Synopsis

Identifier: GM2008/00108/00 **Study Number:** IPA101985

Title: A two-centre, randomised, double-blind, placebo-controlled, 2-period cross-over study to evaluate the effect of treatment with repeat doses of inhaled GSK256066 on the allergen-induced late asthmatic response in subjects with mild asthma.

Investigators: Dr [redacted] and Dr [redacted]

Study centres: King's College London School of Medicine. Department of Asthma, Allergy and Respiratory Science, King's Denmark Hill Campus, Bessemer Road, London SE5 9PJ. Medicines Evaluation Unit Ltd. The Langley Building, Wythenshawe Hospital, Southmoor Road, Manchester M23 9QZ.

Publications: None at the time of this report.

Study period: 26 June 2006 – 07 June 2007.

Phase of development: II.

Objective: The primary objective was to evaluate the effect of treatment with repeat inhaled doses of GSK256066 for 7 days on the late asthmatic response (LAR) to inhaled allergen in mild asthmatic subjects compared with placebo.

Methodology: This was a multi-centre, randomised, double-blind, placebo-controlled, two-period cross-over study to evaluate the effect of treatment with repeat doses of inhaled GSK256066 on the allergen-induced LAR in subjects with mild asthma.

Number of subjects: Subject numbers are summarised in the following table:

Number of Subjects	Total
Planned, N	28
Randomised, N	24
Completed, n (%)	19 (79)
Total Withdrawn (any reason), n (%)	5 (21)
Withdrawn due to adverse events, n (%)	2 (8)
Withdrawn due to protocol violation, n (%)	2 (8)
Withdrawn due to other reason n (%)	1 (4)

A summary of subject demographics is presented in the following table:

Parameter	N=24
Age, years	
Mean [range]	31.1 [20–46]
Sex, n (%)	
Female:	11 (46)
Male:	13 (54)
Race, n(%)	
White: White/Caucasian/European Heritage	20 (83)
Asian: Central/South Asian Heritage	2 (8)
African American/African Heritage	1 (4)
Mixed race	1 (4)
Height, cm	
Mean [range]	171.9 [160–184]
Weight, kg	
Mean [range]	76.2 [61–103]
Body mass index, kg/m^2	
Mean [range]	25.7 [22–30]

Diagnosis and main criteria for inclusion: Males and females aged 18 – 55 years inclusive. Documented history of bronchial asthma, first diagnosed at least 6 months prior to the screening visit and currently being treated only with intermittent short-acting β-agonist therapy by inhalation. Pre-bronchodilator forced expiratory volume in 1 second (FEV1) >75% of predicted at screening.

Treatment administration: GSK256066 87.5 μg (GSK256066 37.5 μg; batch number: 051070244 and GSK256066 50 μg; batch number: 041049179) or placebo (batch number: B132284) were administered using an ACCUHALER™ inhaler device. Subjects were allocated to the sequences GSK256066 87.5 μg or placebo in a 1:1 ratio.

Criteria for evaluation:

- Safety: Adverse events (AEs), serious adverse events (SAEs); blood pressure and heart rate; 12-lead electrocardiogram (ECG); clinical laboratory safety tests (haematology, clinical chemistry and urinalysis), forced expiratory volume in 1 second (FEV1).
- Pharmacokinetics: Blood samples for analysis of GSK256066 and active metabolite GSK614917.
- Pharmacodynamics: Allergen challenge, methacholine challenge and exhaled nitric oxide (exNO).
- Biomarkers: Sputum induction for ribonucleic acid (RNA) analysis, cell count and protein expression, blood samples for protein expression.

Statistical methods: Efficacy**:** Statistical analysis was performed on each of the absolute change from baseline LAR and early asthmatic response (EAR) endpoints to compare GSK256066 with placebo. A mixed effects model was fitted with the factors treatment, period and Day 7 post-saline FEV1 fitted as fixed effects and subject fitted as a random effect. An additional analysis of LAR endpoints was performed, adjusting for Day 1 pre-dose FEV1 as the baseline value. Day 7 FEV1 data (pre-dose and 1 h post-dose) were also analysed using a mixed effects model, adjusting for the fixed effects treatment, period and Day 1 pre-dose FEV1 and the random effect subject. Statistical analysis was performed on the $\log_2$-transformed values of the provocative concentration of methacholine required to produce a 20% reduction in FEV1 (PC20) to compare GSK256066 with placebo. A mixed effects model was fitted with the factors treatment and period fitted as fixed effects and subject fitted as a random effect.
Pharmacodynamics: Exhaled NO concentration change from baseline ratio at all time points were analysed following a $\log_e$-transformation using a mixed effects model to compare GSK256066 with placebo. A mixed effects model was fitted with period, treatment group, subject-level $\log_e$-transformed baseline, period-level $\log_e$-transformed baseline, planned relative time, treatment group by planned relative time interaction term and period-level $\log_e$-transformed baseline by planned relative time interaction term fitted as fixed effects and subject was fitted as a random effect. Pharmacokinetics: Pharmacokinetic analyses of plasma GSK256066 and GSK614917 concentration-time data were conducted using non-compartmental analysis Model 200 (for extravascular administration) of WinNonlin Professional Edition version 4.0.1 (Pharsight Corporation, Mountain View, CA) according to the standard operating procedures. Actual elapsed time from dosing was used to estimate all individual plasma pharmacokinetic parameters for evaluable subjects. Values for the following pharmacokinetic parameters were estimated following single and repeat dosing of GSK256066: maximum observed plasma concentration (Cmax), time of maximum observed concentration (tmax) and the area under the plasma concentration-time curve from time zero to tlast (AUC(0-t)).

