SYNOPSIS

Name of Sponsor/Company: **Mundipharma Research Ltd.**	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: FlutiForm™	Volume:	
Name of Active Ingredient: Fluticasone / Formoterol	Page:	
Title of the study: An open, randomised, parallel group, multicentre study to compare the efficacy and safety of FlutiForm™ pMDI vs Seretide® pMDI in paediatric subjects with mild to moderate persistent, reversible asthma.		
Investigators: 22 investigators took part in this study.		
Study Centres: There were 22 active centres, 6 centres in Poland, 5 centres in the Czech Republic, 5 centres in Hungary, 4 centres in Romania, 1 centre in France and 1 centre in Germany.		
Publication (reference): No publications currently reference this study.		
Study period (years): 1 First subject enrolled in core treatment phase: 30 April 2007 Last subject completed core treatment phase: 18 December 2007	**Phase of development:** III	
Primary objective: The primary objective of this study was to show comparable efficacy of FlutiForm™ with Seretide® based on mean forced expiratory volume in the 1st second (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 rates (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, asthma exacerbations (requiring oral/parenteral steroid use, medical intervention), subject assessment of study medication and spontaneously reported adverse events. Another secondary objective was to monitor the long term safety of FlutiForm™ during the extension phase based on the assessment of growth and plasma cortisol levels.		
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 persistent, reversible asthma in paediatric subjects. The study consisted of a 4- to 10- day screening phase and a 12-week core treatment phase. On completion of the screening phase (Visit 2), eligible subjects entered the core treatment phase. Subjects were randomised in a 1:1 ratio to 12 weeks of treatment with either FlutiForm, administered as 2 puffs of 50/5 µg fluticasone/formoterol every 12 hours or Seretide, administered as 2 puffs of 50/25 µg fluticasone/salmeterol every 12 hours. Throughout the treatment phase, subjects kept an electronic diary recording diurnal peak expiratory flow rate (PEFR) measurements, use of study medication, use of rescue medication, asthma symptom scores and sleep disturbance due to asthma.		

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Subjects returned to the investigator's site at 2, 6 and 12 weeks following the commencement of treatment (Visits 3, 4 and 5 respectively) for lung function assessments, review of the subject diaries, and safety checks. During the treatment phase, subjects were allowed to take salbutamol (1 puff, 100 µg per puff), on up to four occasions per day as rescue medication. All study medications (test/reference and rescue medication) 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, and electrocardiogram (ECG) findings.

Subjects who completed the core treatment phase per protocol specifications were eligible to enter a 24-week extension phase, during which all subjects received FlutiForm at the same dose as that given in the core treatment phase, i.e. 2 puffs of 50/5 µg fluticasone/formoterol every 12 hours. The purpose of the extension phase was to obtain long term safety data on the use FlutiForm in children. The results of the extension phase are provided in a separate report.

Number of subjects:

Planned: 200
Enrolled: 235
Randomised: 211

	FlutiForm	Seretide	Total
Safety set:	106	105	211
Full analysis set:	106	105	211
Per protocol set:	102	99	201

Diagnosis and main criteria for inclusion:

- Male or female subjects between 4-12 years of age. Female subjects had to be pre-menarche to be eligible.
- Known history of mild to moderate persistent asthma for ≥ 6 months prior to the Screening Visit.
- Demonstrated an FEV_1 of ≥ 60% to ≤ 100% of predicted normal values (Zapletal et al., 1977) 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.
- Documented reversibility of ≥ 15% in FEV_1 in the screening phase.
- Able to demonstrate satisfactory technique in the use of the pressurised MDI (pMDI) and spacer device.
- Willing and able to enter information in the electronic diary (parental help was acceptable) 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.

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- Written informed consent obtained from the parent(s)/ legal representative, and where possible, informed assent obtained from the subject.

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

Duration of treatment (core treatment phase): 12 weeks

Reference therapy: pMDI Seretide® (fluticasone/salmeterol)
Dose: 2 puffs of 50/25 µg fluticasone/salmeterol, every 12 hours
Batch number: PN3186, PN3251
Mode of administration: pMDI used with an AeroChamber® Plus (GSK) spacer

Duration of treatment (core treatment phase): 12 weeks

Criteria for evaluation:

Efficacy evaluation (primary):

- FEV_1 pre-dose

Efficacy evaluation (secondary):

- FEV_1 post-dose
- Discontinuations due to lack of efficacy
- Time to onset of action of study medication
- Rescue medication use
- PEFR
- 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 (or subject's parent(s)/legal representative) assessment of study medication

Safety:

- Adverse events (learned through spontaneous reports and observations).
- Laboratory parameters (haematology, biochemistry and urinalysis).
- Vital signs (blood pressure, heart rate, respiration rate, oral temperature, weight).
- 12-lead ECGs.

Statistical methods:

The primary efficacy endpoint was the difference in the pre-dose FEV_1 value at Day 84 (Visit 5) and the pre-dose FEV_1 value at Day 0 (Visit 2).

