SYNOPSIS

Name of Sponsor/Company: **Mundipharma Research Limited**	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
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Title of the study:

A double blind, double dummy, randomised, multicentre, 4 arm parallel group study to assess the efficacy and safety of FlutiForm® pMDI 250/10 µg (2 puffs bid) vs Fluticasone pMDI 250 µg (2 puffs bid) plus Formoterol pMDI 12 µg (2 puffs bid) administered concurrently in adult subjects with severe persistent, reversible asthma.

Investigators:

90 investigators took part in this study.

Study Centres:

There were 90 active centres**,** 11 centres in Bulgaria, 8 centres in the Czech Republic, 15 centres in Hungary, 11 centres in India, 5 centres in Israel, 3 centres in Latvia, 11 centres in Poland, 9 centres in Romania, 5 centres in Russia, and 12 centres in Ukraine.

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

Study period (years): 1	**Phase of development:** III
First subject enrolled: 27 August 2008 Last subject completed study: 15 September 2009	

Primary objectives:

The primary objective of this study was:

- To show non-inferiority in the efficacy of FlutiForm® (hereafter referred to as FlutiForm) pressurised metered dose inhaler (pMDI) 250/10 µg (2 puffs twice daily [bid]) vs Flixotide® pMDI 250 µg (2 puffs bid) (hereafter referred to as Flixotide) plus Foradil® pMDI 12 µg (2 puffs bid) (hereafter referred to as Foradil) administered concurrently, based on the mean change in the pre-morning dose value of forced expiratory volume in the first second (FEV_1) from baseline (end of run-in period) to the end of the 8 week treatment period.

The co-primary objective of this study was:

- To show non-inferiority in the efficacy of FlutiForm pMDI 250/10 µg (2 puffs bid) vs Flixotide pMDI 250 µg (2 puffs bid) plus Foradil pMDI 12 µg (2 puffs bid) administered concurrently, based on the mean change from the pre-morning dose FEV_1 value at baseline (end of run-in period) to the 2 hour post-morning dose FEV_1 value at the end of the 8-week treatment period.

Secondary objectives:

The secondary objectives of this study were:

- To show superiority in the efficacy of FlutiForm pMDI 250/10 µg (2 puffs bid) vs Flixotide pMDI 250 µg (2 puffs bid) alone by means of 12-hour FEV_1 area under the curve ([AUC], in a subset of 47 subjects per treatment group).
- To show superiority of FlutiForm pMDI 250/10 µg (2 puffs bid) vs Flixotide pMDI 250 µg (2 puffs bid) alone in mean change of the pre-morning dose FEV_1 value from baseline (end of run-in period) to the end of the 8-week treatment period.
- To show superiority of FlutiForm pMDI 250/10 µg (2 puffs bid) vs Flixotide pMDI 250 µg

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(2 puffs bid) alone in mean change from the pre-morning dose FEV_1 value at baseline (end of run-in period) to the 2 hour post-morning dose FEV_1 value at the end of the 8-week treatment period.

- To show superiority in the efficacy of FlutiForm pMDI 250/10 µg (2 puffs bid) vs FlutiForm pMDI 50/5 µg (2 puffs bid) in mean change of the pre-morning dose FEV_1 value from baseline (end of run-in period) to the end of the 8-week treatment period.

Additional efficacy assessments included discontinuations due to lack of efficacy and subject-centred outcome assessments such as Asthma Quality of Life Questionnaire (AQLQ), subject's assessment of study medication, compliance with study medication, amount of rescue medication use, asthma symptom scores, sleep disturbance scores and asthma exacerbations. Peak expiratory flow rates (PEFR) and other lung function parameters were also assessed.
Safety assessments included incidence and type of spontaneously reported adverse events ([AEs]; including paradoxical bronchospasm), vital signs, laboratory tests (including serum glucose and serum potassium), and 12-lead electrocardiograms (ECGs).

