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: LPA114387

Title: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Three-Treatment, Three 6-Week Period Cross-Over, Multi-Center Exploratory Study to Evaluate the Effect of Adding GSK2190915 300 mg Tablets Once Daily, Montelukast 10 mg Tablets Once Daily or Placebo Tablets Once Daily to Fluticasone Propionate/Salmeterol 250/50 mcg Inhalation Powder Twice Daily in Uncontrolled Asthmatic Subjects ≥18 Years of Age.

Rationale: The primary purpose of this study was to evaluate the efficacy and safety of adding GSK2190915 300 mg or placebo tablets administered once daily to fluticasone propionate (FP)/salmeterol (SAL) 250/50 mcg inhalation powder administered twice daily in female subjects ≥18 years of age with uncontrolled asthma over the course of 6 weeks' treatment. An exploratory analysis was also undertaken to assess the efficacy and safety of adding montelukast 10 mg administered once daily to FP/SAL 250/50 mcg inhalation powder administered twice daily in the same population.

Phase: IIb

Study Period: 19 December 2010–11 October 2011.

Study Design: Randomised, double-blind, double-dummy, placebo-controlled, three-treatment, three 6-week period crossover, multi-centre, exploratory.

Centres: Multi-centre study conducted at 18 sites in the Ukraine, Bulgaria and Poland.

Indication: Asthma.

Treatment: The following three cross-over treatments were provided by GSK Clinical Trial Supplies:

Treatment	Morning	Evening
A	1 x 100 mg GSK2190915 tablet 1 x 200 mg GSK2190915 tablet 1 x FP/SAL 250/50 mcg DISKUS	1 x FP/SAL 250/50 mcg DISKUS 1 x placebo capsule
B	2 x placebo tablets 1 x FP/SAL 250/50 mcg DISKUS	1 x FP/SAL 250/50 mcg DISKUS 1 x 10 mg montelukast capsule
C	2 x placebo tablets 1 x FP/SAL 250/50 mcg DISKUS	1 x FP/SAL 250/50 mcg DISKUS 1 x placebo capsule

A = Fluticasone propionate/salmeterol 250/50 mcg twice daily plus GSK2190915 300 mg once daily (AM)
B = Fluticasone propionate/salmeterol 250/50 mcg twice daily plus montelukast 10 mg once daily (PM)
C = Fluticasone propionate/salmeterol 250/50 mcg twice daily plus placebo twice daily

Subjects were to receive double-blind add-on treatment for approximately 126 days (three 6-week cross-over periods) and were instructed to take one inhalation at the same time each morning and one inhalation at the same time each evening from the DISKUS inhaler.

Objectives: The primary objective of this study was to evaluate the efficacy and safety of adding GSK2190915 300 mg or placebo tablets administered once daily to FP/SAL 250/50 mcg inhalation powder administered twice daily in uncontrolled asthmatic female subjects ≥18 years of age over the course of 6 weeks' treatment.

Primary Outcome/Efficacy Variable: The primary efficacy endpoint for this study was trough (AM pre-dose and pre-rescue bronchodilator) forced expiratory volume in 1 second (FEV_1) at the end of the 6-week treatment period.

Secondary Outcome/Efficacy Variables: Secondary efficacy endpoints were: daily trough (AM pre-dose and pre-rescue bronchodilator) AM peak expiratory flow (PEF) averaged over the last 3 weeks of the 6-week treatment period; daily PM PEF averaged over the last 3 weeks of the 6-week treatment period; daily (average of AM and PM) PEF averaged over the last 3 weeks of the 6-week treatment period; daily asthma symptom score averaged over the last 3 weeks of the 6-week treatment period; daily rescue salbutamol use averaged over the last 3 weeks of the 6-week treatment period; percentage of symptom-free days and nights during the last 3 weeks of the 6-week treatment period; percentage of rescue-free days and nights during the last 3 weeks of the 6-week treatment period; percentage of nights without awakenings due to asthma during the last 3 weeks of the 6-week treatment period; proportion of subjects withdrawn due to lack of efficacy during the last 3 weeks of the 6-week treatment period.
Safety endpoints were: incidence of adverse events (AEs) throughout the treatment periods; haematology, chemistry (to include liver function tests) and urinalysis parameters; vital signs (change from baseline in pulse rate and systolic and diastolic blood pressures).
Health outcomes endpoints were: mean change in Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) score from baseline.

Statistical Methods: Sample size: Approximately 250 female subjects were planned to be randomised to achieve

96 completed subjects. This sample size was based on the primary endpoint with approximately 90% power to detect a treatment difference of 100 mL between the GSK2190915 add-on and placebo add-on. This assumed statistical significance at the two-sided 5% level.

