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.: SCO104925
Title: Evaluation of Novel Endpoints in Subjects with Chronic Obstructive Pulmonary Disease (COPD) in a Randomized, Double-Blind, Placebo-Controlled Study of Treatment with Fluticasone Propionate/Salmeterol 500/50mcg combination and its individual components, Fluticasone Propionate 500mcg and Salmeterol 50mcg
Rationale: There is a need to identify new and more sensitive endpoints that will effectively demonstrate therapeutic benefit and discriminate new therapies from the current standard drugs. Data from this study should help to inform choice of new endpoints for future clinical development programs.
Phase: IV
Study Period: 07Mar2006 - 13Feb2007
Study Design: Multi-centre, randomized, double-blind, placebo-controlled, parallel-group study
Centres: 11 centres; 4 centres in the Russian Federation, 4 centres in the United States, two centres in Chile, and one centre in Estonia.
Indication: COPD
Treatment: Fluticasone propionate 500mcg with salmeterol xinafoate 50 mcg (FSC 500/50), fluticasone propionate 500 mcg (FP 500), salmeterol xinafoate 50 mcg (SAL 50), and placebo
Objectives: To determine if selected novel endpoints of peripheral airways resistance and reactance (measured by IOS), airway wall dimensions (measured by CT), and systemic inflammation (assessed by serum biomarkers) are sensitive to treatment with inhaled corticosteroids (ICS) and/or long acting beta agonists (LABAs) over a treatment period of 12 weeks in subjects with COPD. For the purposes of the data in this study, the term "ICS" is an indicator variable that encompasses treatment with corticosteroids (FP 500 or FSC 500/50), "LABA" is an indicator variable that encompasses treatment with a long acting beta-agonist (SAL 50 or FSC 500/50), and "ICS*LABA" encompasses the interaction of corticosteroid and LABA (FSC 500/50). The study was not designed to be a test of efficacy for FP 500, SAL 50, or FSC 500/50.
Primary Outcome/Efficacy Variable: Pre-dose resistance difference between 5Hz and 15Hz (R5 – R15) as measured by IOS
Secondary Outcome/Efficacy Variable(s): Pre- and 2-hour post-dose low-frequency reactance area (AX); 2-hour post-dose R5 – R15; Post-albuterol Computed Tomography (CT) parameters of area of airway wall (Aaw) and area of airway lumen (Ai).
Statistical Methods: The primary endpoint of interest was change from baseline at Week 12 in pre-dose frequency dependence of resistance (R5 – R15). The primary comparison was a test of significance in the ANCOVA model for each mechanistic component (ICS, LABA, ICS/LABA interaction), adjusting for baseline value and centre. Means, standard deviations, median, and quartiles were provided for all continuous efficacy summaries. As this study was primarily hypothesis generating, results of analysis models included only effect sizes, standard errors and 95% confidence intervals for mechanistic component effects, with the exception of the primary analysis parameter, which additionally included a p-value for mechanistic effect sizes relative to placebo. Safety data was summarized and/or listed by treatment group for the ITT population.
Study Population: Males or females of non-childbearing potential ≥ 40 years of age were eligible to participate if they had an established clinical history of COPD, evidence of bronchitis as a component of the COPD disease, and had a current or prior history of at least 10 pack-years of cigarette smoking. Subjects had a measured post-albuterol FEV1/FVC ≤ 70% at Visit 1 (Screening) and a measured post-albuterol FEV1 ≥ 30% and ≤ 70% of predicted normal.

Number of Subjects	**Placebo**	**FP500**	**SAL50**	**FSC500/50**
Planned, N	30	30	30	30
Randomised, N	42	42	38	39

Completed, n (%)	38 (90%)	35 (83%)	35 (92%)	35 (90%)
Total Number Subjects Withdrawn, N (%)	4 (10%)	7 (17%)	3 (8%)	4 (10%)
Withdrawn due to Adverse Events n (%)	1 (2%)	3 (7%)	0	0
Withdrawn for other reasons n (%)	3 (8%)	4 (10%)	3 (8%)	4 (10%)
Demographics	**Placebo**	**FP500**	**SAL50**	**FSC500/50**
N (ITT)	42	42	38	39
Females: Males	10:32	13:29	8:30	7:32
Mean Age, years (SD)	65.2 (8.63)	64.2 (11.23)	64.0 (9.31)	63.6 (7.75)
White Race, n (%)	41 (98%)	42 (100%)	38 (100%)	39 (100%)

Primary Efficacy Results:

This study was designed to determine if selected novel endpoints were sensitive to treatment with inhaled corticosteroids (ICS) and/or long acting beta agonists (LABAs) in patients with COPD. For the purposes of the data in this study, the term "ICS" is an indicator variable that encompasses treatment with corticosteroids (FP 500 or FSC 500/50), "LABA" is an indicator variable that encompasses treatment with a long acting beta-agonist (SAL 50 or FSC 500/50), and "ICS*LA BA"en compasses the interaction of corticosteroid and LABA (FSC 500/50). The study was not designed to be a test of efficacy for FP 500, SAL 50, or FSC 500/50

Pre-Dose R5 –R 15 (kPa/L/s)	**Base Model**	**ICS**	**LABA**	**ICS*LABA Interaction**
LS Mean at Week 12 (SE)	0.001 (0.015)	0.015 (0.014)	-0.024 (0.015)	0.006 (0.015)
95% CI	-0.028,0.030	-0.014,0.043	-0.053,0.006	-0.023,0.035
p-value	0.932	0.314	0.111	0.666