Non-inferiority of FlutiForm to Seretide was tested on the per protocol set (PPS) using an analysis of covariance (ANCOVA) with treatment and age group as factors, the pre-dose FEV_1 values at Day 0 as

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a linear covariate, and centre as a random effect. The primary efficacy endpoint and the secondary efficacy endpoints FEV_1 (120 minutes post-dose), discontinuation due to lack of efficacy and time to onset of action were tested in a confirmatory manner using a gate keeping strategy. All hypothesis tests were two-sided: the primary efficacy comparison was conducted at the 4.65% error level, all other hypothesis tests were conducted at the 5% error level.

Post-dose FEV_1 values, peak flow measurements and other lung function parameters were analysed using ANCOVA; time to onset of action was analysed using the multiple failures time model of Wei, Lin and Weissfeld; 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 were calculated for discontinuations due to lack of efficacy. All other efficacy endpoints were summarised using descriptive statistics.

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

Sample size calculation:
Based on the assumption that the adjustment of FEV_1 values would eliminate the variability of the subjects, it was assumed that the standard deviation would be 0.2. Testing the hypothesis that FlutiForm is not inferior to Seretide, a non-inferiority bound of -0.1 in the difference of adjusted FEV_1 values was assumed. On a two-sided level of significance of $\alpha = 0.05$ and with a power of 90% (β = 10%), 86 subjects per treatment group were required. Assuming that approximately 10% of the randomised subjects would not be part of the per protocol set, 200 subjects needed to be randomised to this study.

Interim analysis:
An interim analysis of the first 40 randomised subjects was conducted by the sponsor to ensure the assumptions of the sample size calculation were met. Due to this interim analysis, hypothesis testing of the primary efficacy endpoint was conducted using an alpha level of 0.0465. The interim analysis showed that the original sample size assumptions were met.

Summary

Efficacy results:
Pre-dose FEV_1 increased from Day 0 to Day 84 in both treatment groups (FlutiForm: +182 ml, Seretide: +212 ml, per protocol set). Non-inferiority of FlutiForm to Seretide was demonstrated as the lower limit of the 95.35% CI for the treatment difference was -0.093 L, and thus exceeded the non-inferiority acceptance limit of -0.1 L. Similar results were obtained in the supportive analysis of the full analysis set.

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: +308 ml, Seretide: +325 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.

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None of the subjects discontinued the treatment phase due to lack of efficacy. Non-inferiority of FlutiForm to Seretide with respect to discontinuations due to lack of efficacy was demonstrated for the per protocol set.

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. Analysis of the time to onset of action did not show superiority of FlutiForm over Seretide.

The percentage of study days on which salbutamol rescue medication was used and the number of uses were very low in both treatment groups. No statistically significant difference between the treatment groups was observed.

The overall asthma symptom scores were low and comparable in both treatment groups. The overall sleep disturbance score was slightly higher in the Seretide group than in the FlutiForm group, but the difference was not statistically significant.

The peak flow rates obtained during the lung function tests performed 120 minutes post-dose on Days 0, 14, 42 and 84 were substantially greater than the pre-dose rates on Day 0 in both treatment groups.

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.

Only four subjects in the FlutiForm group (3.8%) and three subjects in the Seretide group (2.9%) experienced mild or moderate asthma exacerbations. There were no severe asthma exacerbations.

Over 95% of subjects in each treatment group assessed the study medication as very good or good.

Safety results:
Altogether, 59 of the 211 subjects (28.0%) of the safety set experienced at least one AE after the start of study treatment.

The overall rate of AEs was low and comparable in the two treatment groups (FlutiForm: 29.2%, Seretide: 26.7%). There were no clinically relevant 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, pharyngitis, bronchitis and nasopharyngitis were most frequent.

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AEs of mild intensity were more frequent than those of moderate intensity. None of the subjects experienced severe AEs.

The frequency of treatment-related AEs was low, reported for only five of the 211 subjects (2.4%) of the safety set. Treatment-related AEs were reported for three subjects in the FlutiForm group: these were one case of possibly related mild dizziness, one case of unlikely related moderate bronchitis acute and one case of unlikely related mild herpes simplex. In the Seretide group, moderate stomatitis and mild pharyngitis were considered unlikely related in one subject each.

There were no deaths during the study.

SAEs with onset after the start of treatment were reported for two subjects in the FlutiForm group (appendicitis in each case) and in one subject in the Seretide group (pneumonia). All of the SAEs were considered not related to study medication by both the investigator and sponsor, and each of the subjects recovered.

None of the subjects were withdrawn due to AEs.

Analyses of haematology, biochemistry and urinalysis parameters did not reveal any clinically relevant 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. No AEs associated with laboratory parameters were reported.

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

Conclusions:

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. Analysis of the other efficacy parameters such as time to onset of action, other pulmonary function tests, patient reported outcomes, rescue medication use and asthma exacerbations yielded comparable results for the FlutiForm and Seretide treatment groups. Treatment with FlutiForm was safe and well tolerated.

Date of report: 26 November 2008