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Study No.: FFA109685
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 250mcg Twice Daily compared with Placebo for 8 Weeks in Adolescent and Adult Subjects with Persistent Asthma Symptomatic on Low-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 low-dose inhaled corticosteroid therapy. Fluticasone Propionate was included as benchmark.
Phase: IIb
Study Period: 20 Dec 2007 – 24 Nov 2008
Study Design: This was a multi-center, randomized, double-blind, double dummy, parallel-group, placebo-controlled study.
Centers: 13 countries at 144 investigative sites (98 sites randomized subjects): 95 centers in North America, 33 centers in Europe, 2 centers in Central and South America, 10 centers in Asia-Pacific, 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 in the evening 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 250 mcg twice daily via DISKUS/ACCUHALER (one inhalation in the morning and one inhalation in the evening) plus placebo once daily in the evening via Novel DPI • Placebo once daily in the evening 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 all pairwise comparisons against placebo were presented together with 95% confidence intervals and p-values.</p>
Study Population: A total of 1406 male and female subjects ≥12 years of age with persistent asthma who were symptomatic on ICS were screened, of which 622 were randomized. Of the 622 subjects, 615 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 250mcg BD
Number of Subjects:	107	103
Planned, N	99	99
Randomised, N	107	103
ITT Population	107	100
Completed, n (%)	66 (62)	81 (81)
Total Number Subjects Withdrawn, N (%)	41 (38)	19 (19)
Withdrawn due to Adverse Events n (%)	0	1 (1)
Withdrawn due to Lack of Efficacy n (%)	35 (33)	14 (14)
Withdrawn for other reasons n (%)	6 (6)	4 (4)
Demographics	Placebo	FP 250mcg BD
N (ITT)	107	100
Females: Males	74:33	62:38
Mean Age, years (SD)	39.1 (16.19)	39.8 (16.70)
White, n (%)	62 (58)	61 (61)
Asian, n (%)	26 (24)	23 (23)
American Indian or Alaska Native, n (%)	0	0
American Indian or Alaska Native and White, n (%)	14 (13)	13 (13)
African American/African Heritage, n (%)	5 (5)	3 (3)
Primary Efficacy Results:		
Statistical Analysis of Change from Baseline in Trough FEV₁ at Week 8 (LOCF) (L)		
	Placebo	FP 250mcg BD
LS Mean	2.215	2.440
LS Mean Change (SE)	-0.065 (0.0395)	0.160 (0.0409)
LS Difference versus Placebo		0.225
95% Confidence Interval		(0.114, 0.337)
p-value		<0.001
Secondary Outcome Variables:		
PM PEF – Weeks 1-8 (L/min)		
	Placebo	FP 250mcg BD
LS Mean	342.8	363.7
LS Mean Change (SE)	-2.8 (3.54)	18.2 (3.69)
LS Difference versus Placebo		21.0
95% Confidence Interval		(10.9, 31.0)
p-value		<0.001
AM PEF – Weeks 1-8 (L/min)		
	Placebo	FP 250mcg BD
LS Mean	329.8	359.5
LS Mean Change (SE)	-4.7 (3.78)	25.1 (3.94)
LS Difference versus Placebo		29.7
95% Confidence Interval		(19.0, 40.5)
p-value		<0.001
Symptom-Free 24-Hour Periods (%)		
	Placebo	FP 250mcg BD
LS Mean Change (SE)	17.1 (2.91)	30.4 (3.02)
LS Difference versus Placebo		13.2
95% Confidence Interval		(5.0, 21.5)
p-value		0.002

Rescue-Free 24-Hour Periods (%)		
	Placebo	FP 250mcg BD
LS Mean Change (SE)	15.6 (3.02)	34.5 (3.15)
LS Difference versus Placebo		18.9
95% Confidence Interval		(10.3, 27.5)
p-value		<0.001
Subjects with Lack of Efficacy as Primary Reason for Withdrawal		
	Placebo	FP 250mcg BD
n (%)	35 (33)	14 (14)
p-value		0.002
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=107	FP 250mcg BD N=100
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	32 (30)	42 (42)
Headache	6 (6)	8 (8)
Nasopharyngitis	8 (7)	7 (7)
Upper respiratory tract infection	3 (3)	6 (6)
Dysphonia	1 (<1)	4 (4)
Oral candidiasis	0	3 (3)
Sinusitis	1 (<1)	3 (3)
Oropharyngeal pain	0	3 (3)
Toothache	0	3 (3)
Cough	1 (<1)	2 (2)
Rhinitis (seasonal)	0	2 (2)
Back pain	0	2 (2)
Myalgia	1 (<1)	2 (2)
Pyrexia	0	2 (2)
Pain in extremity	3 (3)	1 (1)
Rhinitis	3 (3)	0
Hypertension	2 (2)	0
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]		
	Placebo	FP 250mcg BD
	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	0 [0]	0 [0]
Subjects with fatal SAEs, n (%)	0	0

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.