Methodology:
This was a double-blind, double-dummy, 4-arm, parallel-group, multicentre phase III study to show non-inferiority of FlutiForm vs Flixotide plus Foradil administered concurrently in adult subjects with severe persistent, reversible asthma (FEV_1 of ≥ 40% to ≤ 80% for predicted normal values). The study consisted of a screening phase of up to 5 days, a 2-week run-in phase, and an 8-week treatment period.
Subjects were randomised to either FlutiForm pMDI 250/10 µg (2 puffs bid; hereafter named FlutiForm high dose) or FlutiForm pMDI 50/5 µg (2 puffs bid; hereafter named FlutiForm low dose) or Flixotide pMDI 250 µg (2 puffs bid) plus Foradil pMDI 12 µg (2 puffs bid; hereafter named **Error! Reference source not found.**) or Flixotide pMDI 250 µg (2 puffs bid) in a 1:1:1:1 ratio. The study design intended equal allocation of all 4 treatments within each of the moderate (FEV_1 of > 60 to ≤ 80% for predicted normal values) and severe (FEV_1 ≥ 40% to ≤ 60% for predicted normal values) strata. However, due to an error with the interactive voice response system (IVRS) in the original study, the intended treatment distribution of equal allocation to 1 of 4 treatments in each of the moderate and severe asthma strata was not achieved. Instead, subjects in the moderate stratum received 1 of 3 treatments, and all but 3 subjects in the severe stratum received the 4th treatment (Flixotide). The original study was consequently stopped and restarted after correction of the randomisation error. The whole sample size was recruited again to ensure that the study was statistically sound.
Subjects attended a screening visit (Visit 1) to evaluate their eligibility for participation in the study. Potential subjects had to comply with the inclusion/exclusion criteria, have an FEV_1 of ≥ 40% to ≤ 80% of predicted normal values, and show ≥ 14.95% reversibility in FEV_1 after salbutamol inhalation (4 puffs, 100 µg per puff). If FEV_1 reversibility was not demonstrated, it could be re-assessed within another 15 minutes. If reversibility was still not demonstrated, the test could be repeated once more at the start of the run-in phase (Visit 2). During the 2-week run-in phase, all subjects took Flixotide pMDI 125 µg (2 puffs bid) and salbutamol 100 µg (2 puffs on up to 4 occasions per day) was used as rescue

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medication. Subjects kept an electronic diary to record diurnal PEFR and FEV_1 measurements, rescue medication use, use of study medication, asthma symptom scores and sleep disturbance scores. The run-in phase could be extended to a maximum of 28 days if a subject failed to meet the entry criteria after the initial run-in phase of 14 +/-3 days.

On completion of the run-in phase (Visit 3), subjects were re-evaluated and eligible subjects randomised in a 1:1:1:1 ratio to 8 weeks of treatment with either FlutiForm high dose or FlutiForm low dose or Flixotide + Foradil or Flixotide alone. Throughout the treatment period, subjects kept an electronic diary to record diurnal PEFR and FEV_1 measurements, rescue medication use, use of study medication, asthma symptom scores, and sleep disturbance scores. Subjects returned to the investigator's centre at 2, 4, 6 and 8 weeks following the commencement of treatment (Visits 4, 5, 6, and 7) for lung function assessments, review of the subject diaries and safety assessments. At each visit the subjects completed a lung function test prior to their morning dose and 2 hours (+/- 15 minutes) after their morning dose of study medication.

Throughout the study, subjects were allowed to take salbutamol (2 puffs, 100 µg per puff), on up to 4 occasions per day as rescue medication. The test and reference study medications were inhaled using an AeroChamber® Plus spacer device (GlaxoSmithKline [GSK]). Salbutamol rescue medication was inhaled without a spacer.

The dose level of study medication remained the same during the treatment phase. If the subject's asthma was not controlled with study medication and use of salbutamol rescue medication the subject was to be withdrawn from the study. The assessment of asthma control was based on investigator review of the subject's electronic diary data and asthma exacerbations.

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.

The primary efficacy parameter was pre- and post-morning dose FEV_1 recorded at the study visits. Secondary efficacy parameters included FEV_1 12-hour AUC (AUC_{0-12}, in a subset of 47 subjects per treatment group), discontinuation due to lack of efficacy, peak flow measurements, daily FEV_1 measurements (pre-morning and pre-evening dose), forced vital capacity (FVC), forced expiratory flow at 25%, 50% and 75% of the volume to be exhaled (FEF_{25}, FEF_{50}, FEF_{75}, FEF_{25-75}), asthma symptom scores, sleep disturbance scores, rescue medication use, asthma exacerbations, compliance with study medication, subject's assessment of study medication, and the AQLQ.

Safety assessments included incidence and type of spontaneously reported AEs (including paradoxical bronchospasm), vital signs, laboratory tests (including serum glucose and serum potassium) and 12-lead ECGs.

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Number of subjects:

Planned: 1030 (458 for original study, 572 for restarted study)

Enrolled: 1667

Randomised: 1077

	FlutiForm high dose	Flixotide+Foradil	FlutiForm low dose	Flixotide	Total
Full safety set	236	241	239	361	1077
Full analysis set	236	241	239	361	1077
Safety set	154	156	155	155	620
Intent to treat set	154	156	155	155	620
Per protocol set	133	140	127	129	529

Diagnosis and main criteria for inclusion:

- Male or female subjects aged 18 years or older.
- Females less than 1 year post-menopausal had to have a negative urine pregnancy test, be non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study.
- Known history of severe persistent, reversible asthma for ≥ 6 months prior to the screening visit characterised by treatment with inhaled corticosteroids (ICS) at a dose of ≥ 500µg fluticasone or equivalent.
- Demonstrated a FEV_1 of ≥ 40% to ≤ 80% for predicted normal values (Quanjer et al., 1993) during the screening visit (Visit 1) and randomisation visit (Visit 3) following appropriate withholding of asthma medications (if applicable).
- Documented reversibility of ≥14.95% in FEV_1 in the screening phase.
- Demonstrated satisfactory technique in the use of the study medication.
- 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.