Secondary Outcome Variable(s):

This study was designed to determine if selected novel endpoints were sensitive to treatment with inhaled corticosteroids (ICS) and/or long acting beta agonists (LABAs) in patients with COPD. For the purposes of the data in this study, the term "ICS" is an indicator variable that encompasses treatment with corticosteroids (FP 500 or FSC 500/50), "LABA" is an indicator variable that encompasses treatment with a long acting beta-agonist (SAL 50 or FSC 500/50), and "ICS*LA BA"en compasses the interaction of corticosteroid and LABA (FSC 500/50). The study was not designed to be a test of efficacy for FP 500, SAL 50, or FSC 500/50

2 Hour Post-Dose R5 –R 15 (kPa/L/s)	**Base Model**	**ICS**	**LABA**	**ICS*LABA Interaction**
LS Mean at Week 12 (SE)	0.015 (0.013)	0.009 (0.014)	-0.067 (0.015)	0.000 (0.015)
95% CI	-0.011,0.042	-0.019,0.038	-0.096,-0.037	-0.029,0.030
Pre-Dose AX (kPa/L)	**Base Model**	**ICS**	**LABA**	**ICS*LABA Interaction**
LS Mean at Week 12 (SE)	-0.188 (0.254)	0.246 (0.251)	-0.189 (0.258)	0.049 (0.254)
95% CI	-0.692,0.316	-0.253,0.745	-0.701,0.323	-0.454,0.553
Post-Dose AX (kPa/L)	**Base Model**	**ICS**	**LABA**	**ICS*LABA Interaction**
LS Mean at Week 12 (SE)	-0.139 (0.231)	0.235 (0.248)	-0.765 (0.258)	-0.028 (0.254)
95% CI	-0.597, 0.319	-0.258, 0.728	-1.28, -0.254	-0.533, 0.476

Area of Airway Wall (mm^2), Post-Salbutamol (Right Apical Segmental Bronchus)	**Base Model**	**ICS**	**LABA**	**ICS*LABA Interaction**
LS Mean at Week 12 (SE)	-1.88 (1.28)	0.381 (1.39)	-1.62 (1.39)	-0.348 (1.40)
95% CI	-4.43,0.662	-2.38,3.139	-4.39,1.142	-3.12,2.426
Area of Airway Wall (mm^2), Post-Salbutamol (All Airways)	**Base Model**	**ICS**	**LABA**	**ICS*LABA Interaction**
LS Mean at Week 12 (SE)	0.720 (0.590)	-0.109 (0.627)	-0.200 (0.626)	0.101 (0.638)
95% CI	-0.450,1.891	-1.35,1.134	-1.44,1.043	-1.16,1.366
Area of Airway Lumen (mm^2), Post-Salbutamol (Right Apical Segmental Bronchus)	**Base Model**	**ICS**	**LABA**	**ICS*LABA Interaction**
LS Mean at Week 12 (SE)	-0.895 (0.810)	1.785 (0.877)	-0.384 (0.879)	-0.590 (0.878)
95% CI	-2.50,0.713	0.044,3.526	-2.13,1.363	-2.33,1.154
Area of Airway Lumen (mm^2), Post-Salbutamol (All Airways)	**Base Model**	**ICS**	**LABA**	**ICS*LABA Interaction**
LS Mean at Week 12 (SE)	0.649 (0.384)	0.162 (0.408)	-0.181 (0.407)	-0.524 (0.406)
95% CI	-0.112,1.410	-0.647,0.971	-0.988,0.626	-1.33,0.282

Safety Results (ITT Population): On-th erapy'A Es and SAEs were defined as those with onset on or after the start date of study medication but not later than the last date of study medication.

	Placebo N=42	**FP500 N=42**	**SAL50 N=38**	**FSC500/50 N=39**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	10 (24%)	15 (36%)	16 (42%)	6 (15%)
Nasopharyngitis	1 (2%)	4 (10%)	4 (11%)	3 (8%)
Acute bronchitis	1 (2%)	0	0	2 (5%)
Pneumonia	0	1 (2%)	1 (3%)	1 (3%)
Candidiasis	0	2 (5%)	0	0
Headache	0	1 (2%)	1 (3%)	0
Muscle spasms	0	0	2 (5%)	0
Pharyngitis	0	0	2 (5%)	0
Rib fracture	0	1 (2%)	1 (3%)	0
Tracheitis	1 (2%)	0	1 (3%)	0
Urinary tract infection	0	0	2 (5%)	0

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication

	Placebo N=42	**FP500 N=42**	**SAL50 N=38**	**FSC500/50 N=39**
Subjects with non-fatal SAEs, n (%)	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Lung neoplasm	1 (2%) [0]	0	0	0
Pneumonia	0	1 (2%) [0]	0	0
Subjects with fatal SAEs, n (%)	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Sudden cardiac death	0	1 (2%) [0]	0	0

Conclusion: This study was not designed to be a test of efficacy for FP 500, SAL 50, or FSC 500/50. The results of this exploratory study add to our understanding of the novel assessments

of IOS, CT, and systemic serum biomarkers in subjects with COPD. Data from these studies will serve as the basis of hypothesis generation, study design, and decision making for future clinical development work. In the placebo group, 10 subjects reported adverse events; in the FP500 group, 15 subjects reported adverse events; in the SAL50 group, 16 subjects reported adverse events; in the FSC500/50 group, 6 subjects reported adverse events. One serious adverse event was reported in the placebo group, and one fatal serious adverse event was reported in the FP500 group.
Publications: No publication

Date updated: 3-Sep-2008