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| Study No.: SCO100540 |
| Title: A multi-centre, randomised, double-blind, parallel group study to investigate the efficacy and safety of the Salmeterol/fluticasone propionate combination at a strength of 50/500µg BD, compared with placebo via Accuhaler™, added to usual chronic obstructive pulmonary disease (COPD) therapy, in subjects with COPD for 24 weeks |
| Rationale: In order to obtain the approval of Seretide Accuhaler™ 50/500 µg in COPD treatment indication from the Chinese State Food and Drug Administration (SFDA), this study was carried out to evaluate the efficacy and safety of Salmeterol/Fluticasone Propionate combination 50/500µg BD added to usual COPD therapy for 24 weeks. |
| Phase: III |
| Study Period: Sept 2004 – Nov 2005 |
| Study Design: A randomised, double blind, parallel group, multi-centre study with a 2-week run-in period, 24-week treatment period and a 2-week follow-up. The subjects who were enrolled into the study and could satisfy the entry criteria for the treatment period were randomised in a 2:1 ratio to receive either Salmeterol/fluticasone propionate combination 50/500µg BD or Placebo BD for 24 weeks treatment. |
| Centres: 12 centres in China |
| Indication: COPD |
| Treatment: After a two week run-in period, subjects who satisfied the double blind treatment period entry criteria, were randomised, according to a 2:1 ratio, to receive either Salmeterol / fluticasone propionate combination product 50/500µg BD or matched Placebo BD for 24 weeks treatment. <i>Ventolin</i> was permitted to be used as rescue medication on a required basis and sputum reduction medication could also be taken in the treatment period at unchanged doses. |
| Objectives: To compare the efficacy and safety of the Salmeterol /fluticasone propionate combination 50/500µg BD with placebo, added to usual therapy, over 24 weeks of COPD treatment |
| Primary Outcome/Efficacy Variable: Pre-bronchodilator FEV ₁ |
| Secondary Outcome/Efficacy Variable(s): (1) St. George's Respiratory Questionnaire (SGRQ) (2) Use of relief bronchodilator and night time awakenings from Daily Record Cards (3) Post-bronchodilator FEV ₁ |
| Other efficacy Variable(s): COPD exacerbation (CE) |
| Statistical Methods: Pre & Post-bronchodilator FEV₁: Was analyzed mainly using the repeated measurement model. ANCOVA was used to analyze the treatment effect after adjusting for age, sex, smoking status, baseline pre-bronchodilator FEV ₁ and study center. The interaction between the treatment and co-variables was also explored using the repeated measurement model. Pre-bronchodilator FEV ₁ at different visits and the difference between baseline and current pre-bronchodilator FEV ₁ were analyzed. The final pre-bronchodilator FEV ₁ after treatment period was analyzed using the Last Observation Carried Forward (LOCF) method. ANCOVA was used to adjust for co-variables as used in the repeated measurement model. St. George's Respiratory Questionnaire (SGRQ): The SGRQ score was analyzed using the repeated ANCOVA model. The co-variables included age, sex, smoking status, score at baseline visit and study center. Total score and score of three sub-scales were analyzed. The final score after the treatment was also analyzed using ANCOVA. LOCF was used for data of subjects who were withdrawn. Night-time awakening: Median number of night-time awakenings and median percentage of nights with no awakenings were calculated using available data. Each was compared between treatment groups analysed using Van-Elteren extension to the Wilcoxon Rank Sum test. Use of relief bronchodilator: Median use of relief bronchodilator for each time interval was calculated for each subject using available data and was compared between treatment groups analyzed using Van-Elteren extension to the Wilcoxon Rank Sum test. COPD exacerbations: The exacerbation rate was calculated as the number of exacerbations experienced by the subject during the treatment period. It was analyzed using maximum likelihood based analysis, assuming the negative binomial distribution, with time on treatment as an offset variable. The model included adjustment for the effects of age, sex, smoking status, baseline FEV ₁ and study center. The exacerbations included those that needed additional treatment (e.g. systemic corticosteroids and antibiotics) and hospitalization. |

Safety analysis

Adverse Events: The proportion of subjects experiencing adverse events was summarized, together with severity and the relationship with the investigational products

Study Population: Subjects had to satisfy the following to be eligible for inclusion in the study: Male and female subjects (aged 40–79 years) with a diagnosis of COPD as per GOLD criteria; poor reversibility of airflow obstruction which was defined as an increase of less than 10% of the normal predicted FEV₁ value, 30 minutes to 2 hours after inhalation of 400µg salbutamol via MDI and spacer; FEV₁ / FVC ratio (Post-bronchodilator) < 70%.