Inclusion criteria required following run-in:

- Subject had used rescue medication for at least 3 days, and also had either at least 1 night with sleep disturbance (i.e. sleep disturbance score of ≥ 1) or at least 3 days with asthma symptoms (i.e. a symptom score of ≥ 1) during the last 7 days of the run-in period.

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Test product: FlutiForm high dose (fluticasone/formoterol)
Dose: high dose: 2 puffs of 250/10 µg fluticasone/formoterol, every 12 hours (high dose)
Batch numbers: PN3322, PN3293, PN3397
Mode of administration: pMDI used with an AeroChamber® Plus (GSK) spacer

Duration of treatment: 8 weeks

Reference therapy 1: FlutiForm low dose (fluticasone/formoterol)
2: Flixotide+Foradil (fluticasone + formoterol),
3: Flixotide (fluticasone)
Dose: 2 puffs of 50/5 µg fluticasone/formoterol, every 12 hours
2 puffs of 12 µg formoterol followed by 2 puffs of 250 µg fluticasone, every 12 hours
2 puffs of 250 µg fluticasone, every 12 hours
Batch numbers: FlutiForm 50/5 µg: PN3327, PN3398
Flixotide 250 µg: PN3324, PN3404
Foradil 12 µg: PN3325, PN3375
Mode of administration: pMDI used with an AeroChamber® Plus (GSK) spacer

Criteria for evaluation:

Efficacy evaluation (primary endpoint):

- Change in the FEV_1 value from pre-morning dose at Day 0 (Visit 3) to pre-morning dose at Day 56 (Visit 7).

Efficacy evaluation (co-primary endpoint):

- Change in the FEV_1 value from pre-morning dose at Day 0 (Visit 3) to 120 minutes post-morning dose at Day 56 (Visit 7).

Efficacy evaluation (secondary parameters):

- 12-hour FEV_1 AUC
- Discontinuations due to lack of efficacy
- Peak flow measurements
- Daily FEV_1 measurements
- Other lung function parameters: FVC, FEF_{25}, FEF_{50} and FEF_{75} and FEF_{25-75}
- Asthma symptom scores
- Sleep disturbance scores
- Asthma control days
- Asthma exacerbations
- Study rescue medication use
- Compliance with study medication
- Subject assessment of study medication
- AQLQ

Safety:

- AEs (learned through spontaneous reports).
- Laboratory parameters for haematology, biochemistry and urinalysis.

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- Serum potassium and serum glucose.
- Vital signs: blood pressure, heart rate (taken from 12-lead ECG), respiration rate, oral or tympanic temperature.
- 12-lead ECG results.

Statistical methods:

The primary efficacy endpoint was the change in the FEV_1 value from pre-morning dose at Day 0 (Visit 3) to pre-morning dose at Day 56 (Visit 7). The primary analysis was performed on the per protocol set (PPS) and only included those subjects with values observed at Visit 7. Non-inferiority of FlutiForm high dose to Flixotide + Foradil was tested using an analysis of covariance (ANCOVA) with treatment as a factor, the pre-morning dose FEV_1 values at Day 0 (Visit 3) and asthma severity as linear covariates, and centre as a random effect. The test was performed using a 2-sided level of significance of α=0.05. Additionally, the 95% confidence interval (CI) of the mean treatment difference was calculated.

As a supportive analysis, the primary endpoint analysis was also performed on the intent to treat (ITT) set, using a last observation carried forward (LOCF) approach. If the FlutiForm high dose treatment group was shown to be non-inferior to the Flixotide + Foradil treatment group regarding the change in pre-morning dose FEV_1, from Day 0 to Day 56, it was also examined for superiority on the ITT set using the same ANCOVA.

The ANCOVA on the ITT set was also used to evaluate assay sensitivity by comparing the FlutiForm high dose treatment group with the Flixotide treatment group. In addition, dose-response was assessed by comparing the FlutiForm high dose and FlutiForm low dose treatment groups.

