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Study No.: FFA109687
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 Administered Once Daily and Fluticasone Propionate Inhalation Powder 100 mcg Twice Daily compared with Placebo for 8 Weeks in Adolescent and Adult Subjects with Persistent Asthma Symptomatic on Non-Steroidal, Asthma 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 a non-corticosteroid controller or short-acting beta ₂ -agonist bronchodilator alone. Fluticasone propionate was included as a benchmark.
Phase: IIb
Study Period: 19 December 2007 – 2 October 2008
Study Design: Multicenter, Randomized, double-blind, double-dummy, placebo-controlled, parallel-group
Centres: 142 (107 that randomized subjects) in 14 countries (98 centers in North America, 29 centers in Europe, 5 centers in Central and South America and 10 centers in Asia-Pacific).
Indication: Asthma
Treatment: Subjects were randomly assigned to treatment as follows: <ul style="list-style-type: none"> •GW685698X once-daily via a Novel Dry Powder Inhaler (DPI) and placebo twice-daily via DISKUS™/ACCUHALER™ (one inhalation each in the morning and in the evening). •Fluticasone propionate 100 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: 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) FEV ₁
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 430 mL 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 1459 male and female subjects ≥12 years of age with persistent asthma were screened, of which 601 were randomized. Of the 601 subjects, 598 received at least one dose of study medication and comprised the Intent-to-Treat Population. Eligible subjects had 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 an 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). Subjects must have been using a non-corticosteroid controller or short-acting beta ₂ -agonist bronchodilator alone (with no inhaled corticosteroid use for at least 6 weeks) for ≥3 months preceding Visit 1. All subjects must have been able to replace their current short-acting beta ₂ -agonists with albuterol/salbutamol inhalation aerosol at Visit 1 for use as needed for the duration of the study. Subjects must also have had any combination of the daily asthma symptom scores (day-time plus night-time) of ≥1 or albuterol/salbutamol use on at least 4 of the last 7 consecutive days of the run-in period.

	Placebo	FP 100 mcg BD
Number of Subjects:	94	102
Planned, N	99	99
Randomised, N	94	102
Completed, n (%)	76 (81)	84 (82)
Total Number Subjects Withdrawn, N (%)	18 (19)	18 (18)
Withdrawn due to Adverse Events n (%)	0	2 (2)
Withdrawn due to Lack of Efficacy n (%)	14 (15)	11 (11)
Withdrawn for other reasons n (%)	4 (4)	5 (5)
Demographics	Placebo	FP 100 mcg BD
N (ITT)	94	102
Females: Males	47:47	56:46
Mean Age, years (SD)	39.2 (15.82)	39.9 (15.03)
White, n (%)	69 (73)	74 (73)
Asian, n (%)	7 (7)	10 (10)
American Indian or Alaska Native and White, n (%)	8 (9)	8 (8)
African American/African Heritage, n (%)	5 (5)	5 (5)
American Indian /Alaska Native n (%)	5 (5)	5 (5)
Primary Efficacy Results:		
Statistical Analysis of Change from Baseline in Trough FEV₁ at Week 8 (LOCF)		
	Placebo	FP 100 mcg BD
LS Mean	2.515	2.621
LS Mean Change (SE)	0.137 (0.0428)	0.243 (0.0411)
LS Difference		0.106
95% Confidence Interval		(-0.010, 0.223)
p-value		0.074
Secondary Outcome Variable(s):		
PM PEF – Weeks 1-8		
	Placebo	FP 100 mcg BD
LS Mean	368.3	383.2
LS Mean Change (SE)	9.6 (4.21)	24.4 (4.04)
LS Mean Difference		14.9
95% CI		(3.4, 26.3)
p-value		0.011
AM PEF – Weeks 1-8		
LS Mean	361.5	373.6
LS Mean Change (SE)	13.6 (4.27)	25.6 (4.09)
LS Mean Difference		12.1
95% CI		(0.5, 23.7)
p-value		0.041
Symptom-Free 24 Hour Periods		
LS Mean Change (SE)	18.4 (3.21)	33.3 (3.08)
LS Mean Difference		14.9
95% CI		(6.1, 23.6)
p-value		<0.001
Rescue Free 24 Hour Periods		
LS Mean Change (SE)	21.9 (3.32)	35.5 (3.18)
LS Mean Difference		13.7
95% CI		(4.6, 22.7)
p-value		0.003
Subjects with Lack of Efficacy as Primary Reason for Withdrawal		
N (%)	14 (15)	11 (11)
p-value		0.401
Safety Results: 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= 94	FP 100 mcg BD N= 102
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	24 (26)	35 (34)
Headache	10 (11)	12 (12)
Oropharyngeal pain	1 (1)	2 (2)
Nasopharyngitis	1 (1)	2 (2)
Sinusitis	1 (1)	3 (3)
Gastritis	0	2 (2)
Upper respiratory tract infection	0	1 (<1)
Insomnia	1 (1)	1 (<1)
Back pain	0	1 (<1)
Pyrexia	0	1 (<1)
Productive cough	0	1 (<1)
Throat irritation	0	1 (<1)
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	Placebo n (%) [related]	FP 100 mcg BD n (%) [related]
Subjects with non-fatal SAEs, n (%)	0	2 (2) [0]
Gastritis	0	1 (1) [0]
Chest pain ¹	0	1 (1) [0]
Hyperhidrosis ¹	0	1 (1) [0]
Hypertension ¹	0	1 (1) [0]
Subjects with fatal SAEs, n (%)	0	0

1. 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.