Mundipharma Research Ltd.
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CLINICAL STUDY REPORT

An open, randomised, parallel group, multicentre study to compare the efficacy and safety of FlutiForm™ pMDI vs Seretide® pMDI in adult subjects with mild to moderate-severe persistent, reversible asthma.

Name of Test Drug:	Fluticasone propionate / Formoterol fumarate
Indication Studied:	Asthma bronchiale
Protocol Identification:	FLT3501
EudraCT number:	2006-005926-22
Drug Development Phase:	III
Study Initiation Date (first subject first visit):	23 April 2007
Study Completion Date (last subject last visit):	13 March 2008
Co-ordinating Investigator:	Prof. Anna Bodzenta-Lukaszyk Clinic of Allergology and Internal Diseases Medical University Bialystok, Poland
Sponsor's Responsible Medical Officer:	Dr Heikki Mansikka Mundipharma Research Ltd. UK
Author:	Karin Feasey-Truger, PhD Kendle GmbH, Germany
Date of the Report:	Final, 11 December 2008

The study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

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SYNOPSIS

Name of Sponsor/Company: **Mundipharma Research Ltd.**	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
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Title of the study:
An open, randomised, parallel group, multicentre study to compare the efficacy and safety of FlutiForm™ pMDI vs Seretide® pMDI in adult subjects with mild to moderate-severe persistent, reversible asthma.

Investigators:
25 investigators took part in this study.

Study Centres:
There were 25 active centres, 8 centres in Romania, 6 centres in Poland, 5 centres in Hungary, 3 centres in Germany and 3 centres in the UK.

Publication (reference): No publications currently reference this study.

Study period (years): 1 First subject enrolled: 23 April 2007 Last subject completed: 13 March 2008	**Phase of development:** III

Primary objective:

The primary objective of this study was to show comparable efficacy of FlutiForm™ with Seretide® based on mean FEV_1 values.

Secondary objectives:

Secondary objectives of the study were to compare discontinuations due to lack of efficacy, time to onset of action, peak expiratory flow rate (PEFR) and other lung function parameters, amount of rescue medication use, asthma symptom scores, sleep disturbance due to asthma, amount of daily oral or parenteral corticosteroid dose, exacerbations (requiring oral/parenteral steroid use, medical intervention), subject assessment of study medication, Asthma Quality of Life Questionnaire and spontaneously reported adverse events.

Methodology:

This was an open, randomised, active-controlled, parallel group, multicentre, phase III study to show non-inferiority of FlutiForm™ (hereafter referred to as FlutiForm) compared to Seretide® (hereafter referred to as Seretide) in controlling mild to moderate-severe persistent, reversible asthma in adult subjects. The study consisted of a 4- to 10- day screening phase and a 12-week treatment phase. Subjects attended a screening visit (Visit 1) to evaluate their eligibility for participation in the treatment phase. On completion of the screening phase (Visit 2), eligible subjects were randomised in a 1:1 ratio to 12 weeks of treatment with either FlutiForm or Seretide. The starting dose of study medication was based on the patient's asthma history and prior asthma medication. Subjects returned to the investigator's site at 2 weeks, 6 weeks and 12 weeks following the commencement of treatment for lung function assessments and safety checks. At each of these visits the patient completed lung function tests before their morning dose of medication and 5, 10, 30, 60, 90 and 120 minutes following their dose of study medication. Throughout the treatment phase, subjects completed an electronic

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diary recording daily peak flow measures in the morning and evening, use of rescue medication, use of study medication, asthma symptom scores and sleep disturbance due to asthma.
Subjects starting with the low dose of study medication (2 puffs of 50/5 µg FlutiForm every 12 hours or 2 puffs 50/25 µg Seretide every 12 hours) could be switched to the high dose (2 puffs of 125/5 µg FlutiForm every 12 hours or 2 puffs 125/25 Seretide every 12 hours) if their asthma was not controlled. Throughout the study subjects were allowed to take salbutamol (2 puffs, 100 µg per puff), on up to four occasions per day as rescue medication. FlutiForm and Seretide were inhaled using an AeroChamber® Plus spacer device (GlaxoSmithKline [GSK]).
Safety was evaluated on the basis of adverse events (AEs), clinical laboratory tests, vital signs, physical examination and electrocardiograms (ECGs).
On completion or discontinuation of the study, subjects were followed up by telephone 14 days later for reporting of ongoing AEs and any new AEs that may have occurred.

