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.

GSK Medicine: Fluticasone furoate (FF), GW685698X

Study Number: FFA106783

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of GW685698X 200 mcg Twice Daily, GW685698X 200 mcg and 400 mcg OD in the Morning, and GW685698X 200 mcg and 400 mcg OD in the Evening Compared with Placebo for 8 Weeks in Adolescent and Adult Subjects (12 years of age and older) with Persistent Asthma

Rationale: This study was designed to evaluate the relative efficacy and safety of fluticasone furoate (FF) 200 mcg and 400 mcg once-daily (OD) in the morning, FF 200 mcg and 400 mcg OD in the evening, and FF 200 mcg twice-daily (morning and evening, approximately 12 hours apart, BD) in subjects with persistent asthma. FF 200 mcg OD arms (morning and evening) were included in order to assess assay sensitivity of the study for the relative assessment of OD and BD dosing, to assess the relative efficacy and safety of morning and evening dosing, and to obtain some dose response information.

Phase: IIa

Study Period: 15 November 2006 - 30 August 2007

Study Design: This was an 8-week multi-center, randomized, double-blind, parallel group, placebo-controlled study. Subjects who met all of the inclusion criteria and none of the exclusion criteria at the Visit 1 morning clinic visit (screening visit, start of run-in) completed a 14±3 day pre-treatment run-in period. Subjects continued use of their current inhaled corticosteroid (ICS) therapy at stable daily doses during run-in, but stopped their ICS use the day prior to the Visit 2a morning clinic visit. Subjects who then met eligibility criteria for study treatment at the Visit 2a morning clinic visit were randomly assigned to begin one of the study treatments with the first dose of study medication given in the clinic at the Visit 2b evening clinic visit. Subjects were required to return to the clinic for eight on-treatment visits, five visits in the morning (Weeks 1, 2, 4, 6, and 8, respectively) and three evening visits (Weeks 2, 4, and 8, respectively) over a total of 56 days (8 weeks) of double-blind treatment. A follow-up telephone contact was performed 1 week after completing study medication. Subjects participated in the study for up to 11 weeks [including screening (2 weeks), treatment (8 weeks), and follow-up telephone contact (1 week)].

Centres: A total of 70 investigational sites in 16 countries randomized subjects across five regions: 6 centers in North America, 34 centers in Europe, 12 centers in Central and South America, 14 centers in the Asia-Pacific and 4 centers in South Africa.

Indication: Asthma

Treatment: Subjects were treated with one of the six study treatments:

- FF 200 mcg one inhalation in the morning and FF 200 mcg one inhalation in the evening;
- FF 200 mcg one inhalation in the morning and placebo one inhalation in the evening;
- FF 400 mcg one inhalation in the morning and placebo one inhalation in the evening;
- FF 200 mcg one inhalation in the evening and placebo one inhalation in the morning;
- FF 400 mcg one inhalation in the evening and placebo one inhalation in the morning;
- Placebo one inhalation in the morning and placebo one inhalation in the evening.

All subjects were dosed using the DISKUS™/ACCUHALER™.

Objectives: The primary objective of this study was to evaluate the relative efficacy and safety of once-daily and twice-daily dosing and of morning and evening dosing of FF in adolescent and adult subjects with persistent asthma.

Primary Outcome/Efficacy Variable: The single efficacy endpoint was the mean change from baseline at Week 8 (last assessment on treatment using last observation carried forward) in trough (AM or PM pre-dose and pre-rescue bronchodilator) forced expiratory volume in 1 second (FEV_1).

Secondary Outcome/Efficacy Variable(s): Not applicable

Statistical Methods: The primary treatment comparisons were each dose regimen of FF versus placebo for change from baseline in trough FEV_1 at Week 8. Although the comparisons of the two 400 mcg OD regimens with FF 200 mcg BD and of each morning dose with the corresponding evening dose were of interest, the study was not powered to demonstrate non-inferiority of the OD arms relative to the BD arm or of the AM arms relative to the PM arms and therefore, statistical comparisons of all FF arms were against placebo.

The five primary comparisons were performed by use of hypothesis tests and used the Intent-to-Treat (ITT) Population. A 2-sided 5% risk associated with incorrectly rejecting any of the five null hypotheses (significance level) was considered acceptable for this study. Although there was more than one primary comparison, this study was

exploratory in nature and therefore, multiplicity adjustments were not made.