The co-primary efficacy endpoint, change in the FEV_1 value from pre-morning dose at Day 0 (Visit 3) to 120 minutes post-morning dose at Day 56 (Visit 7) as well as the secondary efficacy parameters 12-hour FEV_1 AUC, peak flow measurements, daily FEV_1 measurements, asthma symptoms and sleep disturbance scores, asthma control days, and AQLQ were analysed analogously using ANCOVA; study rescue medication use was analysed using a Wilcoxon rank sum test; subject assessment of asthma medication was analysed using a proportional odds model with treatment group as a factor; the difference in percentages and 95% CI was calculated for discontinuations due to lack of efficacy. P-values were also provided for the analysis of asthma exacerbations (Fisher's exact test). All other endpoints were summarised using descriptive statistics (compliance with study medication, and other lung function parameters). All hypothesis tests were 2-sided and conducted at the 5% error level.

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

Sample size calculation:

The calculation of the sample size applied only to subjects recruited after the correction of the randomisation issue, and was independent of the number of subjects already included in the study prior to the error.

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The sample size was focused on the difference in the pre-morning dose FEV_1 values analysed using ANCOVA. The null hypothesis was that the FlutiForm high dose treatment group is inferior to the Flixotide + Foradil treatment group and the alternative hypothesis was that the FlutiForm high dose treatment group is non-inferior to the Flixotide + Foradil treatment group.
Non-inferiority would be concluded if the lower limit of the 95% confidence interval was greater than or equal to -0.2 L. The non-inferiority margin of -0.2 L is a widely established non-inferiority margin for comparing asthma treatments.
A total sample size of 572 randomised subjects (121 per treatment group in the PPS) would achieve 93% power to reject the null hypothesis (treatment difference of -0.2 L or farther from 0 in the same direction) in the change in pre-morning dose FEV_1 values from baseline to the end of the 8-week treatment period. This assumed an observed difference of 0 between treatment groups, an estimated standard deviation (SD) of 0.45 L, a non-inferiority bound of -0.2L, and a 2-sided alpha of 0.05. This also assumed that 15% of the randomised subjects would not be part of the PPS.
The overall power for a positive outcome for the primary and co-primary endpoints, and the FlutiForm dose-response for the primary endpoint would be 80% (i.e. 0.93*0.93*0.93).
A sample size of 47 subjects in each treatment arm should achieve 90% power to detect a treatment difference of 3.6 L*h in the FEV_1 AUC_{0-12}. This assumed an observed difference of 0, an estimated SD of 5.3 L*h and a 2-sided alpha of 0.05.

Interim analysis:
No interim analysis was performed.

Summary

Efficacy results:

Comparison of FlutiForm high dose with Flixotide + Foradil

The primary objective of this study was to demonstrate non-inferiority in the efficacy of FlutiForm high dose versus Flixotide + Foradil administered concurrently. The primary endpoint was the mean change in the pre-morning dose FEV_1 value from baseline (Day 0, i.e. end of run-in period) to the end of the 8-week treatment period (Day 56). The co-primary endpoint of this study was the mean change in the pre-morning dose FEV_1 value from Day 0 (end of run-in period) to the 2-hour post-morning dose FEV_1 value at the end of the 8-week treatment period.
The confirmatory analysis was performed on the PPS. The mean change in pre-morning dose FEV_1 from Day 0 to Day 56 was 0.345 L in the FlutiForm high dose group and 0.284 L in the Flixotide + Foradil group. The LSMean of the treatment difference was 0.060 L (95% CI: -0.059 to 0.180). Non-inferiority of FlutiForm high dose to Flixotide + Foradil was demonstrated as the lower limit of the 95% CI for the treatment difference exceeded the non-inferiority acceptance limit of -0.2 L ($p < 0.001$). The analysis of the ITT set confirmed this result (LSMean of the treatment difference 0.079 L; 95% CI: -0.032 to 0.190; $p < 0.001$).
Since non-inferiority of FlutiForm high dose versus Flixotide + Foradil was demonstrated for the primary endpoint, a confirmatory analysis was performed for the co-primary endpoint as well. The mean change in FEV_1 from pre-morning dose on Day 0 to 2 hours post-morning dose on Day 56 was

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0.518 L in the FlutiForm high dose group and 0.500 L in the Flixotide + Foradil group. The LSMean of the treatment difference was 0.018 L (95% CI: -0.098 to 0.135). Non-inferiority of FlutiForm high dose to Flixotide + Foradil was demonstrated as the lower limit of the 95% CI for the treatment difference thus exceeded the non-inferiority acceptance limit of -0.2 L ($p < 0.001$). The analysis of the ITT set confirmed this result (LSMean of the treatment difference: 0.040 L; 95% CI: -0.069 to 0.149; $p < 0.001$).

Non-inferiority of FlutiForm high dose compared to Flixotide + Foradil was formally shown for the secondary endpoint, discontinuations due to lack of efficacy. In the PPS, 6 subjects (4.5%) in the FlutiForm high dose group and 11 subjects (7.9%) in the Flixotide + Foradil group discontinued the treatment phase due to lack of efficacy. The upper limit of the 95% CI for the difference was below the pre-defined non-inferiority limit of 10% (95%CI: -9.0 to 2.3). The supportive analysis of the ITT set confirmed this result (95%CI for the treatment difference: -9.0 to 1.4).

