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: LPA111834
Title : A randomised, double-blind, placebo-controlled, 2-period cross-over study to evaluate the effect of treatment with GSK2190915 on the allergen-induced asthmatic response in subjects with mild asthma
Rationale: The intention of clinical study LPA111834 was to evaluate both the safety and pharmacodynamic effect of GSK2190915 in subjects with mild bronchial asthma, including the effect on the early and late asthmatic response following allergen challenge.
Phase: IIa
Study Period: 15 December 2008 to 03 September 2009
Study Design: Randomised, double-blind, placebo-controllled, 2-period crossover
Centres: Multi-centre study
Indication: Asthma
Treatment: GSK2190915 100 mg, placebo
Objectives: The primary objective of this study was to evaluate the effect of treatment with repeat oral doses of GSK2190915 on the early asthmatic response (EAR) to inhaled allergen in mild asthmatic subjects compared with placebo.This study also included several secondary objectives. These were to: - evaluate the effect of treatment with repeat oral doses of GSK2190915 on the late asthmatic response (LAR) to inhaled allergen in mild asthmatic subjects compared with placebo. - assess the safety and tolerability of repeat oral doses of GSK2190915 in mild asthmatic subjects compared with placebo. - evaluate the effect of treatment with repeat oral doses of GSK2190915 on lung function as measured by FEV_1 on Days 1, 3 and 6 in subjects with mild asthma compared with placebo. - evaluate the effect of treatment with repeat oral doses of GSK2190915 on concentrations of exhaled nitric oxide on Days 1, 3, 4 and 6 in subjects with mild asthma compared with placebo. - evaluate the effect of GSK2190915 on induced sputum post allergen challenge (day 4) and on Day 6. - evaluate the effect of treatment with GSK2190915 for 3 days on bronchial hyper-reactivity as measured by methacholine challenge on day 4 compared with placebo in mild asthmatic subjects. - evaluate the effect of treatment with repeat oral doses of GSK2190915 on LTE_4, LTB_4 and IgE in mild asthmatic subjects. - explore potential PK/PD relationship on EAR and LTE_4, LTB_4, IgE activity in mild asthmatic subjects
Statistical Methods: Twenty (20) subjects were required in order to ensure at least 90% power to detect a 50% attenuation, from the change from baseline placebo response for minimum EAR, using a two-sided 5% significance level, assuming a within subject standard deviation of 0.40 (L) and a change from baseline of -0.900 (L). No formal interim analyses were planned or performed. The minimum and weighted mean EAR and minimum and weighted mean LAR after allergen challenge on Day 3 and their change from Day 3 saline baseline were analysed using mixed effects models. Estimates for the treatment difference between active dose and placebo for all derived endpoints were calculated along with two-sided 95% confidence intervals (calculated using the pooled estimate of variance). The percentage attenuations of the placebo response were also calculated. Methacholine challenge Day 1 and Day 4 PC_{20} data was summarised. Day 4 PC_{20} data was log_2 transformed and analysed using a mixed-effects model. The inverse transformed adjusted means and 95% confidence intervals for each treatment group were presented. The difference between the adjusted means was presented on the log_2 scale for treatment comparison (GSK2190915 100mg versus placebo) together with the associated two-sided 95% confidence interval calculated using the pooled estimate of variance. Exhaled NO concentration data was summarized and plotted. All biomarker data: plasma LTB_4, urine LTE_4, sputum LTB_4, LTC_4, LTD_4, LTE_4, and serum IgE, were summarised by treatment and time points. The relationship between GSK2190915 100mg and pharmacodynamic responses on EAR and LTE_4 and LTB_4 were explored by plots.
Study Population: Mild asthmatic subjects.

Number of Subjects	**Total (n=20)**
Number of subjects planned, N:	24
Number of subjects randomized and administered first dose, N:	20
Number of subjects completed, n (%):	20 (100%)
Number of subjects withdrawn (any reason), n (%):	0
Number of subjects withdrawn for SAE, n (%):	0
Number of subjects withdrawn for AE, n (%):	0
Demographics	
Age in Years, Mean (SD)	29.8 (7.80)
Sex, n (%)	
Female:	0
Male:	20 (100%)
BMI (kg/m^2), Mean (SD)	24.18 (2.36)
Height (cm), Mean (SD)	176.7 (7.34)
Weight (kg), Mean (SD)	75.53 (9.091)
Ethnicity, n (%)	
Hispanic or Latino:	2 (10%)
Not Hispanic or Latino:	18 (90%)
Race, n (%)	
White	17 (85%)
African American/African Heritage	1 (5%)
American Indian or Alaska Native	1 (5%)
African American/ African Heritage & White	1 (5%)

Pharmacodynamics (PD) / Pharmacokinetics (PK):

The repeated measure statistical analysis of allergen challenge absolute change from saline baseline on Day 3 FEV_1 data showed a notable separation from placebo at all time points up to 10 hours after allergen challenge. The adjusted mean treatment differences (GSK2190915 100mg vs. placebo) for all the time points range from 0.052L (at 5 min post dose) to 0.675L (at 30 minutes post dose), with most of 95% CI exclude zero, indicating statistically significant differences.