Efficacy analyses: The primary efficacy endpoint was analysed using a mixed effects analysis of covariance model, incorporating baseline, subject, period, age, country and smoking status. Estimated treatment differences, 95% confidence intervals (CIs) and p-values for the difference were presented for the pairwise comparisons between active add-on and placebo add-on. Daily (pre-dose and pre-rescue bronchodilator) AM PEF averaged over the last 3 weeks of the 6-week treatment period was analysed using a mixed effects analysis of covariance model for treatment effects, incorporating baseline, subject, period, age, country and smoking status. Daily PM PEF was analysed in a similar manner.

The percentages of symptom-free days and nights and rescue-free days and nights were compared for GSK2190915 add-on and montelukast 10 mg add-on versus placebo add-on using a mixed effects analysis of covariance model for treatment effects, incorporating baseline, subject, period, age, country and smoking status. Asthma symptom scores, rescue medication use and nights without awakenings were analysed in a similar manner.

The number of withdrawals due to lack of efficacy was summarised for each treatment period and each treatment regimen and Fisher's Exact test was used to compare GSK2190915 add-on and montelukast 10 mg add-on versus placebo add-on.

Safety analyses: There was no formal analysis of safety endpoints. Safety data were summarised descriptively.

Health outcomes analyses: Mean change from baseline to endpoint in ACQ data were analysed using analysis of covariance, adjusting for baseline ACQ score, subject, period, age, country and smoking status. The AQLQ data were analysed in a similar manner.

The study type I error rate was controlled at the 5% level for the primary efficacy analyses using the Week 6 trough FEV_1 endpoint, by performing a statistical test of GSK2190915 add-on versus placebo add-on. No multiplicity adjustment was made on any other efficacy analyses, so any other statistical test p-value ≤ 0.05 is identified as nominally significant.

All 145 randomised subjects were included in the Intent-to-Treat (ITT) population, which was defined as all randomised subjects who received at least one dose of double-blind study drug. This population was the basis for all summaries, analyses, listings and figures of demographic, safety and efficacy data.

Study Population: Female subjects aged $\geq$18 years of age with uncontrolled asthma, as defined by the National Institutes of Health. Subjects had to show a FEV_1 best of 50% to <80% of the predicted normal value during Visit 1/1a (between 5:00 AM and 12:00 noon). Former and current smoking subjects were also required to have a post-salbutamol FEV_1/forced vital capacity ratio of >0.70 at Visit 1/1a. Subjects had to demonstrate a $\geq$12% and $\geq$200 mL reversibility of FEV_1 within approximately 30 minutes [$\pm$15 minutes] following up to four inhalations of salbutamol inhalation aerosol (a spacer was permitted for reversibility testing if required) or one inhalation of nebulised salbutamol solution during Visit1/1a. Subjects must have been using FP/SAL 250/50 mcg inhalation powder twice daily for at least 2 weeks just prior to Visit 1 and were required to be able to replace their current short-acting beta2-agonists with salbutamol inhalation aerosol at Visit 1/1a for use as needed for the duration of the study.

Number of Subjects:	
Planned, N	120
Randomised, N	145
Completed, n (%)	120 (83)
Total Number Subjects Withdrawn, N (%)	25 (17)
Withdrawn due to Adverse Events n (%)	3 (2)
Withdrawn due to Lack of Efficacy n (%)	13 (9)
Withdrawn for other reasons n (%)	9 (6)
Demographics	
N (ITT)	145
Females	145
Mean Age, years (SD)	48.6 (12.52)
Mean Height, cm (SD)	163.2 (6.95)
Mean Weight, kg (SD)	73.0 (13.29)
White – White/Caucasian/European Heritage, n (%)	145 (100)
Asthma duration category (n [%])	

<1 year	4 (3)
≥1 year to <5 years	25 (17)
≥5 years to <10 years	41 (28)
≥10 years to <15 years	37 (26)
≥15 years to <20 years	15 (10)
≥20 years to <25 years	13 (9)
≥25 years	10 (7)

Primary Efficacy Results: Results from the statistical analysis of trough FEV_1 (L) at Week 6 are presented below.

Trough FEV_1 (L)	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	129	132	129
LS Mean (SE)	2.08 (0.03)	2.11 (0.03)	2.12 (0.03)
LS Mean Difference		0.027	0.037
95% Confidence Interval		(-0.02, 0.07)	(-0.01, 0.08)
p-value vs. placebo		0.221	0.098

Secondary Outcome Variables:

Statistical Analysis of AM PEF (L/min) at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	305.40 (2.82)	306.05 (2.81)	308.67 (2.83)
LS Mean Difference		0.644	3.265
95% Confidence Interval		(-2.99, 4.28)	(-0.39, 6.92)

Statistical Analysis of PM PEF (L/min) at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	312.89 (3.05)	313.94 (3.03)	315.60 (3.06)
LS Mean Difference		1.047	2.714
95% Confidence Interval		(-2.49, 4.58)	(-0.85, 6.28)

