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 Fluticasone pMDI plus Formoterol DPI in adolescent and adult subjects with mild to moderate-severe persistent, reversible asthma.

Investigators:
32 investigators took part in this study.

Study Centres:
There were 30 active centres, 9 centres in Poland, 8 centres in Romania, 7 centres in Germany, 4 centres in Hungary, and 2 centres in the Netherlands.

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

Study period (years): 1 First subject enrolled: 25 September 2007 Last subject completed: 01 April 2008	**Phase of development:** III

Primary objective:
The primary objective of this study was to show non-inferiority in the efficacy of FlutiForm™ compared with the individual components Flixotide® (fluticasone) and Foradil® (formoterol) given together, based on mean forced expiratory volume in the 1st second (FEV_1) values.

Secondary objectives:
Secondary objectives of the study were to compare discontinuation due to lack of efficacy, peak expiratory flow rates (PEFR) and other lung function parameters, amount of rescue medication use, asthma symptom scores, sleep disturbance due to asthma, asthma quality of life questionnaire (AQLQ(S) ≥12 years), exacerbations (requiring oral/parenteral steroid use, medical intervention), subject assessment of study medication, and spontaneously reported adverse events.

Methodology:
This was an open, randomised, active-controlled, parallel group, multicentre, phase III study to show non-inferiority in the efficacy of FlutiForm™ (hereafter referred to as FlutiForm) compared with the individual components, Flixotide® (fluticasone, hereafter referred to as Flixotide) plus Foradil® (formoterol, hereafter referred to as Foradil) in controlling mild to moderate-severe persistent, reversible asthma in adolescent and adult subjects. The study consisted of a 4- to 10-day screening phase and a 12-week 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 Flixotide plus Foradil. Depending on their asthma history and prior asthma medication, subjects started treatment with a high or a low dose of study medication/reference medication. The low dose corresponded to FlutiForm, administered as 2 puffs of 50/5 µg fluticasone/formoterol every 12 hours, or Flixotide plus Foradil, administered as 1 puff of 12 µg formoterol followed by 2 puffs of 50 µg fluticasone every 12 hours. The high dose corresponded to FlutiForm, administered as 2 puffs of 125/5 µg fluticasone/formoterol every 12 hours, or Flixotide plus Foradil, administered as 1 puff of 12 µg formoterol followed by 2 puffs of 125 µg fluticasone

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every 12 hours. Subjects starting with the low dose of study medication could be switched to the high dose if their asthma was not controlled. 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. At each of these visits, the subjects completed lung function tests 30-60 minutes after their morning dose of study medication. A pre-morning dose lung function test was also performed at Visit 2.

Throughout the treatment phase, subjects kept a diary recording diurnal peak expiratory flow rate (PEFR) measurements, use of study medication, rescue medication use, asthma symptom scores and sleep disturbance due to asthma.

Subjects were allowed to take salbutamol (2 puffs, 100 µg per puff), on up to four occasions per day as rescue medication throughout the study. FlutiForm and Flixotide were inhaled using an AeroChamber® Plus spacer device (GlaxoSmithKline [GSK]) whereas Foradil was inhaled without a spacer.

Safety was evaluated on the basis of adverse events (AEs), clinical laboratory tests (including serum cortisol), vital signs, physical examinations and electrocardiograms (ECGs). In a subset of subjects, 24-hour urine collections were undertaken for the assessment of urinary free cortisol at the start and end of the treatment phase. 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: 227

Randomised: 210 (169 adults, 41 adolescents)

	FlutiForm	Flixotide+Foradil	Total
Safety set:	105	105	210
Full analysis set:	105	105	210
Per protocol set:	99	103	202

Diagnosis and main criteria for inclusion:

- Male or female subjects aged 12 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, had to be non-lactating, and had to be willing to use adequate and highly effective methods of contraception throughout the study if they were sexually active.
- Known history of mild to moderate-severe persistent asthma for ≥ 6 months prior to the screening visit.
- Demonstrated an FEV_1 of ≥ 40% to ≤ 85% for predicted normal values (Quanjer et al., 1993 [3]) during the screening phase following appropriate withholding of asthma medications (if applicable).
  - No β_2-agonist use on day of screening.