Allergen challenge: The primary statistical analysis of LAR and EAR absolute change from baseline minimum and weighted mean FEV1 is summarised in the following table:

			Adjusted Mean (L)		Treatment Difference (vs. Placebo)	
Treatment	Endpoint	n	Estimate	SE	Estimate	95% CI
Placebo	Min LAR	19	-1.127	0.1264		
	WM LAR	19	-0.692	0.0992		
	Min EAR	19	-0.858	0.0825		
	WM EAR	19	-0.419	0.0625		
GSK256066 87.5 μg	Min LAR	18	-0.831	0.1280	0.295	0.093, 0.498
	WM LAR	18	-0.455	0.1004	0.238	0.080, 0.395
	Min EAR	18	-0.507	0.0850	0.351	0.081, 0.622
	WM EAR	18	-0.179	0.0644	0.240	0.054, 0.425

SE = standard error, CI = confidence interval, Min = minimum, LAR = late asthmatic response, WM = weighted mean, EAR = early asthmatic response

There was statistical evidence of a significant increase in LAR minimum and weighted mean FEV1, with an attenuation of the placebo response of 26.2% (p=0.0069) and 34.3% (p=0.0054), respectively. There was also statistical evidence of a significant increase in EAR minimum and weighted mean FEV1, with an attenuation of the placebo response of 40.9% (p=0.0140) and 57.2% (p=0.0143), respectively.

The statistical analysis of FEV1 data on Day 7 is summarised in the following table:

			Adjusted Mean (L)		Treatment Difference (vs. Placebo)	
Treatment	Time	n	Estimate	SE	Estimate	95% CI
Placebo	Pre-dose	20	-0.020	0.0566		
	1h	20	0.081	0.0685		
GSK256066 87.5 μg	Pre-dose	19	0.069	0.0576	0.089	-0.025, 0.204
	1h	19	0.173	0.0699	0.092	-0.084, 0.268

Source Data: Table 10.10
SE = standard error, CI = confidence interval.

There was no statistical evidence of a significant increase in FEV1 for GSK256066 compared with placebo on Day 7, pre-dose and at 1 h post-dose. The estimated difference pre-dose was 0.089 mL (-0.025, 0.204) and 1 h post-dose was 0.092 mL (-0.084, 0.268).

Methacholine challenge: The primary statistical analysis of methacholine PC20 data is summarised in the following table:

		Adjusted Geometric Mean (ng/mL)		Doubling Dose Difference (vs Placebo)	
Treatment	n	Estimate	SD logs	Estimate	95% CI
Placebo	20	0.386	0.3669		
GSK256066 87.5 μg	18	0.312	0.3852	-0.307	-1.182, 0.568

SD = standard deviation, CI = confidence intervals

There was no statistical evidence of a significant change in methacholine PC20 for GSK256066 compared with placebo on Day 7 at 2 h post-dose. The estimated doubling dose difference was -0.31 (-1.18, 0.57).

Pharmacodynamics: The statistical analysis of exhaled NO data on Day 7 is summarised in the following table:

			Adjusted Geometric Mean (ng/mL)		Treatment Ratio (vs. Placebo)	
Treatment	Time	n	Estimate	SE logs	Estimate	95% CI
Placebo	Pre-dose	18	0.91	0.059		
	1 h	18	0.90	0.063		
	24 h	18	1.41	0.080		
GSK256066 87.5 µg	Pre-dose	19	0.89	0.059	0.981	0.850, 1.131
	1 h	19	0.93	0.063	1.027	0.878, 1.200
	24 h	19	1.19	0.079	0.846	0.686, 1.044

SE = standard error, CI = confidence interval.

There was no statistical evidence of a significant decrease in exNO for GSK256066 compared with placebo on Day 7 at 24 h post-dose. The estimated treatment ratio was 0.85 (0.69, 1.04). The treatments were very similar pre-dose and at 1 h post-dose.