Subjects were excluded if: they had a diagnosis of asthma and other respiratory disease such as lung cancer, sarcoidosis, active tuberculosis, primary or severe subsequent lung fibrosis and bronchiectasis, and serious, uncontrolled other system disorders; required long-term oxygen therapy (LTOT); had received inhaled corticosteroids at a dose of >1000ug/day (BDP or BUD) or >500ug/day (FP) or had received systemic corticosteroids in the last 4 weeks before entry to the run-in period. After the run-in, at randomization, subjects also had to satisfy the following criteria criteria, Post-bronchodilator FEV₁ in the range of 25% - 70% of predicted normal and FEV₁/FVC ratio < 70%. Subjects who had received systemic corticosteroids, had changes in COPD medication, received antibiotic therapy or had been hospitalized for COPD exacerbation were not randomized.

| | Seretide 50/500 µg | Placebo |
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| Number of Subjects | | |
| Planned, N | 280 | 140 |
| Randomised, N | 297 | 148 |
| Completed, n (%) | 261 (87.9) | 132 (89.1) |
| Total Number Subjects Withdrawn, N (%) | 36 (12.1) | 16 (10.8) |
| Withdrawn due to Adverse Events n (%) | 11 (3.7) | 4 (2.7) |
| Withdrawn due to Lack of Efficacy n (%) | 2 (0.7) | 3 (2.0) |
| Withdrawn for other reasons n (%) | 23 (7.7) | 9 (6.1) |
| Demographics | Seretide 50/500 µg | Placebo |
| N (ITT) | 297 | 148 |
| Females: Males | 28:269 | 20:128 |
| Mean Age, years (SD) | 66.04 (8.16) | 66.60 (7.66) |
| Chinese, n (%) | 100 | 100 |
| Primary Efficacy Results - ITT | | |
| FEV₁ (L)_ (pre-bronchodilator) | Seretide 50/500 µg | Placebo |
| Mean Baseline (SD) | 1.063 (0.377) | 1.030 (0.366) |
| Adjusted mean change from baseline at week 24 (SE) | 0.176 (0.026) | -0.004 (0.037) |
| 95% Confidence Interval (CI) | 0.125-0.227 | -0.076-0.069 |
| P value | P < 0.0001 | |
| Secondary Outcome Variables | | |
| SGRQ (total score) - ITT | Seretide 50/500 µg | Placebo |
| Mean Baseline (SD) | 44.772 (18.063) | 44.458 (17.592) |
| Adjusted mean change from baseline at week 24 (SE) | -9.381 (0.866) | -3.641 (1.217) |
| 95% C I | -11.083, -7.679 | -6.035, -1.248 |
| Number of night time awakening (every 4 weeks) - completers | Seretide 50/500 µg | Placebo |
| Quartile at baseline – week 4 | 0-1 | 0-3 |
| Quartile at week 20~24 | 0-0 | 0-2 |
| Percentage of days without night-time awakening (every 4 ws)- completers | Seretide 50/500 µg | Placebo |
| Quartile at baseline – week 4 | 96-100 | 89-100 |
| Quartile at week 20~24 | 100-100 | 96-100 |
| Use of Relief Bronchodilator (Day & night use times | Seretide 50/500 µg | Placebo |

