPR107498

Title: An 8 day, randomised, double blinded, placebo-controlled 2-way crossover trial of repeat doses of intranasal GSK256066 and placebo in the [redacted] in subjects with seasonal allergic rhinitis (SAR).

Investigator: Professor [redacted] MD.

Study centre: [redacted] Austria.

Publications: None at the time of this report.

Study period:: [15 Jan 2007-1 Mar.2007]]

Phase of development: I

Objectives:

Primary

- Investigate effect of repeat intranasal doses of GSK256066 vs. placebo on nasal symptoms of allergic rhinitis provoked by spending 4 h in the [redacted] after morning dosing on Day 7.

Secondary

- Investigate effect of repeat intranasal doses of GSK256066 vs. placebo on nasal symptoms of allergic rhinitis provoked by spending 4 h in the [redacted] after morning dosing on Day 2.
- Explore effects of repeat doses GSK256066 vs. placebo on eye and global symptoms, nasal obstruction and secretions in allergic rhinitis provoked by spending 4 h in the [redacted] post-morning dose on days 2 and 7.
- Establish effect of repeat intranasal doses of GSK256066 vs. placebo on nasal, eye and global symptoms, nasal obstruction and secretions in allergic rhinitis provoked by spending 4 h in the [redacted] on Day 8 (10–14 h post-last evening dose on Day 7) as a measure of duration of action.
- Explore the safety and tolerability of repeat doses of GSK256066 in mild to moderate allergic rhinitic subjects.
- Explore the effects of GSK256066 on novel markers of phosphodiesterase-4 (PDE4) inhibition in nasal lavage and scrape samples in mild to moderate allergic rhinitic subjects.

Methodology: Subjects underwent screening 7 to 28 days prior to study start. During screening they participated in a challenge session to check that they had an adequate response to allergen in the chamber. There was a minimum 7-day washout between the challenge session at screening and the start of treatment.

There were two treatment periods, each lasting for 8 days, with the last dose on the evening of Day 7. During the dosing periods subjects took GSK256066 50 μg or placebo twice-daily.

Subjects attended the Unit on days 1, 2 and 7 to be dosed. The Day 1 evening dose was taken at home. On Day 2 subjects collected their medication for Day 2 (evening) to Day 6, which they took at home. Subjects returned to the unit on Day 8 for an allergen challenge, 10–14 h after the last dose of GSK256066.

Immediately following morning dosing on days 2 and 7 of each period, subjects entered the [redacted] for a 4-h period. A third allergen challenge took place on Day 8, 10 –14 h after the last evening dose on Day 7.

The washout period between dosing periods was at least 14 days. Each volunteer had a follow-up visit at least 14 days (and no more than 28 days) after their last visit to the [redacted]

The total duration of the study per subject was 10–12 weeks: up to 4 weeks screening (including 1 week run-in) + 2 weeks dosing + 2 weeks washout between dosing + 2–4 weeks follow-up.

Number of subjects:

Number of Subjects	
Planned, N	45
Randomised, N	44
Completed, n(%)	42 (95)
Total Withdrawn (any reason), n(%)	2 (5)
Withdrawn due to Serious Adverse Event, n(%)	0
Withdrawn due to Adverse Events, n(%)	1 (2)
Subject Lost to Follow-Up, n(%)	1 (2)

Diagnosis and main criteria for inclusion: Healthy males and females aged 18 to 50 years inclusive with a history of seasonal allergic rhinitis. Subjects had to exhibit a moderate response to grass pollen after 2 h in the [redacted] and have a positive skin prick test and radioallergosorbent test for grass pollen.

Treatment administration: Subjects were randomised to receive either GSK256066 50 μg or placebo twice-daily on days 1 to 7 inclusive via intranasal administration. There were two dosing periods, each lasting for 7 days, with the last dose on the evening of Day 7. Subjects attended the Unit on days 1, 2 and 7 to be dosed and on Day 2 collected their medication for Day 2 (evening) to Day 6, which they took at home. The Day 1 evening dose was also taken at home.