Number of subjects:
Planned: 200
Enrolled: 228
Randomised: 202

	FlutiForm	Seretide	Total
Safety set:	101	101	202
Full analysis set:	101	101	202
Per protocol set:	96	95	191

- Diagnosis and main criteria for inclusion:
- Male or female subjects aged 18 years or older (females less than one year post-menopausal had to have a negative serum or urine pregnancy test recorded at the screening visit prior to the first dose of study medication, were non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study. A highly effective method of birth control was defined as that which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (intrauterine device, hormonal), sexual abstinence or vasectomised partner).
- Known history of mild to moderate-severe, persistent, reversible asthma for ≥ 6 months prior to the screening visit.
- Demonstrated an FEV_1 of ≥ 40% to ≤ 85% for predicted normal values (Crapo et al, 1981) during the screening phase following appropriate withholding of asthma medications (if applicable).
  - No β_2-agonist use on day of screening.
  - No use of inhaled combination asthma therapy on day of screening.
  - Inhaled corticosteroids were allowed on day of screening.

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- Documented reversibility of ≥ 15% in FEV_1 in the screening phase.
- Able to demonstrate satisfactory technique in the use of the pMDI
- Willing and able to enter information in the electronic diary and attend all study visits.
- Willing and able to substitute study medication for their pre study prescribed asthma medication for the duration of the study.
- Written informed consent obtained.

Test product: FlutiForm™ (fluticasone/formoterol)
Dose: 2 puffs of 50/5 µg or 125/5 µg fluticasone/ formoterol, every 12 hours
Batch numbers: 50/5 µg, PN3183; 125/5 µg, PN3184
Mode of administration: pressurised MDI (pMDI) used with an AeroChamber® Plus (GSK) spacer

Duration of treatment: 12 weeks

Reference therapy: pMDI Seretide® (fluticasone/salmeterol)
Dose: 2 puffs of 50/25 µg or 125/25 µg fluticasone/ salmeterol, every 12 hours
Batch numbers: 50/25 µg, PN3186, PN3251, PN3259; 125/25 µg, PN3187, PN3252, PN3260
Mode of administration: pMDI used with an AeroChamber® Plus (GSK) spacer

Duration of treatment: 12 weeks

Criteria for evaluation:

Efficacy evaluation (primary):

- Pre-dose FEV_1 at Day 84.

Efficacy evaluation (secondary):

- Change in pre-dose FEV_1.
- Post-dose FEV_1.
- Discontinuations due to lack of efficacy.
- Time to onset of action of study medication.
- Rescue medication use.
- PEFR measurements.
- Other lung function parameters: forced vital capacity (FVC), maximum expiratory flow at 25, 50 and 75% of volume to exhale (MEF_{25}, MEF_{50}, MEF_{75}).
- Asthma symptom scores.
- Sleep disturbance scores.
- Asthma exacerbations.
- Compliance with study medication.
- Subject's assessment of study medication.
- Asthma Quality of Life Questionnaire (AQLQ).

Safety:

- Adverse events.
- Laboratory parameters for haematology, biochemistry and urinalysis.
- Vital signs: blood pressure, heart rate, respiration rate, oral temperature.
- 12-lead ECG results.

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Statistical methods:

The primary efficacy endpoint was the pre-dose FEV_1 value at Day 84 (Visit 5).

Non-inferiority of FlutiForm to Seretide was tested on the per protocol set (PPS) using an analysis of covariance (ANCOVA) with treatment and dose group (high/low) as factors and the pre-dose FEV_1 values at Day 0 (Visit 2) as a linear covariate, and centre as a random effect. The test was performed using a two-sided level of significance of α=0.05. Additionally, the 95% confidence interval (CI) of the mean treatment difference was calculated. Post-dose FEV_1 values, peak flow measurements and other lung function parameters were analysed analogously using ANCOVA; time to onset of action was analysed using the multiple failures time model; study rescue medication use was analysed using a Wilcoxon rank sum test; asthma symptoms and sleep disturbance scores were analysed using a linear model; subject assessment of asthma medication was analysed using a proportional odds model; the difference in percentages and 95% CI was calculated for discontinuations due to lack of efficacy. P-values were also provided for the analyses of AQLQ (ANCOVA) and for the analysis of asthma exacerbations (Fisher's exact test). All other endpoints were summarised using descriptive statistics.