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| within 4 weeks) - completers | | |
| Median at baseline – week 4 | 40 | 60 |
| Median at week 20~24 | 30 | 63 |
| Post –bronchodilator FEV1 - ITT | Seretide 50/500 µg | Placebo |
| Mean Baseline (SD) | 1.218 (0.379) | 1.178 (0.384) |
| Adjusted mean change from baseline at week 24 (SE) | 0.094 (0.015) | 0.029 (0.021) |
| 95% CI | 0.065, 0.123 | -0.012, 0.070 |
| COPD Exacerbation-ITT | Seretide 50/500 µg /Placebo | 95% CI |
| Estimated Annual Occurrence Rate and Ratio of COPD exacerbation based on long-linear model | | |
| CE needing to be treated with antibiotics | 0.60 | 0.41, 0.48 |
| CE needing to be treated with systemic corticosteroids | 0.33 | 0.17, 0.64 |
| CE needing to be hospitalized | 0.77 | 0.31, 1.94 |
| Total CE | 0.60 | 0.42, 0.84 |
| Safety Results: | | |
| An “treatment emergent” adverse event (AE) or serious adverse event (SAE) was defined as any event that occurred during the treatment or post treatment follow up phase. | | |
| Most Frequent Adverse Events – treatment emergent | Seretide 50/500 µg N=297 | Placebo N=148 |
| Subjects with any AE(s), n(%) | 158 (53.20) | 78 (52.70) |
| Nasopharyngitis | 53 (17.85) | 28 (18.92) |
| Upper Respiratory Tract Infection | 32 (10.77) | 14 (9.46) |
| Chronic Obstructive Airway Disease exacerbation | 12 (4.04) | 8 (5.41) |
| Pneumonia | | |
| Pharyngolaryngeal Pain | 12 (4.04) | 0 (0.00) |
| Hoarseness | 10 (3.37) | 5 (3.38) |
| Headache | 7 (2.36) | 0 (0.00) |
| Pyrexia | 6 (2.02) | 2 (1.35) |
| Cough | 4 (1.35) | 1 (0.68) |
| Palpitations | 4 (1.35) | 2 (1.35) |
| Mouth ulceration | 0 (0.00) | 4 (2.70) |
| Toothache | 0 (0.00) | 4 (2.70) |
| Urinary Tract Infection | 2 (0.76) | 3 (2.03) |
| Dyspnoea | 2 (0.76) | 3 (2.03) |
| Blood Glucose Increased | 2 (0.76) | 3 (2.03) |
| Insomnia | 1 (0.34) | 3 (2.03) |
| | 0 (0.00) | 3 (2.03) |
| Serious Adverse Events – Treatment emergent | Seretide 50/500 µg N=297 | Placebo N=148 |
| Subjects with non-fatal SAEs, n (%) [n considered by the investigator to be related to study medication] | 22 (7.41) [3] | 10 (6.76) [0] |
| Chronic Obstructive Airway Disease exacerbation | 11 (3.94) [1] | 8 (5.40) [0] |
| Pneumonia | 3 (1.07) [1] | 0 (0.00) [0] |
| Pneumothorax | 0 (0.00) [0] | 1 (0.68) [0] |
| Lung infection | 1 (0.34) [0] | 0 (0.00) [0] |
| Cerebral haemorrhage | 1 (0.34) [0] | 0 (0.00) [0] |
| Pulmonary tuberculosis | 1 (0.34) [1] | 0 (0.00) [0] |
| Acute Myocardial infarction | 2 (0.67) [0] | 0 (0.00) [0] |
| Pancreatitis acute | 1 (0.34) [0] | 0 (0.00) [0] |
| Acute monocytic Leukaemia | 1 (0.34) [0] | 0 (0.00) [0] |

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| Nasopharyngitis | 1 (0.34) [0] | 0 (0.00) [0] |
| Haemoptysis | 0 (0.00) [0] | 1 (0.68) [0] |
| Cor pulmonale chronic | 0 (0.00) [0] | 1 (0.68) [0] |
| | Seretide 50/500 µg N=297 | Placebo N=148 |
| Subjects with fatal SAEs, n (%) | 2 (0.7) ,[0] | 0 (0.00) ,[0] |
| Abdominal Cancer | 1 (0.35) ,[0] | 0 (0.00) ,[0] |
| Chronic Obstructive Airway Disease exacerbation/renal failure | 1 (0.35) ,[0] | 0 (0.00) ,[0] |
| Conclusion: | | |
| <p>Compared with placebo, Salmeterol/fluticasone propionate via Accuhaler™ 50/500 added to usual therapy significantly increased COPD patients' pre and post bronchodilator FEV₁, reduced number of night time awakening and use of bronchodilator, improved quality of life, and decreased the risk of COPD exacerbation. One hundred and fifty eight (53%) subjects taking Salmeterol/fluticasone propionate and 78 (53%) subjects taking placebo experienced AEs. The most frequently reported AEs in both groups were nasopharyngitis and upper respiratory tract infection. Twenty-four (8%) subjects receiving Salmeterol/fluticasone propionate and 10 subjects (7%) on placebo reported SAEs; COPD exacerbation was the most frequently reported SAE in both groups. Two fatalities were reported in the Salmeterol/fluticasone propionate group. They were not considered to be related to study medication.</p> | | |
| Publications: | | |
| No Publication | | |

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