Treatment with FlutiForm high dose was also comparable to treatment with Flixotide + Foradil for the remaining secondary efficacy endpoints with statistical tests performed on the ITT set.

On Day 0, the LSMean of the 12-hour serial FEV_1 AUC reached 24.915 L*hours with FlutiForm high dose and 24.815 L*hours with Flixotide + Foradil treatment (95% CI for the treatment difference: -1.113 to 1.312). On Day 56, the respective values were 26.183 L*hours and 26.597 L*hours (95% CI for the treatment difference: -1.086 to 0.257).

Mean pre-dose peak flow rates and FEV_1 values obtained from subject diaries increased from Day 0 to Day 56 in both treatment groups. No statistically significant differences were observed between the 2 treatment groups for the morning and evening pre-dose peak flow rates or the morning and evening pre-dose FEV_1.

Increases were also observed for mean peak flow rates, FVC, FEF_{25}, FEF_{50}, FEF_{75}, and FEF_{25-75} values recorded pre- and 2 hours post-morning dose during the pulmonary function tests. With few exceptions, larger changes from Day 0 to Day 56 were observed in the FlutiForm high dose treatment group than in the group treated with Flixotide + Foradil (no statistical tests were performed).

The mean asthma symptom scores decreased, i.e. improved, from Day 0 to Day 56 in both treatment groups. The overall asthma symptom scores were low (mean values <1.2), with no statistically significant differences between treatments (95% CI for the treatment difference: -0.21 to 0.05). The proportion of symptom free days increased by 48.51% in the FlutiForm high dose group and by 45.61% in the Flixotide + Foradil group (95% CI for the treatment difference: -5.38 to 11.17) from Day 0 to Day 56.

The mean sleep disturbance scores decreased, i.e. improved, over the course of the study as well. Again, the overall scores were low (mean values <0.7), with no statistically significant differences between treatments (95% CI for the treatment difference: -0.08 to 0.09). The proportion of awakening free nights increased by approximately 36% in both treatment groups (95% CI for the treatment difference: -5.09 to 7.19) from Day 0 to Day 56.

Asthma control days were defined as an asthma symptom score of 0 (no symptoms), a sleep disturbance score of 0 (slept through the night) and no inhalations of rescue medication. From Day 0

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to Day 56, the proportion of asthma control days increased by 44.14% in both treatment groups (95% CI for the treatment difference -8.27 to 8.27).
Fewer subjects in the Flixotide + Foradil group (57.7%) compared to the FlutiForm high dose group (72.7%) suffered from at least 1 mild or moderate asthma exacerbation (p = 0.006). Severe asthma exacerbations were experienced by only 3 subjects (1.9%) in the FlutiForm high dose group and no subject in the Flixotide + Foradil group (p = 0.121).
The median percentage of study days on which salbutamol rescue medication was used was comparable in the FlutiForm high dose and Flixotide + Foradil groups (median: 23.95% and 21.05%, respectively; 95% CI for the treatment difference: -4.29 to 4.44). The median number of uses of rescue medication was very low in both treatment groups (0.3 and 0.2 uses per day, respectively). The treatment difference was not statistically significant (95% CI: -0.06 to 0.05). The proportion of rescue medication-free days increased by 52.80% in the FlutiForm high dose group and by 53.95% in the Flixotide + Foradil group (95% CI for the treatment difference: -9.57 to 7.27) from Day 0 to Day 56.
The odds ratio for the overall subject assessment of study medication on Day 56 was 1.281 (95% CI: 0.838 to 1.956). More subjects in the FlutiForm high dose group (42.2%) than in the Flixotide + Foradil group (33.3%) assessed the study medication as very good.
The AQLQ overall score increased by 0.88 units in the FlutiForm high dose group and by 0.72 units in the Flixotide + Foradil group (95% CI for the treatment difference: -0.04 to 0.36) from Day 0 to Day 56.

