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Study No.: FFA109684
Title: A Randomized Double-Blind, Double Dummy, Placebo-Controlled, Parallel-Group, Multicenter Dose Ranging Study to Evaluate the Efficacy and Safety of GW685698X Inhalation Powder Once Daily and Fluticasone Propionate Inhalation Powder 500mcg Twice Daily compared with Placebo for 8 Weeks in Adolescent and Adult Subjects with Persistent Asthma Symptomatic on Moderate-Dose ICS Therapy
Rationale: This trial was designed to assess the dose response, efficacy, and safety of GW685698X administered once daily versus placebo in patients with persistent asthma who remain symptomatic despite use of moderate dose inhaled corticosteroid therapy. Fluticasone Propionate was included as benchmark
Phase: IIb
Study Period: 20 Dec 2007 – 20 Sep 2008
Study Design: This was a multi-center, randomized, double-blind, double dummy, parallel-group, placebo-controlled study.
Centers: 16 countries at 137 investigative sites (94 that randomized subjects) 87 centers in North America, 29 centers in Europe, 12 centers in Central and South America, 2 centers in Asia-Pacific, 3 centers in Australia, and 4 centers in South Africa.
Indication: Asthma
Treatment: Subjects were randomly assigned to treatments as follows: <ul style="list-style-type: none"> • GW685698X once daily via novel dry powder inhaler (Novel DPI) and placebo twice daily via DISKUS™/ACCUHALER™ (one inhalation each in the morning and in the evening). • Fluticasone propionate 500 mcg twice daily via DISKUS/ACCUHALER (one inhalation in the morning and one inhalation in the evening) plus placebo once daily via Novel DPI • Placebo once daily via Novel DPI and placebo twice daily via DISKUS/ACCUHALER (one inhalation in the morning and one inhalation in the evening).
Objectives: The objective of this study was to evaluate the dose response, efficacy and safety of GW685698X administered once daily in adolescent and adult subjects 12 years of age and older with persistent uncontrolled asthma.
Primary Outcome/Efficacy Variable <ul style="list-style-type: none"> • Mean change from baseline to the end of the 8-week treatment period (last assessment on treatment using last observation carried forward) in trough (pre-dose and pre- rescue bronchodilator) FEV₁.
Secondary Outcome/Efficacy Variable(s) <ul style="list-style-type: none"> • Mean change from baseline in daily trough (pre-dose and pre-rescue bronchodilator) PM PEF averaged over the 8-week treatment period. • Mean change from baseline in daily AM PEF averaged over the 8-week treatment period. • Mean change from baseline in the percentage of symptom-free 24-hour periods and rescue-free 24-hour periods during the 8-week treatment period. • The number of withdrawals due to lack of efficacy during the 8-week treatment period.
Statistical Methods: <p>A planned 99 evaluable subjects per group would give the study 90% power to detect a difference of 200 mL in pairwise comparisons of change from baseline in trough FEV₁ between any active dose and placebo. This assumed a standard deviation of 430mL and significance declared at the two-sided 5% level.</p> <p>The primary analysis was performed using an ANCOVA model with effects due to baseline FEV₁, country, sex, age and treatment group. Estimated treatment differences for pairwise comparisons against placebo were presented together with 95% confidence intervals and p-values.</p>
Study Population: A total of 1175 male and female subjects ≥12 years of age with persistent asthma who were symptomatic on ICS were screened, of which 627 were randomized. Of the 627 subjects, 622 received at least one dose of study medication and comprised the Intent-to-Treat Population. The study was planned to enroll at least 594 evaluable subjects (99 per treatment group). Eligible subjects had persistent asthma as defined by the National Institutes of Health [National Institutes of Health, 2007], with a ≥12% and ≥200mL reversibility of FEV ₁ at Visit 1 and asthma severity determined by a best FEV ₁ of 40%-90% of the predicted normal value if the Visit occurred between 5:00 PM and 11:00 PM (or 40%-85% of the predicted normal value if the Visit occurred between 5:00 AM and 12:00