Criteria for evaluation: Efficacy: weighted mean total nasal symptom score (TNSS) (sneeze, itch, rhinorrhoea and obstruction), eye symptom scores, global symptom score, nasal airflow resistance and nasal secretion weight.

Safety: Forced expiratory volume in 1 second (FEV1), electrocardiography (ECGs), adverse events (AEs) and laboratory safety parameters.

Pharmacodynamics: Effects of GSK256066 on ribonucleic acid (RNA) levels indicative of PDE4 inhibition in nasal scrape samples and on protein biomarkers of PDE4 inhibition in lavage samples.

Statistical methods: The sample size calculation was based on the requirement to detect a difference of -1.1 in weighted mean TNSS (1–4 h) between GSK256066 and placebo with 90% power at the 5% one-side significance level. Based on the average estimate of within subject variance of 2.63, 39 subjects were required to detect such a difference. Therefore 54 subjects were to be selected to enrol up to 45 subjects to gain at least 39 evaluable patients.

The primary analysis was the comparison of weighted mean (1–4 h) of TNSS between GSK256066 50 μg and placebo on Day 7. The data were analysed using a mixed effects analysis of variance model adjusting for terms due to period, challenge (Day 2 1–4 h, Day 7 1–4 h or Day 7 11–14 h), treatment and treatment-by-challenge fitted as fixed effects, with subject fitted as a random effect. Baseline (pre-chamber on day of challenge) was only to be included as a covariate if it did not adversely affect the fit of the model. An estimate of the treatment comparison (GSK256066 50 μg – placebo) was calculated between adjusted means (least squares means) along with the associated 90% confidence interval.

All secondary efficacy endpoints (eye symptom score, global symptom score, nasal airflow and nasal secretion) were analysed in a similar fashion to the primary endpoint.

Pharmacodynamic data obtained from nasal scrape and nasal lavage were listed and summarised. In addition, Taqman assay data were analysed for each non-housekeeper gene using a mixed effects analysis of variance model adjusting for terms due to period, sample variability and treatment fitted as fixed effects, with subject fitted as a random effect. Sample variability was derived from a principal components analysis, based on all housekeeper genes. An estimate of the treatment comparison (GSK256066 50 μg – placebo) was calculated for each non-housekeeper gene between adjusted means (least squares means) along with the associated 90% confidence interval.

Summary:

Demographics

		N=44
Sex, n (%)	Males	27 (61)
	Females	17 (39)
Age, years	Mean	28.3
	Range	21–43
Height, cm	Mean	176.0
	Range	157–194
Weight, kg	Mean	72.2
	Range	50–95
Body Mass Index, kg/m^2	Mean	23.1
	Range	18–29
Race, n (%)	White – White/Caucasian/European Heritage	42 (95)
	Mixed Race	2 (5)
Ethnicity, n(%)	Hispanic or Latino	0
	Not Hispanic or Latino	44 (100)

Efficacy: GSK256066 50 μg twice-daily statistically significantly lowered weighted mean TNSS, global symptom score and nasal secretion weight compared with placebo over 1–4 h post-dose in the [redacted] on days 2 and 7. The effect was not maintained during a challenge over 11–14 h post the last dose on Day 7. There was no evidence to suggest a statistically significant difference in eye symptom scores between GSK256066 50 μg twice-daily and placebo for any of the three challenges. The results of the efficacy analyses are shown in the table below.