Provided the FF treatment regimens demonstrated a statistically significant difference relative to placebo, the relative effects of OD and BD dosing and of morning and evening dosing were to be evaluated by assessment of the degree of overlap between the 95% confidence intervals relating to the treatment differences of the relevant dose regimen versus placebo. If the point estimate of the treatment/placebo difference for any given FF regimen lied within the 95% confidence interval for another FF regimen, the treatment effect estimates would be within 0.12L of each other.

The primary population of interest was the ITT Population, which was defined as all randomized subjects who received a dose of study medication.

Study Population: Male and female subjects were eligible for treatment as outpatients if they had a diagnosis of asthma as defined by the National Institutes of Health, were ≥12 years of age at screening for all countries except for Germany and Canada (who enrolled only adult subjects ≥18 years of age), used an ICS for at least 3 months prior to Visit 1 and maintained on a stable dose for 4 weeks prior to Visit 1, and were symptomatic. Subjects must have had a best morning FEV_1 of 50% to 80% of the predicted value during Visit 1 and must have been able to demonstrate a ≥12% and 200mL reversibility of the Visit 1 FEV_1 measure within 30 minutes following 200 to 400 mcg albuterol/salbutamol inhalation aerosol (2 to 4 puffs) administration.

Subjects were excluded from the trial if they had a history of life-threatening asthma, experienced an asthma exacerbation within 4 weeks of Visit 1, any asthma exacerbation requiring oral corticosteroids within 3 months of Visit 1 or any hospitalization due to asthma exacerbation within 6 months of Visit 1, used a prohibited asthma medication within a predefined period prior to Visit 1, had historical or current evidence of clinically significant uncontrolled disease, had evidence of oropharyngeal candidiasis, used tobacco products within 12 months of visit 1, or had a clinically significant abnormal laboratory finding or concurrent disease/abnormality.

		Fluticasone Furoate Dose				
	Placebo	**200 mcg OD/AM**	**200 mcg OD/PM**	**400 mcg OD/AM**	**400 mcg OD/PM**	**200 mcg BD**
Number of Subjects:						
Planned, N	108	108	108	108	108	108
Randomised, N	102	106	104	112	115	113
Intent-to-Treat, N	101	105	103	111	113	113
Completed, n (%)	65 (64)	85 (81)	82 (80)	96 (86)	96 (85)	96 (85)
Total Number Subjects Withdrawn, N (%)	36 (36)	20 (19)	21 (20)	15 (14)	17 (15)	17 (15)
Withdrawn due to Adverse Events, n (%)	0	1 (<1)	1 (<1)	2 (2)	3 (3)	1 (<1)
Withdrawn due to Lack of Efficacy, n (%)	21 (21)	10 (10)	13 (13)	7 (6)	9 (8)	13 (12)
Withdrawn for other reasons, n (%)	15 (15)	9 (9)	7 (7)	6 (5)	5 (4)	3 (3)
Demographics						
N (ITT)	101	105	103	111	113	113
Females: Males	62:39	62:43	74:29	73:38	70:43	78:35
Mean Age, years (SD)	44.4 (14.95)	45.0 (15.28)	43.7 (14.36)	46.9 (16.09)	45.0 (14.77)	45.6 (14.72)
White, n (%)	60 (60)	68 (65)	67 (66)	74 (67)	75 (68)	76 (67)
Asian, n (%)	16 (16)	14 (13)	15 (15)	16 (15)	15 (14)	17 (15)
American Indian or Alaskan Native and White, n (%)	13 (13)	13 (13)	11 (11)	12 (11)	10 (9)	11 (10)
American Indian or	8 (8)	7 (7)	8 (8)	7 (6)	7 (6)	8 (7)

Alaskan Native, n (%)						
African American/African Heritage, n (%)	2 (2)	1 (<1)	1 (<1)	1 (<1)	3 (3)	1 (<1)
Native Hawaiian or other Pacific Islander, n (%)	1 (1)	0	0	0	1 (<1)	0
Asian and White, n (%)	0	1 (<1)	0	0	0	0

Primary Efficacy Results:

Change from Baseline in Trough AM FEV_1 (L) at Week 8

		Fluticasone Furoate Dose		
	Placebo	**200 mcg OD/AM**	**400 mcg OD/AM**	**200 mcg BD**
Trough FEV1, n	85	100	106	102
LS Mean (SE)	2.029 (0.0434)	2.203 (0.0389)	2.230 (0.0397)	2.344 (0.0400)
LS Mean Change (SE)	0.053 (0.0434)	0.228 (0.0389)	0.255 (0.0397)	0.368 (0.0400)
Difference from Placebo		0.174	0.202	0.315
95% CI		0.067, 0.282	0.096, 0.307	0.208, 0.421
p-value		0.002	<0.001	<0.001

Change from Baseline in Trough PM FEV_1 (L) at Week 8

		Fluticasone Furoate Dose		
	Placebo	**200 mcg OD/PM**	**400 mcg OD/PM**	**200 mcg BD**
Trough FEV1, n	77	92	103	100
LS Mean (SE)	2.198 (0.0458)	2.322 (0.0437)	2.438 (0.0398)	2.432 (0.0411)
LS Mean Change (SE)	0.084 (0.0458)	0.208 (0.0437)	0.324 (0.0398)	0.319 (0.0411)
Difference from Placebo		0.124	0.240	0.235
95% CI		0.010, 0.238	0.129, 0.351	0.123, 0.346
p-value		0.033	<0.001	<0.001

Secondary Outcome Results: Not applicable

Safety Results: An on therapy adverse event (AE) or serious adverse event (SAE) was defined as an AE with onset on or after the start date of study medication and on or before the stop date of study medication.

		Fluticasone Furoate Dose				
	Placebo	**200 mcg OD/AM**	**200 mcg OD/PM**	**400 mcg OD/AM**	**400 mcg OD/PM**	**200 mcg BD**
N	101	105	103	111	113	113
Most Frequent Adverse Events – On-Therapy, n (%)						
Subjects with any AE(s), n (%)	28 (28)	36 (34)	32 (31)	43 (39)	35 (31)	38 (34)
Headache	6 (6)	8 (8)	7 (7)	10 (9)	7 (6)	9 (8)
Nasopharyngitis	4 (4)	8 (8)	8 (8)	3 (3)	7 (6)	6 (5)
Bronchitis	2 (2)	1 (<1)	3 (3)	4 (4)	4 (4)	0
Pharyngolaryngeal pain	1 (<1)	2 (2)	3 (3)	2 (2)	1 (<1)	3 (3)
Upper respiratory tract infection	2 (2)	3 (3)	2 (2)	2 (2)	1 (<1)	1 (<1)
Dysphonia	0	1 (<1)	1 (<1)	1 (<1)	2 (2)	3 (3)
Rhinitis	0	4 (4)	1 (<1)	0	1 (<1)	2 (2)
Rhinitis allergic	1 (<1)	2 (2)	3 (3)	0	0	1 (<1)
Dizziness	0	3 (3)	0	2 (2)	1 (<1)	0
Influenza	2 (2)	0	1 (<1)	3 (3)	0	0
Pharyngitis	4 (4)	2 (2)	0	0	0	0
Respiratory tract infection	0	1 (<1)	0	3 (3)	1 (<1)	0

Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]						
		Fluticasone Furoate Dose				
	Placebo	200 mcg OD/AM	200 mcg OD/PM	400 mcg OD/AM	400 mcg OD/PM	200 mcg BD
N	101	105	103	111	113	113
Subjects with non-fatal SAEs, n (%)						
Subjects with any AE(s), n (%)	0	0	1 (<1) [1]	1 (<1) [0]	0	0
Acute localized Quincke's edema of the eyes	0	0	1 (<1) [1]	0	0	0
Recurrent paroxysm of atrial fibrillation	0	0	0	1 (<1) [0]	0	0
Subjects with fatal SAEs, n (%)						
Subjects with fatal SAE(s), n (%)	0	0	0	0	0	0

Conclusion: This study demonstrated statistically significant improvement in lung function, as measured by trough FEV_1, for all treatment doses of FF compared with placebo after 8 weeks of dosing. The most frequent AEs included headache, nasopharyngitis, bronchitis, pharyngolaryngeal pain and upper respiratory tract infection. Two serious adverse events occurred on treatment, one in the FF 200 mcg OD PM group and one in the FF 400 mcg OD AM group. One of the serious AEs (acute localized Quincke's edema of the eyes in one subject in the FF 200 mcg OD PM group) was considered related to treatment. There were no fatal events in this study.