The pre-dose FEV_1 value at Day 84, change from Day 0 to Day 84 of pre-dose and of 120 minutes post-dose FEV_1 value, discontinuation due to lack of efficacy and time to onset of action were tested in a confirmatory manner. All hypothesis tests were two-sided and conducted at the 5% error level.

Safety parameters, i.e. adverse events, laboratory values, vital signs and ECG data were analysed using descriptive statistics.

Sample size calculation:

The sample size was focused on the difference in the 12 weeks FEV_1 values analysed within a linear model with the baseline FEV_1 value as a covariate. It was assumed that the observed treatment difference would not exceed 0.02 and the standard deviation would be 0.5. The non-inferiority bound was fixed to 0.2, corresponding to an effect size of 0.4, which could be interpreted as 'mild' to 'moderate'. On a two-sided level of significance of α = 0.05 and with a power of 80% (β = 20%) 113 patients per treatment group were required. Assuming a correlation of the 12 weeks FEV_1 values and the baseline FEV_1 values of approximately 0.5, the sample size would be reduced to 85 patients per treatment group. The comparison was focused on the per protocol population. Assuming that approximately 10% of the randomised patients would not be part of the per protocol set, 200 patients needed to be randomised to this study.

Interim analysis:

No interim analysis was performed.

Summary

Efficacy results:

The mean pre-dose FEV_1 value at Day 84 was approximately 2.4 L in both treatment groups of the per protocol set. Non-inferiority of FlutiForm to Seretide was demonstrated as the lower limit of the 95% CI for the treatment difference was -0.161 L, and thus exceeded the non-inferiority acceptance limit of -0.2 L. Similar results were obtained in the supportive analysis of the full analysis set.

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A sensitivity analysis of the primary efficacy endpoint was performed for the modified per protocol set, which excluded an additional nine subjects who discontinued the study prematurely, but who were not designated as protocol deviators, and re-included one subject who was erroneously excluded from the PPS. The sensitivity analysis also demonstrated non-inferiority of FlutiForm to Seretide. Thus, the results of the primary efficacy endpoint analysis were not influenced by the inclusion of nine subjects who discontinued the study prematurely and the erroneous exclusion of one subject.

Approximately 75% of subjects in each treatment group started with the high dose of study medication. Only eight subjects required a change in dose strength from low to high during the study (five in the FlutiForm group and three in the Seretide group).

Analysis of the secondary efficacy endpoint, change in pre-dose FEV_1 from Day 0 to Day 84, showed a clear increase in pre-dose FEV_1 from Day 0 to Day 84 in both treatment groups (FlutiForm: +196 ml, Seretide: +257 ml). Non-inferiority of FlutiForm to Seretide was demonstrated as the lower limit of the 95% CI for the treatment difference was -0.161 L, and thus exceeded the non-inferiority acceptance limit of -0.2 L. The results for the full analysis set were comparable.

A supportive ANCOVA of the change in pre-dose FEV_1 from Day 0 to Day 84, which included the dose strength by treatment interaction, also demonstrated non-inferiority of FlutiForm to Seretide in both analysis sets.

The mean FEV_1 values obtained 120 minutes post-dose on Day 84 were clearly greater than the pre-dose FEV_1 values on Day 0 in both treatment groups (FlutiForm: +464 ml, Seretide: +477 ml, per protocol set). Non-inferiority of FlutiForm to Seretide was demonstrated confirmatorily for the per protocol set and supportively for the full analysis set.

In the per protocol set, one subject in the FlutiForm group and two subjects in the Seretide group discontinued the treatment phase due to lack of efficacy. The difference in the percentages was -1.1% (95%CI: -4.6, 2.5). Non-inferiority of FlutiForm to Seretide was demonstrated with respect to discontinuations due to lack of efficacy as the upper limit of the CI was less than 10%.

Superiority of FlutiForm over Seretide was demonstrated with regard to the onset of action of study medication. The probability of the event onset of action occurring was higher in the FlutiForm group than in the Seretide group at each post-dose time point on Days 0, 14, 42 and 84. In both treatment groups, onset of action of study medication was most robustly demonstrated on Day 0, reflecting the fact that the subjects were least well controlled on Day 0, and thus most responsive to study medication.

The percentage of study days on which salbutamol rescue medication was used was slightly higher in the FlutiForm group than in the Seretide group, but the difference was not statistically significant. The number of uses of rescue medication was low and comparable in the two treatment groups.