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- 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 study medications.
- Willing and able to enter information in the 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 fluticasone/formoterol, every 12 hours (low dose),
2 puffs of 125/5 µg fluticasone/formoterol, every 12 hours (high dose)
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 (treatment phase): 12 weeks

Reference therapy: Flixotide+Foradil (fluticasone/formoterol)
Dose: 2 puffs of 50 µg Flixotide plus 1 puff 12 µg Foradil, every 12 hours (low dose),
2 puffs of 125 µg Flixotide plus 1 puff 12 µg Foradil, every 12 hours (high dose)
Batch numbers: Flixotide 50 µg, PN3241; Flixotide 125 µg, PN3242; Foradil 12 µg, PN3245, PN3291
Mode of administration:
Flixotide: pMDI used with an AeroChamber® Plus (GSK) spacer
Foradil: dry powder inhaler (DPI) without spacer

Duration of treatment (treatment phase): 12 weeks

Criteria for evaluation:
Efficacy evaluation (primary):

- Post-dose FEV_1

Efficacy evaluation (secondary):

- Discontinuations due to lack of efficacy.
- Rescue medication use.
- PEFR measurements.
- Other lung function parameters: FVC and MEF_{25}, MEF_{50} and MEF_{75}.
- Asthma symptom scores.
- Sleep disturbance scores.
- Asthma exacerbations.
- Compliance with study medication.
- Use of oral or parenteral corticosteroids.
- Subject's assessment of study medication.
- AQLQ(S) ≥ 12 years.

Safety:

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- Adverse events.
- Laboratory parameters (haematology, biochemistry and urinalysis).
- Serum cortisol.
- 24 hour urinary free cortisol (selected subjects only).
- Vital signs (blood pressure, heart rate, respiration rate, oral temperature, weight).
- 12-lead ECGs.

Statistical methods:

The primary efficacy endpoint was the post-dose FEV_1 value at Day 84 (Visit 5). Non-inferiority of FlutiForm to Flixotide+Foradil was tested on the PPS using an analysis of covariance (ANCOVA) with treatment and dose group (high/low) as factors, the pre-dose FEV_1 value at Day 0 (Visit 2) as 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; 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(S) ≥ 12 years (ANCOVA) and for the analysis of asthma exacerbations (Fisher's exact test), All other endpoints were summarised using descriptive statistics . All hypothesis tests were two-sided and conducted at the 5% error level. Safety parameters, i.e. adverse events, laboratory values (including serum cortisol and 24 hour urinary free cortisol), 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 with a linear model with the baseline FEV_1 value as a covariate. The treatment difference was assumed to be 0 and the SD was assumed to be 0.5. The non-inferiority bound was fixed to 0.2. On a two-sided level of significance of $\alpha = 0.05$, a power of 85% ($\beta = 15\%$) and assuming a correlation of the 12 weeks FEV_1 values and the baseline FEV_1 value of approximately 0.5, 86 subjects per treatment group were required. The comparison was focused on the PPS. Assuming that approximately 10% to 15% of the randomised subjects would not be part of the PPS, 200 subjects needed to be randomised in this study.

Interim analysis:

No interim analysis was conducted.

Summary

Efficacy results:

The mean post-dose FEV_1 value at Day 84 was approximately 2.6 L in both treatment groups of the per protocol set. Non-inferiority of FlutiForm to Flixotide+Foradil was demonstrated as the lower limit of the 95% CI for the treatment difference was -0.148 L, and thus exceeded the non-inferiority

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acceptance limit of -0.2 L. Similar results were obtained in the supportive analysis of the full analysis set.

A sensitivity analysis of the primary efficacy endpoint was performed for the modified per protocol set, which additionally excluded six subjects who discontinued the study prematurely, but who were not designated as protocol deviators prior to unblinding of the study statisticians. The sensitivity analysis also demonstrated non-inferiority of FlutiForm to Flixotide+Foradil as the lower limit of the 95% CI for the treatment difference was -0.113 L. Thus, the results of the primary efficacy endpoint analysis were not influenced by the inclusion of six subjects who discontinued the study prematurely.

Slightly more than 70% of subjects in each treatment group started with the high dose of study medication. Only one subject in each treatment group required a change in dose strength from low to high during the study.

Analysis of the secondary efficacy endpoint, change in FEV_1 from pre-dose on Day 0 to 30-60 minutes post-dose on Day 84, showed that the mean FEV_1 values obtained 30-60 minutes post-dose on Day 84 were clearly greater than the pre-dose FEV_1 values on Day 0 in both treatment groups (FlutiForm: +401 ml, Flixotide+Foradil: +435 ml, per protocol set). Non-inferiority of FlutiForm to Flixotide+Foradil was demonstrated confirmatorily for the per protocol set and supportively for the full analysis set.