Safety: A summary of the most frequently reported adverse events (≥2 subjects per treatment group) is presented in the following table:

Adverse Event	Placebo N = 21 n (%)	GSK256066 87.5 µg N = 22 n (%)
Any Event (n%)	14 (67)	16 (73)
Headache	5 (24)	6 (27)
Pharyngolaryngeal pain	2 (10)	2 (9)
Wheezing	1 (5)	3 (14)
Nasopharyngitis	1 (5)	2 (9)
Palpitations	0	2 (9)
Procedural complication	1 (5)	2 (9)
Post procedural complication	2 (10)	0

All the AEs were mild or moderate in intensity. No serious adverse events were reported. Five subjects experienced laboratory abnormalities that were reported as AEs: increased blood creatine kinase, increased blood creatinine, white blood cells in urine, haemturia and proteinuria. [redacted] There were no clinically relevant abnormalities in vital signs and 12-lead ECG parameters.

Pharmacokinetics: A summary of the derived GSK256066 and GSK614917 pharmacokinetic parameters is presented in the following table:

Analyte	Parameter	Day	N	n	Geometric Mean (%CV)
GSK256066	AUC(0-t) (pg.h/mL)	1	22	17	36.8 (93)
		7		14	64.8 (89)
	Clast (pg/mL)	1	22	18	7.9 (36)
		7		17	7.5 (20)
	Cmax (pg/mL)	1	22	18	18.3 (68)
		7		17	17.3 (63)
	tmax (h)[1]	1	22	18	1.00 (0.17 - 3.00)
		7		17	1.02 (0.17 - 11.00)
	tlast (h)[1]	1	22	18	3.00 (0.50 – 6.03)
		7		17	4.080 (1.00 – 24.00)
GSK614917	AUC(0-t) (pg.h/mL)	1	22	3	26.4 (20.8)
		7		4	34.6 (30.0)
	Clast (pg/mL)	1	22	8	6.9 (19.5)
		7		9	6.3 (18.6)
	Cmax (pg/mL)	1	22	8	7.9 (22.7)
		7		9	8.7 (47.5)
	tmax (h)[1]	1	22	8	2.00 (0.50 - 3.02)
		7		9	2.00 (1.93 - 4.08)
	tlast (h)[1]	1	22	8	3.50 (0.50 - 6.05)
		7		9	4.00 (1.93 - 6.03)

1. Median (range),

N: represents the number of subjects who had pharmacokinetic samples analysed,

n: represents the number of who had ≥1 concentration above LLQ.

CV = coefficient of variation, AUC (0-t) = area under the plasma concentration-time curve from time zero to last measurable concentration, Cmax = maximum observed plasma concentration, tmax = time to maximum observed plasma concentration, LLQ = lower limit of quantification, tlast = Last observed plasma concentration, Clast = last measurable concentration.

Results of statistical analyses assessing AUC(0-t) and Cmax accumulation ratios are presented in the following table:

Parameter	Comparison	Ratio (90% CI)
AUC(0-t)	Day 7 vs Day 1	1.69 (1.29, 2.19)
Cmax	Day 7 vs Day 1	0.98 (0.851, 1.13)

CI = confidence interval, AUC (0-t) = area under the plasma concentration-time curve from time zero to last measurable concentration, Cmax = maximum observed plasma concentration.

Conclusions:

- Repeat dosing with GSK256066 87.5 μg for 7 days demonstrated a statistically significant superiority compared with placebo for both EAR and LAR (over 0–2 h and 4–10 h) after allergen challenge on Day 7. The late attenuation of effect from placebo response was 26.2%. The early attenuation of effect from placebo response was 40.9%.
- No statistically significant change in FEV1 was noted after 7 days of dosing with GSK256066 87.5 μg compared with placebo. The treatment difference was 0.09 L pre-dose and at 1 h post-dose.
- GSK256066 showed no effect on exNO or methacholine challenge PC20 compared with placebo.
- GSK256066 87.5 μg was generally well tolerated. All the AEs were mild or moderate in intensity. There were no serious adverse events. Five subjects experienced laboratory abnormalities that were reported as AEs: increased blood creatine kinase, increased blood creatinine, white blood cells in urine, heamaturia and proteinuria. One subject had increased troponin and mild transaminitis noted at follow up. There were no clinically relevant abnormalities in vital signs and 12-lead ECG parameters.
- A 1.7-fold accumulation of AUC(0-t) of GSK256066 was observed. In contrast, no accumulation of Cmax was observed over the same period of treatment.
- There was no statistical evidence of significant differences in mRNA raw abundance from scrape samples for any gene after one dose of GSK256066 87.5μg compared with placebo.

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