Endpoint (weighted mean)	Least Squares Means		Difference	90% Confidence Intervals
	GSK256066 50 μg bid	Placebo bid		
TNSS (Day 2 1–4 h)	6.66	7.63	-0.97	(-1.58, -0.36)[1]
TNSS (Day 7 1–4 h)	6.67	7.57	-0.90	(-1.42, -0.38)[1]
TNSS (Day 7 11–14 h)	7.78	8.10	-0.32	(-0.75, 0.11)
Eye SS (Day 2 1–4 h)	1.64	2.07	-0.43	(-0.87, 0.01)
Eye SS (Day 7 1–4 h)	1.89	2.29	-0.40	(-0.91, 0.10)
Eye SS (Day 7 11–14 h)	2.16	2.24	-0.08	(-0.53, 0.37)
Global SS (Day 2 1–4 h)	9.13	10.88	-1.76	(-2.68, -0.83)[1]
Global SS (Day 7 1–4 h)	9.54	11.05	-1.52	(-2.30, -0.73)[1]
Global SS (Day 7 11–14 h)	11.26	11.80	-0.54	(-1.27, 0.20)
Nasal airflow (cm^3/s) (Day 2 1–4 h)	323.77	344.79	-21.02	(-52.52, 10.47)

Continued

Endpoint (weighted mean)	Least Squares Means		Difference	90% Confidence Intervals
	GSK256066 50 μg bid	Placebo bid		
Nasal airflow (cm^3/s) (Day 7 1–4 h)	332.98	317.41	15.57	(-14.18, 45.31)
Nasal airflow (cm^3/s) (Day 7 11–14 h)	355.93	345.76	10.17	(-32.48, 52.82)
Nasal secretion weight (g) (Day 2 1–4 h)	2.38	3.16	-0.78	(-1.26, -0.30)[1]
Nasal secretion weight (g) (Day 7 1–4 h)	2.49	3.11	-0.62	(-1.00, -0.24)[1]
Nasal secretion weight (g) (Day 7 11–14 h)	2.78	3.15	-0.37	(-0.76, 0.02)

Bid=twice-daily; SS=symptom score.
1. Statistically significant at the 5% one-sided level.

Safety:

	Pre-treatment (N=44) n(%)	Placebo bid (N=42) n(%)	GSK256066 50 μg bid (N=44) n(%)
Any AE	1 (2)	4 (10)	3 (7)
Any AE related to investigational product	-	1 (2)	1 (2)
All AEs			
Headache	0	2 (5)	1 (2)
Diarrhoea	0	0	1 (2)
Toothache	0	0	1 (2)
Vomiting	0	0	1 (2)
Anaemia	1 (2)	0	0
Eye pruritus	0	1 (2)	0
Malaise	0	1 (2)	0
Blood electrolytes decreased	1 (2)	0	0

Pharmacodynamics: There were no clear differences between placebo and GSK256066 50 μg twice-daily for any of the nasal lavage analytes. There was statistical evidence of significant differences in mRNA raw abundance from lavage samples for DAF, ETS2, LAMB1, NR4A3, PDE4B, RGS1 and SNF1LK after one dose of GSK256066 50 μg compared with placebo. The highest difference was found in SNF1LK, with a treatment ratio of 1.47.

Conclusions:

- GSK256066 50 μg twice-daily statistically significantly lowered weighted mean TNSS compared with placebo over 1–4 h post-dose in the [redacted] on days 2 and 7. The effect was not maintained during a challenge over 11–14 h post the last dose on Day 7.
- GSK256066 50 μg twice-daily statistically significantly lowered weighted mean global symptom score compared with placebo over 1–4 h post-dose in the [redacted] on days 2 and 7.
- GSK256066 50 μg twice-daily statistically significantly lowered weighted mean nasal secretion weight compared with placebo over 1–4 h post-dose in the [redacted] on days 2 and 7, and over 10–14 h following last evening dose (Day 8).
- Repeat dosing of GSK256066 50 μg twice-daily for 8 days was safe and well tolerated in subjects with a history of seasonal allergic rhinitis. There were no SAEs; the most frequently reported AE was headache.
- All subjects were negative for troponin T throughout the study. There were no treatment-emergent clinical laboratory values, vital sign or ECG values of clinical significance.
- There was statistical evidence of significant differences in mRNA raw abundance from lavage samples for DAF, ETS2, LAMB1, NR4A3, PDE4B, RGS1 and SNF1LK after one dose of GSK256066 50 μg compared with placebo. The highest difference was found in SNF1LK, with a treatment ratio of 1.47.

Date of Report: October 2007.