In the per protocol set, one subject in the Flixotide+Foradil group discontinued the treatment phase due to lack of efficacy. The difference in the percentages was -1.0% (95%CI: -2.9, 0.9). Formally, non-inferiority of FlutiForm to Flixotide+Foradil was demonstrated with respect to discontinuations due to lack of efficacy, as the upper limit of the CI was less than 10%.

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

The peak flow rates obtained during the PFTs performed 30-60 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. The post-dose peak flow rates remained stable over the course of the study. No statistically significant difference was observed between the two treatment groups with regard to the 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 30-60 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

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function parameters.

The mean asthma symptom scores decreased, i.e. improved, over the course of the study in both treatment groups. With regard to the mean sleep disturbance scores, the baseline scores were already extremely low in both treatment groups, so that notable decreases were not to be expected. The overall asthma symptom and sleep disturbance scores were low (mean values <1) in both treatment groups, with no statistically significant differences between the treatments.

In the full analysis set, five of the 210 subjects (2.4%) experienced mild or moderate asthma exacerbations. Severe asthma exacerbation was experienced by four subjects in the FlutiForm group (3.8%) and by three subjects in the Flixotide+Foradil group (2.9%). The differences between the treatment groups were not statistically significant.

A total of seven subjects (3.3%) received oral or parenteral corticosteroids during the study. For six of these subjects this was for treatment of severe exacerbations.

The odds ratio for the overall patient assessment of study medication for FlutiForm compared to Flixotide+Foradil was 1.250 (95% CI: 0.738, 2.118), indicating that there was no difference between the treatments. The study medication was assessed as very good or good by 87% of subjects in the FlutiForm group and by 92% of subjects in the Flixotide+Foradil group.

A comparable increase, i.e. improvement, in the AQLQ(S) ≥12 years overall scores was observed from Day 0 to Day 84 in the two treatment groups. An ANCOVA of the AQLQ(S) ≥12 years overall scores obtained at Day 84 revealed no statistically significant difference between the two treatment groups.

Safety results:

Slightly more than 70% of subjects in each treatment group started with the high dose of study medication. Only one subject in each treatment group required a change in dose strength from low to high during the study.

Altogether, 69 of the 210 subjects (32.9%) in 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 (FlutiForm: 34.3%, Flixotide+Foradil: 31.4%). 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, the most common AEs were nasopharyngitis, bronchitis and asthma in the FlutiForm group, and nasopharyngitis, asthma and dysphonia in the Flixotide+Foradil group.

The vast majority of AEs reported for subjects in each treatment group were of mild or moderate intensity. Few subjects experienced severe AEs (FlutiForm: 2.9%, Flixotide+Foradil: 3.8%).

The incidence of treatment-related AEs was low, being reported for only five subjects in the FlutiForm

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group (4.8%) and for six subjects in the Flixotide+Foradil group (5.7%). Dysphonia was the most common treatment-related AE, reported for three subjects in the Flixotide+Foradil group and for one subject in the FlutiForm group.

There were no deaths during this study.

SAEs were reported for one subject in the FlutiForm group (carbon monoxide poisoning), and in three subjects in the Flixotide+Foradil group (upper limb fracture, peripheral ischaemia, and respiratory tract infection). The case of peripheral ischaemia was considered unlikely related to treatment with study medication by both the investigator and the sponsor. This event was reported as a suspected unexpected serious adverse reaction (SUSAR). The other SAEs were considered not related to study medication by both the investigator and the sponsor. All of the subjects recovered.

One subject in the FlutiForm group was withdrawn due to an AE (asthma exacerbation).

Analyses of haematology, biochemistry and urinalysis parameters did not reveal any noteworthy changes over the course of the study in either treatment group. Increased ALT and AST were documented as AEs in one subject in the FlutiForm group. There were no other AEs concerning laboratory parameters.

Systemic effects of LABAs such as elevation of serum glucose or reduction in serum potassium were not observed.

Analyses of serum and urine free cortisol showed no difference in hypothalamic pituitary adrenal (HPA)-axis suppression between treatment groups.

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

Conclusions:

In conclusion, FlutiForm was shown to be non-inferior to its individual components, Flixotide plus Foradil, with regard to post-dose FEV_1, change in pre-dose to post-dose FEV_1, and discontinuations due to lack of efficacy. 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 Flixotide+Foradil treatment groups. Treatment with FlutiForm was safe and well tolerated.

Date of report: 11 December 2008