Statistical Analysis of Daytime Symptom Scores at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	0.98 (0.05)	0.96 (0.05)	0.92 (0.05)
LS Mean Difference		-0.023	-0.064
95% Confidence Interval		(-0.08, 0.03)	(-0.12, -0.01)

Statistical Analysis of Night-time Symptom Scores at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	0.77 (0.04)	0.74 (0.04)	0.74 (0.04)
LS Mean Difference		-0.031	-0.031
95% Confidence Interval		(-0.07, 0.01)	(-0.07, 0.01)

Statistical Analysis of Daytime Short-Acting Beta-Agonist Use at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	1.02 (0.06)	0.95 (0.06)	0.92 (0.06)
LS Mean Difference		-0.070	-0.097

95% Confidence Interval		(-0.13, -0.01)	(-0.16, -0.04)
Statistical Analysis of Night-time Short-Acting Beta-Agonist Use at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	0.80 (0.05)	0.74 (0.05)	0.75 (0.05)
LS Mean Difference		-0.058	-0.046
95% Confidence Interval		(-0.11, -0.00)	(-0.10, 0.01)
Statistical Analysis of Percentage of Symptom-Free Days at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	33.72 (2.82)	32.98 (2.81)	35.22 (2.83)
LS Mean Difference		-0.737	1.504
95% Confidence Interval		(-3.99, 2.51)	(-1.79, 0.480)
Statistical Analysis of Percentage of Symptom-Free Nights at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	43.18 (2.77)	44.91 (2.75)	45.31 (2.78)
LS Mean Difference		1.732	2.127
95% Confidence Interval		(-1.58, 5.04)	(-1.24, 5.49)
Statistical Analysis of Percentage of Rescue-Free Days at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	37.70 (2.92)	39.39 (2.90)	40.35 (2.93)
LS Mean Difference		1.691	2.649
95% Confidence Interval		(-1.80, 5.19)	(-0.89, 6.19)
Statistical Analysis of Percentage of Rescue-Free Nights at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	47.56 (2.98)	50.17 (2.96)	49.01 (2.99)
LS Mean Difference		2.616	1.456
95% Confidence Interval		(-1.42, 6.65)	(-2.62, 5.53)
Statistical Analysis of Percentage of Nights without Awakenings due to Asthma at Weeks 4–6	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	130	133	128
LS Mean (SE)	43.18 (2.77)	44.91 (2.75)	45.31 (2.78)
LS Mean Difference		1.732	2.127
95% Confidence Interval		(-1.58, 5.04)	(-1.24, 5.49)
Statistical Analysis of Withdrawals due to Lack of Efficacy	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
Number (%) Withdrawn	4 (3)	5 (4)	2 (2)

Statistical Analysis of Change from Baseline in AQLQ at Endpoint – Total Scores	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	128	133	129
LS Mean (SE)	0.62 (0.06)	0.64 (0.06)	0.63 (0.06)
LS Mean Difference		0.022	0.011
95% Confidence Interval		(-0.07, 0.12)	(-0.08, 0.11)

Statistical Analysis of Change from Baseline in ACQ at Endpoint	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
n	121	130	125
LS Mean (SE)	-0.65 (0.06)	-0.66 (0.06)	-0.71 (0.06)
LS Mean Difference		-0.012	-0.064
95% Confidence Interval		(-0.11, 0.09)	(-0.16, 0.04)

Safety Results: Adverse events and serious adverse events (SAEs) were collected from the start of investigational product until the follow-up contact. 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 GlaxoSmithKline concomitant medication, were to be recorded from the time a subject consented to participate in the study up to and including any follow-up contact. All AEs reported by more than one subject are presented below.

Most Frequent Adverse Events – On-Therapy	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
Subjects with any AE(s), n(%)	15 (11)	22 (16)	10 (8)
Headache	8 (6)	8 (6)	8 (6)
Nasopharyngitis	3 (2)	2 (1)	0
Abdominal pain upper	1 (<1)	2 (1)	2 (2)
Pyrexia	0	2 (1)	1 (<1)
Respiratory tract infection	0	2 (1)	0

Serious Adverse Events - On-Therapy
n (%) [n considered by the Investigator to be related to study medication]

Subjects with non-fatal SAEs, n (%)	FP/SAL + Placebo (N=135)	FP/SAL + GSK2190915 300 mg (N=136)	FP/SAL + Mont (N=132)
	n (%) [related]	n (%) [related]	n (%) [related]
Jaw fracture	0	0	1 (<1) [0]
Subjects with fatal SAEs, n (%)			
	n (%) [related]	n (%) [related]	n (%) [related]
	0	0	0

Conclusion:
There were no statistically significant differences for the primary endpoint between treatment regimens. Similar numbers of subjects reported AEs during treatment with FP/SAL + placebo and FP/SAL + GSK2190915. No deaths were reported during the study and one SAE (jaw fracture) was reported for FP/Sal 250/50 mcg bid plus montelukast 10mg qd which was considered to be unrelated to study medication by the investigator.