Early asthmatic response (EAR), the minimum and weighted mean FEV_1 absolute change from saline baseline 0-2 hours after allergen challenge on Day 3. GSK2190915 100mg showed a statistically significant increase in both minimum and weighted mean FEV_1 (0-2 hours) absolute change from saline baseline. Adjusted mean values for the minimum FEV_1 absolute changes from saline baseline were -1.225L for placebo (95% CI, -1.495 to -0.955), -0.817L for GSK2190915 100mg (95% CI, -1.087 to -0.547), corresponding to a mean attenuation of 33.3% of the placebo response to allergen challenge. Adjusted mean values for the weighted mean FEV_1 absolute change from saline baseline were -0.679L for placebo (95% CI, -0.881 to -0.477), -0.254L for GSK2190915 100mg (95% CI, -0.456 to -0.052), corresponding to a mean attenuation of 62.6% of the placebo response to allergen challenge.

Late asthmatic response (LAR), the minimum and weighted mean FEV_1 absolute change from saline baseline 4-10 hours after allergen challenge on Day 3. GSK2190915 100mg showed a statistically significant increase in both minimum and weighted mean FEV_1 (4-10 hours) absolute change from saline baseline. Adjusted mean values for the minimum FEV_1 absolute changes from saline baseline were -1.448L for placebo (95% CI, -1.753 to -1.144) and -1.219L for GSK2190915 100mg (95% CI, -1.524 to -0.914), corresponding to a mean attenuation of 15.8% of the placebo response to allergen challenge. Adjusted mean values for the weighted mean FEV_1 absolute change from saline baseline were -0.982L for placebo (95% CI, -1.250 to -0.714), and -0.759L for GSK2190915 100mg (95% CI, -1.027 to -0.491), corresponding to a mean attenuation of 22.7% of the placebo response to allergen challenge.

No obvious differences were observed between GSK2190915 100mg and placebo in non-challenge FEV_1 or exhaled Nitric Oxide (NO) change from baseline data at all timepoints. Similarly, no obvious difference was observed between GSK2190915 100 mg and placebo in Methacholine challenge PC_{20} data on Day 4.

Suppression of plasma LTB_4 following three daily doses of GSK2190915 100mg (Day 3) was notable at both 1 hour post dose and 12 hours post challenge (i.e. 14 hours post dose) timepoints. Approximately 50% of subjects receiving GSK2190915 100mg had at least 90% suppression of LTB_4 from their pre-dose baseline at both timepoints.

Subjects receiving placebo had no obvious change from baseline in LTB_4 at 1 hour post dose, but had an increase from baseline in LTB_4 at 12 hours following allergen challenge. No obvious difference was noted for Serum Immunoglobulin (IgE) between GSK2190915 100 mg and placebo.

Suppression of urine LTE_4 in GSK2190915 100mg was evident at all timepoints. Approximately 50% of subjects

receiving GSK2190915 100mg had over 75% suppression of LTE_4 from their pre-dose baseline pre and post challenge on Day 3. Subjects receiving placebo had no obvious change from baseline in LTE_4 on Day 3 at all timepoints except for 0-3 hour post challenge, where a median increase of 90% from baseline in LTE_4 was observed.

The median and range for sputum eosinophils percentage cell count on Day 4 pre-dose in the 6 subjects who had data in both treatment periods was 27.42% (95% CI, 4.0% to 37.4%) for placebo and 10.87% (95% CI, 0 to 33.2%) for GSK2190915 100mg, indicating a reduction on GSK2190915 100mg compared with placebo. Sputum eosinophils percentage cell count on Day 4 pre-dose for each of the 6 subjects with evaluable data for both treatment periods was significantly reduced following three daily doses of GSK2190915 100mg compared to placebo, with an adjusted mean difference between GSK2190915 100mg and placebo of -9.95% (95% CI, -18.15%, -1.77%). On Day 4 predose and Day 5 24 hours post dose, there were notable differences in sputum LTB_4 between GSK2190915 100mg and placebo, indicating sputum LTB_4 suppression in subjects receiving GSK2190915 100mg. A notable difference in sputum LTE_4 between GSK2190915 100mg and placebo on Day 4 pre-dose was also evident, indicating sputum LTE_4 suppression in subjects receiving GSK2190915 100mg at this time-point. There was no obvious change between GSK2190915 100mg and placebo in sputum LTC_4 and LTD_4.

Derived pharmacokinetic (PK) parameters on Day 3 following three days once daily dosing with GSK2190915 100 mg are presented in the following Table. Derived PK parameters were in-line with previous data generated during the first time in human study (CL-AM803-01).

Safety results: Adverse event (AE) data was collected and recorded from the first administration of investigational product until the final follow up visit. All serious adverse event (SAE) data was collected over this same time period. During the period between consent and first administration of investigational product, adverse event reporting was limited to SAEs assessed as related to study participation.

Preferred Term	**Placebo (n=20)**	**GSK2190915 100mg (n=20)**
Any Event	9 (45%)	8 (40%)
Headache	5 (25%)	2 (10%)
Asthma	4 (20%)	3 (15%)
Cough	1 (5%)	1 (5%)
Fatigue	1 (5%)	2 (10%)
Hypoxia	1 (5%)	0
Rhinorrhoea	1 (5%)	0
Dizziness	1 (5%)	0
Pre-syncope	1 (5%)	0
Pyrexia	1 (5%)	0
Hyperhidrosis	1 (5%)	0
Rash	0	1 (5%)
Dyspepsia	0	1 (5%)
Seasonal allergy	1 (5%)	0
Myalgia	1 (5%)	0

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: No non-fatal or fatal SAEs were reported for this study.