Comparison of FlutiForm high dose with Flixotide alone
One secondary objective of this study was to show superiority to Flixotide alone. Statistical tests were performed on the ITT set with the aim to show superiority of treatment with FlutiForm high dose over Flixotide alone.
In general, the high dose of FlutiForm provided better outcomes than Flixotide alone for a substantial number of clinically important endpoints.
Superiority of FlutiForm high dose compared to Flixotide alone was established for the following endpoints:
The mean change in FEV_1 from pre-morning dose on Day 0 to 2 hours post-morning dose on Day 56 (recorded at the study visits) was 0.517 L in the FlutiForm high dose group and 0.396 L in the group treated with Flixotide alone. (LSMean of the treatment difference: 0.120 L; 95% CI: 0.011 to 0.230; p = 0.032). Superiority of FlutiForm high dose versus Flixotide alone was also shown for each individual study visit (post-hoc analysis based on the ITT set).
Data from the 12-hour serial FEV_1 AUC analysis further supported better efficacy of FlutiForm high dose versus Flixotide. Treatment with FlutiForm high dose resulted in numerically larger improvements in FEV_1 than treatment with Flixotide alone, both on Day 0 and on Day 56 (ITT, not statistically significant). A post-hoc analysis showed superiority of FlutiForm high dose versus Flixotide for change in FEV_1 from pre-dose to 1 hour and 2 hours post-dose at Day 0 (ITT). Superiority of FlutiForm high dose versus Flixotide was also demonstrated for the FAS (sensitivity analysis based on subjects with moderate asthma at screening) at Day 56 (LSMean of the treatment difference for 12-hour serial FEV_1

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AUC: 1.138 L*hours; 95% CI: 0.358 to 1.918, p = 0.004).
Discontinuations due to lack of efficacy were reported for 6 subjects (3.9%) in the FlutiForm high dose group, and 17 subjects (11.0%) in the Flixotide group. The 95% CI for the difference between the 2 treatment groups was -12.9 to -1.3, thus indicating superiority of FlutiForm high dose. In the Flixotide group, subjects started to discontinue soon after Day 14 reflecting that patients were not optimally treated with Flixotide alone. Most of the discontinuations had occurred by around Day 42. FlutiForm high dose was superior to Flixotide with regard to time to discontinuation due to lack of efficacy (hazard ratio for Flixotide versus FlutiForm high dose: 3.063; p = 0.0184; ITT). Since significantly more patients whose asthma was not appropriately controlled were discontinued prematurely in the Flixotide group the observed differences in various efficacy outcomes between the FlutiForm high dose and the Flixotide groups might have been even larger if the patients had continued to the end of the study.
Mean evening pre-dose peak flow rates (obtained from subject diary) increased from Day 0 to Day 56 by 27.2 L/min in the FlutiForm high dose group and by 13.1 L/min in the group treated with Flixotide alone (LSMean of the treatment difference: 14.1 L/min; 95% CI: 1.3 to 27.0; p = 0.031).
The mean asthma symptom scores decreased, i.e. improved, over the course of the study in both treatment groups. The decrease was larger in the FlutiForm high dose group (-0.76 units), than in the group treated with Flixotide alone (-0.60 units; LSMean of the treatment difference: -0.16 units; 95% CI: -0.29 to -0.02; p = 0.020). The proportion of symptom-free days increased by 48.51% in the FlutiForm high dose group and by 39.81% in the group treated with Flixotide alone (LSMean of the treatment difference: 8.69%; 95% CI: 0.39 to 17.00; p = 0.040) from Day 0 to Day 56.
The proportion of awakening-free nights increased by 36.56% in the FlutiForm high dose group and by 29.89% in the group treated with Flixotide alone (LSMean of the treatment difference: 6.67%; 95% CI: 0.51 to 12.83; p = 0.034) from Day 0 to Day 56.
The odds ratio for the overall subject assessment of study medication at Day 56 for FlutiForm high dose compared to Flixotide alone was 2.119 and thus clearly in favour of FlutiForm high dose (95% CI: 1.377 to 3.262 and thus statistically significant). Noticeably more subjects in the FlutiForm high dose group (42.2%) than in the Flixotide group (23.2%) assessed the study medication as very good.
The AQLQ overall score increased by 0.88 units in the FlutiForm high dose group and by 0.66 units in the Flixotide group (LSMean of the treatment difference: 0.22 units; 95% CI: 0.01 to 0.42; p = 0.036) from Day 0 to Day 56.
For the following endpoints results were numerically in favour of FlutiForm high dose, although the differences were not statistically significant: change in FEV_1 from pre-morning dose on Day 0 to pre-morning dose on Day 56 (recorded at the study visits), changes in morning pre-dose peak flow rates from Day 0 to Day 56 (obtained from subject diary), changes in peak flow rates, FEF_{25}, FEF_{50}, and FEF_{25-75} from pre-morning dose on Day 0 to pre-morning dose on Day 56 (recorded at the study visits), changes in peak flow rates, FVC, FEF_{25}, FEF_{50}, FEF_{75}, and FEF_{25-75} from pre-morning dose on Day 0 to 2 hours post-morning dose on Day 56 (recorded at the study visits), sleep disturbance score, percentages of asthma control days and rescue medication-free days.
Flixotide alone showed comparable performance to FlutiForm high dose with regard to the following

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endpoints: changes in morning and evening pre-dose FEV_1 from Day 0 to Day 56 (obtained from subject diary), changes in FVC and FEF_{75}, from pre-morning dose on Day 0 to pre-morning dose on Day 56 (recorded at the study visits), number of mild/moderate or severe asthma exacerbations, and use of rescue medication (i.e. percentage of study days rescue medication was used and number of uses per day).

