Synopsis

Identifier: GM2006/00280/00 **Study Number:** IPR101987

Title: A 14 day, randomised, double blinded, placebo-controlled 2-way crossover trial of repeat doses of intranasal GSK256066 and placebo in an environmental exposition unit [redacted] in subjects with seasonal allergic rhinitis (SAR).

Investigator: Professor Dr. [redacted]

Study centre: [redacted] Austria.

Publications: None at the time of this report.

Study period: 21 March 2006 – 15 May 2006.

Phase of development: I

Objectives:

Primary Objective:

Investigate effect of repeat intranasal doses of GSK256066 vs. placebo after 8 and 14 days' dosing on nasal symptoms of allergic rhinitis provoked by spending 6 h in the [redacted]

Secondary Objectives

Explore effects of repeat doses GSK256066 vs. placebo after 8 and 14 days' dosing on nasal, eye and global symptoms, nasal obstruction and secretions in allergic rhinitis provoked by spending 6 h in the [redacted]

Establish effect of repeat intranasal doses of GSK256066 vs. placebo after 8 and 14 days' dosing on late phase inflammatory markers in allergic rhinitis provoked by spending 6 h in the [redacted]

Establish effect of repeat intranasal doses of GSK256066 vs. placebo after 8 and 14 days' dosing on nasal, eye and global symptoms, nasal obstruction and secretions in allergic rhinitis provoked by spending 4 h in the [redacted] on Day 9 or 15 (22 – 26 h post-dose Day 14, i.e., 0 – 4 h post-challenge Day 15, 22 – 26 h post-dose Day 8) as a measure of duration of action.

To explore the effects of GSK256066 on novel cellular markers and secreted markers of phosphodiesterase 4 (PDE4) inhibition in nasal lavage and scrape samples in mild to moderate allergic rhinitic subjects.

Methodology: This was a randomised, double blinded, placebo-controlled two-way crossover trial of 14 days' repeated doses in treatment period 1 and 8 days' repeated doses in period 2 of intranasal GSK256066 and placebo in the [redacted] in subjects with allergic rhinitis.

There were two dosing periods in this study. The original protocol stated that subjects would receive 14 days' dosing with GSK256066 in both periods 1 and 2. However, due to new 28-day toxicology findings in the monkey following inhaled administration, the dosing duration in period 2 was reduced from the original 14 days.

The first treatment period lasted 15 days, with the last dose on the morning of Day 14. During this dosing period subjects took 200 μg GSK256066 or placebo twice-daily on days 1 to 13 inclusive and a single dose of 200 μg on Day 14. Subjects attended the Unit on Day 1 to be dosed and collect their medication for subsequent days. Subjects were instructed to bring back the medication at Day 7 and Day 14 visits for dosing. They also returned to the unit on Day 15 for an allergen challenge, 22 to 26 h after the last dose of GSK256066.

The second treatment period lasted 9 days, with the last dosing on the morning of Day 8. During this dosing period subjects took 200 μg GSK256066 twice-daily or placebo twice-daily on Days 1 to 7 inclusive and a single dose of 200 μg or placebo on Day 8. Subjects attended the Unit on Day 1 and Day 8 to be dosed and on Day 1 collected their medication for subsequent days. They also returned to the unit on Day 9 for an allergen challenge, 22 to 26 h after the last dose of GSK256066.

Immediately following morning dosing on Day 14 in treatment period 1 and Day 8 of treatment period 2, subjects entered the [redacted] for a 6-h period. A second allergen challenge took place on Day 15, 22 to 26 h after the last dose on Day 14 in treatment period 1 and Day 9, 22 to 26 h after the last dose on Day 8 in treatment period 2.

Each volunteer had a follow-up visit 7 to 14 days after their last visit to the [redacted]

Number of subjects:

Number of Subjects	
Planned, N	50
Randomised, N	44
Completed, n (%)	41 (93)
Total Withdrawn (any reason), n (%)	3 (7)
Withdrawn due to Serious Adverse Event, n (%)	0
Withdrawn due to Adverse Events, n (%)	1 (2)
Withdrawn due to other reason, n (%)	2 (5)

Diagnosis and main criteria for inclusion: Healthy subjects aged 18 to 50 years with a history of seasonal allergic rhinitis, a moderate response to 1500 grass pollen grains/m^3 after 2 h in the [redacted] and a positive skin prick test and radioallergosorbent test for grass pollen.

Treatment administration: During period 1, subjects took 200 μg GSK256066 or placebo twice-daily on days 1 to 13 inclusive and a single dose of 200 μg on Day 14. During period 2, subjects took 200 μg GSK256066 twice-daily or placebo twice-daily on Days 1 to 7 inclusive and a single dose of 200 μg or placebo on Day 8.

Criteria for evaluation:

Efficacy: total nasal symptom score (TNSS), global and eye symptom scores, secretion weight and nasal airflow, nasal scrape and lavage and visual assessment.

Pharmacodynamics: eosinophil cationic protein (ECP), tumour necrosis factor-α (TNF-α), eosinophils, total protein concentration, total vasodilator stimulated phosphoprotein (VASP) protein levels, phospho157 VASP and phospho239 VASP.

Safety: adverse events (AEs), serious AEs (SAEs), clinical laboratory evaluations, electrocardiography, vital signs and pulmonary function tests (forced expiratory volume in 1 second [FEV1].

Pharmacokinetics: plasma concentrations of GSK256066 and circulating metabolites.

