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: LPA112356
Title : A randomised, double-blind, placebo-controlled, 3-period cross-over study to evaluate the effect of two doses of GSK2190915 on the allergen-induced asthmatic response in subjects with mild asthma
Rationale: The intention of clinical study LPA112356 was to describe the dose response of GSK2190915 in mild asthmatic subjects. This study evaluated both the safety and pharmacodynamic effect of two doses of GSK2190915 as assessed by the attenuation of the early asthmatic response (EAR) to inhaled allergen administered two hours post the final dose following three daily doses in subjects with mild asthma.
Phase: IIa
Study Period: 11 December 2008 to 28 July 2009
Study Design: The study comprised of three treatment periods. Subjects were administered study medication once daily in the morning for the first three days of each treatment period. Allergen challenge was conducted on Day 3, 2 hours post dose. A minimum 14 day washout was completed between treatment periods. The follow up visit was 5-21 days following last dose.
Centres: Multi-centre study
Indication: Asthma
Treatment: GS2190915 10 mg, 50 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 lung function as measured by forced expiratory lung volume in one second (FEV_1) on Days 1 and 3 in subjects with mild asthma compared with placebo - assess the safety and tolerability of repeat oral doses of GSK2190915 in mild asthmatic subjects compared with placebo.
Statistical Methods: At least 16 completed subjects were required in order to ensure at least 90% power to detect a 40% attenuation of the placebo response in the minimum FEV_1 absolute change from saline baseline 0-2 hours after challenge, using a two-sided 5% significance level, assuming a within subject standard deviation of 0.272L and a mean placebo response of -0.87L. No formal interim analyses were planned or performed. The 'All Subjects' population was defined as all subjects who received at least one dose of study medication. The 'Efficacy' population was defined as all subjects who received at least one dose of study medication and were not major protocol violators. The 'PK' population was defined as all subjects in the 'All subjects' population for whom a pharmacokinetic sample was obtained and analysed. The change from saline baseline FEV_1 over time was analysed using a repeated measures model. Adjusted mean estimates as well as treatment differences for each dose at each time point were summarised and plotted. The minimum FEV_1 absolute change from saline baseline 0-2 hours after allergen challenge on Day 3 of treatment was analysed using a mixed effects model. Estimates for the treatment difference between each active dose and placebo were calculated. Similar analyses were performed for the maximum percentage fall in FEV_1 and weighted mean FEV_1 between 0-2 hours after allergen challenge on Day 3. Change from pre-dose Day 1 baseline in non-challenge FEV_1 (Day 1 at 2 hours post dose, and Day 3 at pre-dose and 2 hours post dose) was analysed using appropriate mixed effects models. Pharmacokinetic and safety data were summarised and listed by treatment group.
Study Population: Mild asthmatic subjects

Number of Subjects	**Total (n=19)**
Number of subjects planned, N:	18
Number of subjects randomized and administered first dose, N:	19
Number of subjects completed as planned, n (%):	16 (84%)
Number of subjects withdrawn (any reason), n (%):	3 (16%)
Number of subjects withdrawn for SAE, n (%):	0
Number of subjects withdrawn for AE, n (%):	3 (16%)
Demographics	
Age in Years, Mean (SD)	35.0 (10.32)
Sex, n (%)	
Female:	1 (5%)
Male:	18 (95%)
BMI (kg/m²), Mean (SD)	25.24 (3.78)
Height (cm), Mean (SD)	177.8 (7.38)
Weight (kg), Mean (SD)	79.86 (12.95)
Ethnicity, n (%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	19 (100%)
Race, n (%)	
White	16 (84%)
African American / African Heritage & White	1 (5%)
Asian – Central /South Asian Heritage	1 (5%)
Asian - Japanese / East Asian Heritage / South East Asian Heritage	1 (5%)

Pharmacodynamics (PD) / Pharmacokinetic (PK) Endpoints: The adjusted mean change from saline baseline FEV_1 data over time from the repeated measures model showed notable separation from placebo for both GSK2190915 10mg and 50mg between 5 and 60 minutes after allergen challenge, with evidence of increasing attenuation of the placebo response to allergen challenge with increasing dose. Treatment differences for GSK2190915 50mg from placebo were statistically significant at all time points from 15 to 120 minutes.

The statistical analysis of the minimum FEV_1 absolute change from saline baseline 0-2 hours after allergen challenge for GSK2190915 10mg and 50mg showed a statistically significant increase in the minimum FEV_1 absolute change from saline baseline. There was evidence of a dose related increase, with a statistically significant difference between GSK2190915 50mg and GSK2190915 10mg also observed. Adjusted mean values for the minimum FEV_1 absolute change from saline baseline were -1.137L for placebo, -0.925L for GSK2190915 10mg and -0.728L for GSK2190915 50mg, corresponding to a mean attenuation of 18.6% and 36.0% of the placebo response to allergen challenge.

The statistical analysis of the maximum percentage fall in FEV_1 0-2 hours after allergen challenge on Day 3 were supportive of the primary endpoint, minimum FEV_1. The statistical analysis of weighted mean FEV_1 absolute change from saline baseline 0-2 hours after allergen challenge on Day 3 also supported the results seen for the primary endpoint. Adjusted mean values for the weighted mean FEV_1 absolute change from saline baseline were -0.540L for placebo, -0.434L for GSK2190915 10mg and -0.236L for GSK2190915 50mg, corresponding to a mean attenuation of 21.5% and 56.2% of the placebo response to allergen challenge

The statistical analysis of the change from pre-dose Day 1 baseline in non-challenge FEV_1 (Day 1 2 hours post dose, Day 3 pre-dose, Day 3 2 hours post dose) showed a statistically significant increase from placebo in the change from baseline FEV_1 with GSK2190915 50mg, with a mean increase of 0.1L, at pre-dose and 2 hours post-dose on Day 3. A mean difference of a similar magnitude was observed with GSK2190915 10mg at pre-dose on Day 3. However, this was not observed at 2 hours post dose on Day 3. Further, the mean pre-dose baseline value for the placebo group was slightly higher than seen for the active groups, contributing to the significance of the effects observed. These statistical differences are therefore thought unlikely to be of clinical importance.

Observed pharmacokinetic data were comparable to the first time in human study, CL-AM803-01. Thus, the drug exposure was confirmed as expected in the subject population for this study.

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.

		GSK2190915	
Preferred Term, n (%)	**Placebo (n=17)**	**10mg (n=18)**	**50mg (n=19)**
Any events	**3 (18%)**	**8 (44%)**	**4 (21%)**
Headache	2 (12%)	4 (22%)	0
Dizziness	0	0	1 (5%)
Oropharyngeal pain	0	1 (6%)	1 (5%)
Cough	0	0	1 (5%)
Influenza	1 (6%)	0	0
Nasopharyngitis	0	1 (6%)	0
Arthralgia	0	1 (6%)	0
Myalgia	0	1 (6%)	0
Dental caries	1 (6%)	0	0
Nausea	1 (6%)	1 (6%)	0
Chest pain	0	1 (6%)	0
Alanine aminotransferase increased	0	0	1 (5%)

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 serious adverse events were reported for this study.