Comparison of FlutiForm high dose with FlutiForm low dose

A further secondary objective of this study was to demonstrate a dose-response effect. Statistical tests were performed on the ITT set with the aim to show superiority of treatment with FlutiForm high dose over FlutiForm low dose.

In general, the high dose of FlutiForm provided better outcomes than the low dose of FlutiForm for a substantial number of clinically important endpoints.

Superiority of FlutiForm high dose compared to FlutiForm low dose was established for the following endpoints:

Discontinuations due to lack of efficacy were reported for 6 subjects (3.9%) in the FlutiForm high dose group, and 18 subjects (11.6%) in the FlutiForm low dose group. The 95% CI for the difference between the 2 treatment groups was -13.6 to -1.8, thus indicating superiority of FlutiForm high dose. In the FlutiForm low dose group subjects started to discontinue soon after Day 14 reflecting that patients were not optimally treated. Most of the discontinuations had occurred by around Day 42. FlutiForm high dose was superior to FlutiForm low dose with regard to time to discontinuation due to lack of efficacy (hazard ratio for FlutiForm low dose versus FlutiForm high dose: 3.202; p = 0.0136; ITT). Since significantly more patients whose asthma was not appropriately controlled were discontinued prematurely in the FlutiForm low dose group the observed differences in various efficacy outcomes between the FlutiForm high dose and the FlutiForm low dose groups might have been even larger if the patients had continued to the end of the study. As the lung function values from the discontinuation visit were carried forward to Day 56, the results for subjects in the FlutiForm low dose group might be more favourable than they would have been if the subjects had completed the study as planned.

The decrease in sleep disturbance score from Day 0 to Day 56 was larger in the FlutiForm high dose group (-0.47 units), than in FlutiForm low dose group (-0.35 units; LSMean of the treatment difference: -0.12 units; 95% CI: -0.20 to -0.04; p = 0.005). The proportion of awakening-free nights increased by 36.56% in the FlutiForm high dose group and by 26.69% in the FlutiForm low dose group (LSMean of the treatment difference: 9.87%; 95% CI: 3.66 to 16.08; p = 0.002).

The odds ratio for the overall subject assessment of study medication on Day 56 for FlutiForm high dose compared to FlutiForm low dose was 1.775 and thus in favour of FlutiForm high dose (95% CI: 1.160, 2.717). More subjects in the FlutiForm high dose group (42.2%) than in the FlutiForm low dose group (27.7%) assessed the study medication as very good.

The data for the mean change in FEV_1 from pre-morning dose on Day 0 to pre-morning dose on Day 56 (recorded at the study visits) supported better efficacy of FlutiForm high dose versus FlutiForm low dose. Treatment with FlutiForm high dose resulted in numerically larger changes in FEV_1 than

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treatment with FlutiForm low dose. A post-hoc analysis showed superiority ($p < 0.05$) of FlutiForm high dose versus FlutiForm low dose overall (including all study visits) as well as at each study visit (Day 14, Day 28 and Day 42) except Day 56. The failure to show a statistically significant difference at Day 56 may be explained by more patients discontinuing prematurely due to lack of efficacy in the low dose group (see above).

For the following endpoints, results were numerically in favour of FlutiForm high dose, although the differences were not statistically significant: changes in FEV_1 from pre-morning dose on Day 0 to 2 hours post-morning dose on Day 56 (recorded at the study visits), asthma symptom scores, percentages of symptom-free days, asthma control days and rescue medication-free days, and AQLQ.

FlutiForm low dose showed comparable performance to FlutiForm high dose with regard to the following endpoints: 12-hour serial FEV_1 AUC on Day 0 and on Day 56, changes in morning and evening pre-dose peak flow rates and FEV_1 from Day 0 to Day 56 (obtained from subject diary), changes in peak flow rates, FVC, FEF_{25}, FEF_{50}, FEF_{75}, and FEF_{25-75} from pre-morning dose on Day 0 to pre-morning dose or 2 hours post-morning dose on Day 56 (recorded at the study visits), number of mild/moderate or severe asthma exacerbations, and use of rescue medication (i.e. percentage of study days rescue medication was used and number of uses per day).

Safety results:

Altogether, 232 of the 1077 subjects (21.5%) of the full safety set experienced at least 1 AE after the start of study treatment.

The overall rate of AEs ranged from 19.1% in the FlutiForm high dose group to 23.0% in the Flixotide treatment group. There were no noteworthy differences between the treatment groups regarding the profile of AEs. In all treatment groups, AEs classed as 'infections and infestations' were most common. At the preferred term level, the most common AEs were nasopharyngitis, headache, pharyngitis, asthma, and viral infection.

