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.: B2E106359

Title: Multi-center, randomized, double-blind, placebo-controlled, four-way incomplete block crossover study to examine efficacy, safety, tolerability, pharmacodynamics and pharmacokinetics of single and repeat administration of a novel long-acting beta$_2$-agonist

Rationale: The present study tested the safety, tolerability, pharmacodynamics and pharmacokinetics of a new chemical entity (NCE) (dosed once daily) as single and repeat inhaled doses in female subjects with asthma, compared with salmeterol 50mcg (dosed twice daily) and placebo.

Phase: IIa

Study Period: 19Apr2006 – 23Jan2007

Study Design: Randomized, double-blind, placebo-controlled four-way incomplete block crossover

Centres: Seven sites: two sites in Germany, one site in Russia, one site in Sweden, one site in UK, one site in the Netherlands and one site in New Zealand

Indication: asthma

Treatment: Subjects were randomized to a four-way crossover sequence including: two of the three doses of the NCE, salmeterol 50mcg and placebo.

Objectives: To determine the trough (mean of 23 and 24 hour) FEV_1 after 14 day repeat dose inhaled NCE administered once daily in persistent asthmatic subjects.

Primary Outcome/Efficacy Variable: Mean change from baseline in the mean of the 23 and 24 hour clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 after repeat dosing for 14 days.

Secondary Outcome/Efficacy Variable(s):

- Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 after a single dose (Day 1).
- Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 on Day 7.
- Change from baseline in weighted mean clinic FEV_1 over 0-2 hours, 0-4 hours and 0-24 hours on Day 1 and Day 14.
- Mean change from baseline in AM PEFR from electronic flow meter over Days 2-15.
- Mean change from baseline in PM PEFR from electronic flow meter over Days 1-14.
- Mean change from baseline in AM FEV_1 from electronic flow meter over Days 2-15.
- Mean change from baseline in PM FEV_1 from electronic flow meter over Days 1-14.

Statistical Methods: The study was a four-way incomplete block crossover study, powered (94%) to detect a 200mL difference between any dose of the NCE and placebo in change from baseline in trough FEV_1 derived from the mean of the 23 and 24 hour post-dose assessments on Day 14. Additionally, the study was powered (98%) to detect a 200mL difference in trough FEV_1 between salmeterol and placebo.

The primary analysis was performed using mixed effects analysis of covariance with baseline trough FEV_1, center, sex, age, treatment, period and the mean of the subjects' baseline values as fixed effects and subject as a random coefficient.

A two-sided 5% risk associated with incorrectly rejecting the null hypothesis of no treatment difference (significance level) was considered acceptable for this study. Although there is more than one primary comparison, this study was exploratory in nature and therefore no multiplicity adjustments were performed. The population used for this analysis was the Full Analysis Set, which consisted of all subjects randomized to treatment who received at least one dose of trial medication.

Study Population: Subjects with clinically stable persistent asthma within the 4 weeks preceding the screening visit and with a screening pre-bronchodilator FEV_1 between 60 and 90% (having abstained from bronchodilators for the required period) were eligible for the study. During the screening visit, subjects had to demonstrate the presence of reversible airway disease, defined as an increase in FEV_1 of ≥12.0% over baseline and an absolute change of ≥300mL within 30 minutes following a single 400mcg salbutamol dose. Subjects were required to be using inhaled corticosteroids at a total daily dose of 200 to 500mcg of fluticasone propionate or equivalent inhaled corticosteroid.

Data regarding the NCE will be provided in the even the NCE is marketed. Data regarding salmeterol and placebo is provided at this time.

Number of Subjects:	
Planned, N	60
Randomised, N	54
Completed, n (%)	49 (91)
Total Number Subjects Withdrawn, N (%)	5 (9)
Withdrawn due to Adverse Events n (%)	2 (4)
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for other reasons n (%)	3 (6)
Demographics	
N (Full Analysis Set)	54
Females	54
Mean Age, years (SD)	44.8 (14.9)
White, n (%)	48 (92)
Primary Efficacy Results:	
Change from Baseline and Treatment Difference in Trough Clinic FEV_1 (L)	
Day 14	Salmetereol – Placebo
Least square mean difference	0.143
95% Confidence Interval	0.074, 0.212
p-value	<0.001
Secondary Outcome Variable(s):	
Change from Baseline and Treatment Difference in Trough Clinic FEV_1 (L)	
Day 1	Salmeterol – Placebo
Least square mean difference	0.204
95% Confidence Interval	0.146, 0.263
Change from Baseline and Treatment Difference in Trough Clinic FEV_1 (L)	
Day 7	Salmeterol – Placebo
Least square mean difference	0.107
95% Confidence Interval	0.038, 0.177
Weighted Mean Change from Baseline in Clinic FEV_1 (L)	
Day 1	
0-2 hours	Salmeterol – Placebo
Least square mean difference	0.196
95% Confidence Interval	0.143, 0.249
0-4 hours	Salmeterol – Placebo
Least square mean difference	0.223
95% Confidence Interval	0.167, 0.279
0-24 hours	Salmeterol – Placebo
Least square mean difference	0.219
95% Confidence Interval	0.165, 0.273
Day 14	
0-2 hours	Salmeterol – Placebo
Least square mean difference	0.228
95% Confidence Interval	0.161, 0.295
0-4 hours	Salmeterol – Placebo
Least square mean difference	0.232
95% Confidence Interval	0.166, 0.297
0-24 hours	Salmeterol – Placebo
Least square mean difference	0.210
95% Confidence Interval	0.149, 0.272

Change from Baseline in AM PEFR (L/min) from Electronic Flow Meter		
Least square mean difference	16.56	
95% Confidence Interval	6.99, 26.13	
Change from Baseline in PM PEFR (L/min) from Electronic Flow Meter		
Least square mean difference	20.90	
95% Confidence Interval	11.86, 29.94	
Change from Baseline in AM FEV_1 (L) from Electronic Flow Meter		
Least square mean difference	0.069	
95% Confidence Interval	0.019, 0.120	
Change from Baseline in PM FEV_1 (L) from Electronic Flow Meter		
Least square mean difference	0.095	
95% Confidence Interval	0.040, 0.150	
Safety Results: Adverse events were elicited from the investigators, using non-leading questions throughout the study and at the follow-up visit. Data regarding the NCE will be provided in the even the NCE is marketed. Data regarding salmeterol and placebo is provided at this time.		
	Salmeterol	Placebo
Most Frequent Adverse Events – During Treatment	n (%)	n (%)
Subjects with any AE(s), n(%)	23 (44)	23 (44)
Headache	15 (29)	11 (21)
Nasopharyngitis	8 (15)	4 (8)
Nausea	0	3 (6)
Toothache	3 (6)	0
Tremor	2 (4)	0
Migraine	0	2 (4)
Cough	2 (4)	0
Fatigue	0	2 (4)
Palpitiations	2 (4)	1 (2)
Serious Adverse Events – During Treatment n (%) [n considered by the investigator to be related to study medication]		
	Salmeterol	Placebo
Subjects with non-fatal SAEs, n (%)	0	0
Subjects with fatal SAEs, n (%)	0	0
PK Results: The PK of salmeterol following single and repeated inhaled administration (50mcg) was characterized by rapid absorption into the plasma (median t_{max} 0.1 to 0.2 hour post-dose). The t_{max} of salmeterol was similar following single and repeat dosing (Day 14). C_{max} of salmeterol was similar following single and 7 days repeat dosing, but was greater following 14 days repeat dosing (1.3-fold).		
Publications: No Publication		

Date Updated: 11-Sep-2007