The mean asthma symptom and sleep disturbance scores decreased, i.e. improved, over the course of the study in both treatment groups. The overall asthma symptom and sleep disturbance scores were low (mean values <1) in both treatment groups, with no statistically significant differences between the

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treatments.

The peak flow rates obtained during the PFTs performed 120 minutes post-dose on Days 0, 14, 42 and 84 were substantially greater than the pre-dose peak flow rates on Day 0 in both treatment groups. .No statistically significant difference was observed between the two treatment groups with regard to the pre-dose and 120 minutes post-dose peak flow rates at Day 84.

Mean morning and evening peak flow rates, averaged from the measurements recorded in the subject diary during the 14 days prior to the study visits on Days 14, 42 and 84, were comparable in the two treatment groups. No relevant changes in the mean morning and evening peak flow rates were observed from Day 14 to Day 84 in either treatment group.

Mean FVC, MEF_{25}, MEF_{50} and MEF_{75} values obtained 120 minutes post-dose on Day 84 were clearly greater than the corresponding pre-dose values on Day 0 in both treatment groups. No statistically significant differences between the treatment groups were observed for any of these lung function parameters.

In total, 23 of the 202 subjects (11.4%) experienced mild or moderate asthma exacerbations. Severe asthma exacerbations were experienced by three subjects in the FlutiForm group (3.0%) and by one subject in the Seretide group (1.0%). The differences between the treatment groups were not statistically significant.

The odds ratio for the overall patient assessment of study medication for FlutiForm compared to Seretide was 0.495 (95% CI: 0.289, 0.848), and thus in favour of Seretide. Nevertheless, the study medication was assessed as very good or good by 84% of subjects in the FlutiForm group and by 91% of subjects in the Seretide group.

A comparable increase, i.e. improvement, in the AQLQ overall scores was observed from Day 0 to Day 84 in the two treatment groups. An ANCOVA of the AQLQ overall scores obtained at Day 84 revealed no statistically significant difference between the two treatment groups.

Safety results:
Approximately 75% of subjects in each treatment group started with the high dose of study medication. Only eight subjects required a change in dose strength from low to high during the study.

Altogether, 48 of the 202 subjects (23.8%) of the safety set experienced at least one AE after the start of study treatment.

The overall rate of AEs was comparable in the two treatment groups (23.8% in each group). There were no noteworthy differences between the treatment groups regarding the profile of AEs. In both treatment groups, the most common AEs were classed as ‘infections and infestations’. At the preferred term level, nasopharyngitis was most common in each treatment group, together with asthma (exacerbation) in the FlutiForm group.

The vast majority of AEs were of mild or moderate intensity. Two subjects in the FlutiForm group

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experienced severe AEs: asthma (exacerbation) in one subject and haemorrhagic stroke and cardiac arrest in one subject.

The frequency of treatment-related AEs was extremely low, reported for only one subject in each treatment group. In the FlutiForm group, mild palpitations was considered definitely related to treatment with study medication and in the Seretide group, mild dyspnoea was considered unlikely related to treatment with study medication. This subject was withdrawn from the study. Neither of the treatment-related AEs was serious.

There was one death during the study.

SAEs were reported for one subject in each treatment group. In the FlutiForm group, the SAEs haemorrhagic stroke and cardiac arrest were fatal. In the Seretide group, one subject was hospitalised due to pneumococcal pneumonia. All three SAEs were assessed as not related to study medication by both the investigator and the sponsor.

One subject in the FlutiForm group was withdrawn due to the SAEs haemorrhagic stroke and cardiac arrest. In the Seretide group, one subject was withdrawn due to dyspnoea.

Analyses of haematology, biochemistry and urinalysis parameters did not reveal any noteworthy changes over the course of the study in either treatment group. Systemic effects of LABAs such as elevation of serum glucose or reduction in serum potassium were not observed. Very few AEs associated with laboratory parameters were reported.

There were no noteworthy findings regarding vital signs or ECGs in either treatment group.

Conclusions:
In conclusion, non-inferiority of FlutiForm to Seretide was demonstrated with regard to pre-dose and post-dose FEV_1 and discontinuations due to lack of efficacy. Superiority of FlutiForm over Seretide could be shown for time to onset of action of study medication. Analysis of the other efficacy parameters such as other pulmonary function tests, patient reported outcomes, rescue medication use, asthma exacerbations and AQLQ yielded comparable results for the FlutiForm and Seretide treatment groups. Treatment with FlutiForm was safe and well tolerated.

Date of report: 11 December 2008