The profile of AEs in the FlutiForm high dose and low dose groups showed no apparent dose-response relationship.

The majority of AEs were mild or moderate in intensity; severe AEs were reported for a total of 11 subjects (1.0%). Asthma was the only AE considered severe in more than 1 subject, reported for 2 subjects (0.8 %) in the FlutiForm high dose group, 4 subjects (1.7%) in the FlutiForm low dose group and 4 subjects (1.1%) in the Flixotide group, and for no subjects in the Flixotide + Foradil group.

Treatment-related AEs were slightly more frequent in the Flixotide + Foradil group (4.6%) and the Flixotide group (4.4%) than in the FlutiForm high dose and low dose groups (3.0% and 3.3%, respectively). The only treatment-related AEs to occur in more than 1 subject in any treatment group were asthma (8 subjects in total), dysphonia (8 subjects in total), tremor (3 subjects in total) and electrocardiogram PR shortened (3 subjects in total).

There were no deaths during the study.

Treatment-emergent SAEs were reported for 9 subjects: 1 subject in the FlutiForm high dose group, 2 subjects in the Flixotide + Foradil group and in 3 subjects each in the FlutiForm low dose and Flixotide

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groups. There were 3 treatment-related SAEs: cerebral infarction with possible relationship in 1 subject treated with Flixotide + Foradil, myocardial ischaemia with possible relationship in 1 subject treated with Flixotide, and pneumonia with unlikely relationship in 1 subject treated with FlutiForm low dose. Each of the treatment-related SAEs was reported as a SUSAR (suspected unexpected serious adverse reaction). SAEs led to the withdrawal of 4 subjects from the study: cerebral infarction in 1 subject treated with Flixotide + Foradil, sciatica and unstable angina in 1 subject each treated with FlutiForm low dose, and pneumonia in 1 subject treated with Flixotide. For 3 subjects, the outcome of the SAE was reported as recovered with sequelae (cerebrovascular accident, pneumonia and, myocardial ischaemia). The other 6 subjects recovered.

AEs leading to withdrawal from the study were reported for 15 subjects: 3 in the FlutiForm high dose group (1.3%), 3 in the Flixotide + Foradil group (1.2%), 3 in the FlutiForm low dose group (1.3%) and 6 in the Flixotide treatment group (1.7%). Asthma (exacerbation) was the most common AE leading to withdrawal, reported for 7 of the subjects. Pneumonia led to the withdrawal of 2 subjects. None of the other AEs leading to withdrawal occurred in more than 1 subject. AEs leading to the withdrawal of 4 subjects were reported as SAEs (cerebral infarction, sciatica, unstable angina and pneumonia). The outcome of pneumonia in 1 subject in the Flixotide group was documented as recovered with sequelae. All other AEs leading to withdrawal resolved.

Analyses of haematology, biochemistry and urinalysis parameters did not reveal any noteworthy changes over the course of the study in any treatment group. Systemic effects of LABAs in terms of 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 in any of the treatment groups.

Clinically significant ECG findings were reported as AEs for 10 subjects (2 subjects in the FlutiForm high dose group, 3 subjects in the Flixotide + Foradil group, 3 subjects in the FlutiForm low dose group and 2 subjects in the Flixotide group). AEs in 4 subjects were considered to be treatment-related: arrhythmia supraventricular and bundle branch block left in 1 subject and tachycardia in 1 subject in the Flixotide + Foradil group, and ECG T wave inversion and ECG T wave amplitude decreased in 1 subject each in the Flixotide group. None of the clinically significant ECG findings documented as AEs in subjects treated with FlutiForm were considered to be treatment-related.

The evaluation of safety based on the 620 subjects of the safety set generally yielded similar results to those obtained for the 1077 subjects of the full safety set.

In conclusion, analyses of AEs, laboratory parameters, vital signs and ECG findings did not reveal any safety concerns regarding administration of FlutiForm in adult subjects with severe persistent, reversible asthma. The treatment was safe and well tolerated.

Conclusions:

In summary, the efficacy results obtained in this study confirm that FlutiForm high dose provides comparable efficacy to Flixotide + Foradil administered concurrently in terms of pulmonary function, discontinuations due to lack of efficacy, asthma symptoms, disease control, and subject-centred

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outcomes. It was confirmed that the study design was sensitive to detect differences between treatments as FlutiForm high dose was superior to Flixotide alone for many endpoints. FlutiForm high dose also showed better efficacy than FlutiForm low dose for clinically important endpoints. The safety profile of this combination product was consistent with the safety profiles of its components, fluticasone and formoterol. Treatment with FlutiForm was safe and well tolerated.		
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