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**: LPA112046

**Title:** The efficacy of orally administered GSK2190915 as an add-on to current therapy in subjects with moderate to severe asthma who have elevated sputum neutrophils.

**Rationale:** Neutrophils are known to be elevated in the sputum of persons with chronic moderate to severe asthma. Neutrophils are an important source of LTB4, a potent chemo attractant of inflammatory cells, which is thought to contribute to the persistent airflow obstruction, epithelial damage and airway remodelling in asthma. It has been demonstrated that GSK2190915 is well tolerated and effective at decreasing the production of LTB4. The objective of this study was to evaluate both the safety and pharmacodynamic effect of GSK2190915 in the treatment of subjects with moderate to severe asthma, using a number of clinical and biological markers of efficacy.

**Phase:** 2a

**Study Period:** Initiation Date: 26 JUN 2009, Completion Date: 02 JUN 2010, Early Termination Date: 02 JUN 2010

**Study Design:** Randomised, double-blind, placebo-controlled, parallel group, to evaluate the effect of treatment with GSK2190915 as add-on to current inhaled corticosteroid therapy in subjects with moderate to severe asthma with elevated sputum neutrophils

**Centres:** Canada: Hospital Laval, Hospital Sacre-Coeur, St. Joseph's Hospital. United Kingdom: Gartnavel General Hospital; Glenfield Hospital, Medicines Evaluation Unit.

**Indication:** Asthma

**Treatment:** There was one treatment period. The randomisation schedule allocated subjects to treatment (100mg GSK2190915 or Placebo) in solution formulation for 12 days, in a 1:1 ratio and subjects were stratified by smoking status (smoker/non-smoker).

**Objectives:** The primary objective was to evaluate the effect of treatment with repeat oral doses of GSK2190915 on the number of neutrophils (% and total) in induced sputum in moderate to severe asthmatic subjects compared with placebo.

**Statistical Methods:** Due to the small sample of subjects, the study concentrated on assessing individual responses rather than intra-comparisons between treatments. Pharmacodynamic and biomarker data were listed, summarised and plotted. Pharmacodynamic, pharmacokinetic and safety data were listed and summarised. There was no statistical analysis undertaken due to the limited number of subjects enrolled in the study.

**Study Population:** Healthy male and female subjects aged 18–65 years, inclusive.

| **Number of Subjects** | **Placebo** | **100mg GSK2190915** |
|---|---|---|
| Planned N | 20 | 20 |
| Dosed N | 3 | 4 |
| Completed n (%) | 3 (100) | 4 (100) |
| Total Number Subjects Withdrawn N (%) | 0 | 0 |
| Withdrawn due to Adverse Events n (%) | 0 | 0 |
| Withdrawn due to Lack of Efficacy n (%) | 0 | 0 |
| Withdrawn for Other Reasons n (%) | 0 | 0 |
| **Demographics** | **Placebo** | **100mg GSK2190915** |
| N (ITT) | 3 | 4 |
| Females: Males | 1:2 | 3:1 |
| Mean Age in Years (sd) | 52.0 (12.12) | 57.8 (6.65) |
| Mean Weight in Kg (sd) | 76.33 (23.094) | 77.53 (22.485) |
| White n (%) | 3 (100) | 4 (100) |

**Pharmacodynamic (PD) and Biomarker Endpoints:** Only 5 of the 7 subjects provided an evaluable sputum sample on Day 12, of which three subjects were on active and two subjects were on placebo. Two out of the three subjects who received GSK2190915 had substantial falls in percentage (%) neutrophils whilst none of the subjects on placebo had a fall in neutrophil %. Of note, the two subjects who received GSK2190915 and had falls in sputum % neutrophils had an increase in sputum neutrophil % by the follow up visit. However, also of note is that one of these subjects had positive sputum culture at follow-up. The 100mg GSK2190915 solution dose was accompanied by suppression of at

| | | |
|---|---|---|
| least 85% from baseline in both LTE4 in the urine and ionophore challenged LTB4 in the blood. | | |
| **Pharmacokinetic (PK) and PK/PD Endpoints:**<br>Mean (+/-SD) GSK2190915 concentrations (ng/mL) at Day 1 (2h post-dose), Day 12 (pre-dose) and Day 12 (2h post-dose) were 1609 (958.5), 1074 (627.8) and 2334 (1252.5) respectively. Although the number of subjects was small there was evidence of a PK/PD relationship with increasing GSK2190915 concentration yielding lower LTB4 levels. | | |
| **Safety results:** Adverse event and serious adverse event (SAE) data were recorded from the start of investigational product administration and until follow-up. In addition, any SAEs assessed as related to study participation (e.g. investigational product, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication were to be recorded from the time a subject consented to participate in the study up to and including follow-up. Most frequently reported AEs are summarised below. | | |
| **Adverse Events:** | **Placebo** | **100mg GSK2190915** |
| N (Safety) | 3 | 4 |
| No. subjects with AEs n (%) | 2 (67) | 3 (75) |
| Most Frequent AEs (more than one subject in the study): | | |
| Headache | 1 (33) | 2 (50) |
| Chills | 1 (33) | 0 |
| Palpitations | 0 | 1 (25) |
| Supraventricular extrasystoles | 0 | 1 (25) |
| Decreased appetite | 0 | 1 (25) |
| Nasal congestion | 0 | 1 (25) |
| Productive cough | 0 | 1 (25) |
| Bacterial test positive | 0 | 1 (25) |
| Constipation | 0 | 1 (25) |
| Nasopharyngitis | 0 | 1 (25) |
| Abdominal pain | 0 | 1 (25) |
| **Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:** There were no SAEs. | | |