Statistical methods: All safety, efficacy, pharmacodynamic and pharmacokinetic data were listed and summarised. Repeated measures analysis of variance was used to analyse the weighted mean for each the efficacy endpoints. Differences between GSK256066 and placebo were estimated for the 0 – 6 h and the 22 – 26 h challenge along with 95% confidence intervals. Mean profile plots were produced for each efficacy endpoint. Boxplots of the pharmacodynamic data were produced.

Summary:

Demographics

Sex, n (%)	Males Females	30 (68) 14 (32)
Age, years	Mean Standard Deviation	28.1 5.86
Race	Asian – South East Asian Heritage White – White/Caucasian/European Heritage	1 (2) 43 (98)
Ethnicity	Hispanic or Latino	0
	Not Hispanic or Latino	44 (100)

Efficacy: GSK256066 200 μg twice-daily statistically significantly lowered weighted mean TNSS, global symptom score and nasal secretion weight compared with placebo during 6 h post-dose in the [redacted] There was some evidence that GSK256066 200 μg twice-daily lowered weighted mean TNSS compared with placebo during 22 to 26 h post-dose in the [redacted] however, this was not statistically significant. The results of the efficacy analyses are shown in the table below.

Endpoint (weighted mean)	Least squares means		Difference	95% confidence interval	p value
	GSK256066 200 μg twice-daily	Placebo twice-daily			
TNSS (0 – 6 h)	6.0	7.2	-1.1	-1.9, -0.4	0.004[1]
TNSS (22 – 26 h)	6.3	6.9	-0.6	-1.2, 0.0	0.065
Eye SS (0 – 6 h)	1.8	2.1	-0.3	-0.8, 0.2	0.186
Eye SS (22 – 26 h)	1.6	1.7	-0.1	-0.5, 0.4	0.815
Global SS (0 – 6 h)	8.7	10.5	-1.8	-3.1, -0.5	0.009[1]
Global SS (22 – 26 h)	8.9	9.5	-0.6	-1.7, 0.5	0.290
Nasal airflow (cm^3/s) (0 – 6 h)	316.9	312.1	4.7	-26.7, 36.2	0.760
Nasal airflow (cm^3/s) (22 – 26 h)	293.3	310.7	-17.4	-49.4, 14.6	0.278
Nasal secretion weight (g) (0 – 6 h)	2.1	2.9	-0.8	-1.2, -0.4	<0.001[1]
Nasal secretion weight (g) (22 – 26 h)	2.5	2.8	-0.3	-0.8, 0.3	0.327

1. Statistically significant at the 5% level.

TNSS = total nasal symptom score; SS = symptom score.

Pharmacodynamics: There was no evidence of differences in ECP, total protein or TNF-α during treatment with GSK256066 200 μg compared with placebo. There was significantly higher expression of the experimental biomarker SNF1LK in subjects administered GSK256066 compared with placebo.

Safety: [redacted] The subject was withdrawn during the placebo dosing period (see Section **Error! Reference source not found.**).

All Adverse Events	Pre-treatment N=44	Placebo (8 days) N=22	Placebo (14 days) N=22	GSK256066 200 μg (8 days) N=20	GSK256066 200 μg (14 days) N=22
	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	1 (2)	0	1 (5)	0	6 (27)
Any AE related to investigational product	0	0	0	0	1 (2)
All AEs					
Headache	0	0	1 (5)	0	2 (9)
Transaminases increased	1 (2)	0	0	0	0
Troponin	0	0	0	0	1 (5)
Cough	0		0	0	1 (5)
Pharyngolaryngeal pain	0	0	0	0	1 (5)
Lymphocytosis	1 (2)	0	0	0	0
Neutropenia	1 (2)	0	0	0	0
Toothache	0	0	0	0	1 (5)

Pharmacokinetics: Only very sparse pharmacokinetic samples on days 1, 7, 14 and 15 in treatment period 1 and on days 1, 7 and 8 in treatment period 2 were collected. Systemic levels were generally low, with 58% GSK256066 and 74% metabolite GSK614917 plasma concentrations below the lower limit of quantification (LLOQ was 5 pg/mL for both compounds). No circulating metabolite GSK364659 was detected (LLOQ=10 pg/mL). Metabolite GSK614917 showed much lower exposures compared with parent GSK256066. Overall pharmacokinetic properties of GSK2560066 following single and repeat intranasal administration observed in this study were broadly in line with the previous clinical experience in healthy subjects.

Conclusions:

GSK256066 200 μg twice-daily statistically significantly lowered weighted mean total nasal symptom score compared with placebo during 6 h post-dose in the [redacted]

GSK256066 200 μg twice-daily statistically significantly lowered weighted mean global symptom score compared with placebo during 6 h post-dose in the [redacted]

GSK256066 200 μg twice-daily statistically significantly lowered weighted mean nasal secretion weight compared with placebo during 6 h post-dose in the [redacted]

There was some evidence that GSK256066 200 μg twice-daily lowered weighted mean total nasal symptom score compared with placebo during 22 to 26 h post-dose in the [redacted] however, this was not statistically significant.

There was no evidence of differences in eosinophilic cationic protein, total protein or tumour necrosis factor-α during treatment with GSK256066 200 μg compared with placebo.

GSK256066 was well tolerated during the study and few AEs were reported. One subject was withdrawn from the study after he was found to have an elevated troponin level 21 days after completing administration of GSK256066 200 μg twice-daily for 14 days.

Systemic exposures of GSK256066 and its metabolites were generally low, which was in line with the previous clinical experience in healthy subjects.

Date of Report: November 2006.