Noon) at Visit 1.		
	Placebo	FP 500mcg BD
Number of Subjects:	104	111
Planned, N	99	99
Randomised, N	104	111
ITT Population	103	110
Completed, n (%)	65 (63)	97 (88)
Total Number Subjects Withdrawn, N (%)	38 (37)	13 (12)
Withdrawn due to Adverse Events n (%)	2 (2)	4 (4)
Withdrawn due to Lack of Efficacy n (%)	34 (33)	8 (7)
Withdrawn for other reasons n (%)	2 (2)	1 (<1)
Demographics	Placebo	FP 500mcg BD
N (ITT)	103	110
Females: Males	64:39	68:42
Mean Age, years (SD)	47.2 (14.03)	46.1 (13.86)
White, n (%)	83 (81)	83 (76)
Asian, n (%)	6 (6)	7 (6)
American Indian or Alaska Native, n (%)	6 (6)	7 (6)
American Indian or Alaska Native and White, n (%)	6 (6)	8 (7)
African American/African Heritage, n (%)	2 (2)	4 (4)
Primary Efficacy Results:		
Statistical Analysis of Change from Baseline in Trough FEV₁ at Week 8 (LOCF) (L)		
	Placebo	FP 500mcg BD
LS Mean	2.093	2.291
LS Mean Change (SE)	-0.043 (0.0338)	0.155 (0.0332)
LS Difference versus Placebo		0.198
95% Confidence Interval		(0.105, 0.291)
p-value		<0.001
Secondary Outcome Variables:		
PM PEF – Weeks 1-8 (L/min)		
	Placebo	FP 500mcg BD
LS Mean	333.5	349.8
LS Mean Change (SE)	-5.1 (3.32)	11.1 (3.17)
LS Difference versus Placebo		16.3
95% Confidence Interval		(7.2, 25.3)
p-value		<0.001
AM PEF – Weeks 1-8 (L/min)		
	Placebo	FP 500mcg BD
LS Mean	320.1	343.9
LS Mean Change (SE)	-7.3 (3.32)	16.5 (3.19)
LS Difference versus Placebo		23.8
95% Confidence Interval		(14.7, 32.8)
p-value		<0.001
Symptom-Free 24-Hour Periods (%)		
	Placebo	FP 500mcg BD
LS Mean Change (SE)	6.4 (2.71)	15.4 (2.61)
LS Difference versus Placebo		9.1
95% Confidence Interval		(1.7, 16.5)
p-value		0.017
Rescue-Free 24-Hour Periods (%)		
	Placebo	FP 500mcg BD
LS Mean Change (SE)	3.6 (2.75)	16.7 (2.63)
LS Difference versus Placebo		13.2
95% Confidence Interval		(5.7, 20.6)
p-value		<0.001

Subjects with Lack of Efficacy as Primary Reason for Withdrawal		
	Placebo	FP 500mcg BD
n (%)	34 (33)	8 (7)
p-value		<0.001
An on therapy adverse event (AE) or serious adverse event (SAE) was defined as an AE or SAE with onset on or after the start date of study medication but not later than one day after the last date of study medication.		
	Placebo N=103	FP 500mcg BD N=110
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	23 (22)	39 (35)
Headache	10 (10)	10 (9)
Nasopharyngitis	4 (4)	4 (4)
Oropharyngeal candidiasis	1 (<1)	4 (4)
Pharyngolaryngeal pain	1 (<1)	4 (4)
Upper respiratory tract infection	1 (<1)	3 (3)
Dysphonia	1 (<1)	2 (2)
Sinusitis	0	2 (2)
Cough	1 (<1)	2 (2)
Musculoskeletal pain	0	2 (2)
Non-cardiac chest pain	0	2 (2)
Angioedema	0	2 (2)
Bronchitis	2 (2)	1 (<1)
Conjunctivitis	2 (2)	0
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	Placebo	FP 500mcg BD
	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	1 (<1) [0]	2 (1.8) [0]
Asthma exacerbation	1 (<1) [0]	1 (<1) [0]
Amitriptyline overdose ^a	0	1 (<1) [0]
Attempted suicide ^a	0	1 (<1) [0]
Nonspecific T-wave abnormality ^a	0	1 (<1) [0]
Subjects with fatal SAEs, n (%)	0	0

a. These 3 events occurred in the same subject

Conclusion:

The data presented includes a partial summary of the placebo and fluticasone propionate treatment arms. A conclusion will be included with the full study summary.

Publications: Not applicable

National Institutes of Health (NIH). *Guidelines for the Diagnosis and Management of Asthma - Expert Panel Report 3* 2007. U.S. Department of Health and Human Services, Bethesda, MD; 2007. NIH Publication No. 07-4051.