CLINICAL STUDY REPORT

A double-blind, randomised, incomplete block, crossover, placebo-controlled, dose-response study to assess bronchial hyperresponsiveness and airway inflammation effects of FlutiForm® pMDI low and high dose in adult subjects with mild to moderate asthma.

Protocol Number:	FLT2503
EudraCT Number:	2009-009873-87
Kendle Study Number:	32041
Test Drug:	Fluticasone propionate / Formoterol fumarate
Indication:	Asthma bronchiale
Phase:	Phase 2
Study Initiation Date:	First subject first visit: 29 October 2009
Study Completion Date:	Last subject last follow-up visit: 21 July 2010
Co-ordinating Investigator:	Dr. Frank Kanniess KLB Healthresearch Lübeck GmbH Pferdemarkt 6-8 23552 Lübeck, Germany
Sponsor:	Mundipharma Research Ltd. Cambridge Science Park Milton Road Cambridge CB4 0GW, UK
Date of Report:	30 January 2014
Version of Report:	Final

GCP Statement: This study was conducted in accordance with the guidelines of current Good Clinical Practice (GCP) including the archiving of essential documents.

1 Study Synopsis

<table>
<tr><td>Name of Sponsor/Company:
Mundipharma Research Ltd.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Test Drug:
FlutiForm®</td></tr>
<tr><td>Name of Active Ingredient:
Fluticasone propionate / Formoterol fumarate</td></tr>
<tr><td colspan="3">Title of Study: A double-blind, randomised, incomplete block, crossover, placebo-controlled, dose-response study to assess bronchial hyperresponsiveness and airway inflammation effects of FlutiForm® pMDI low and high dose in adult subjects with mild to moderate asthma.</td></tr>
<tr><td colspan="3">Investigators:
Seven principal investigators participated in the study. The co-ordinating investigator for this study was Dr. Frank Kanniess, Lübeck, Germany.</td></tr>
<tr><td colspan="3">Study Centre(s):
There were 7 active centres in Germany. Dr. Frank Kanniess, KLB Healthresearch Lübeck GmbH, Lübeck, Germany was the co-ordinating investigator.</td></tr>
<tr><td colspan="2">Publication (Reference):
No publications currently reference this study

ClinicalTrials.gov Identifier:
NCT00995800</td><td>Phase of Development: II</td></tr>
<tr><td colspan="3">Studied Period: 29 October 2009 to 21 July 2010 (last subject follow-up visit)</td></tr>
<tr><td colspan="3">Primary Objective:
To demonstrate a dose-response relationship between high dose (500/20 µg) and low dose (100/10 µg) FlutiForm® (hereafter referred to as FlutiForm) by comparing the effects of each dose on the changes in bronchial hyperresponsiveness to inhaled adenosine 5’-monophosphate (AMP) challenge.
Secondary Objectives:
To compare the effect of high and low doses of FlutiForm on the changes from baseline in other measures of airway inflammation (exhaled nitric oxide (eNO) and percentage of eosinophils in induced sputum) and to compare the changes in bronchial</td></tr>
</table>

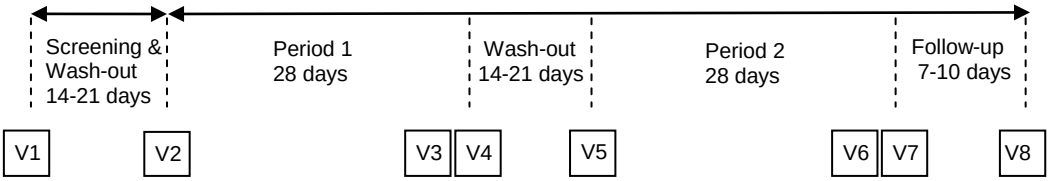
hyperresponsiveness to AMP challenge for each FlutiForm dose group with placebo.

Additional secondary objectives were to measure lung function, amount of rescue medication use, asthma symptom scores, sleep disturbance due to asthma, asthma exacerbations, discontinuation due to lack of efficacy, and spontaneously reported adverse events (AEs).

Methodology:

This was a double-blind, randomised, incomplete block, crossover, placebo-controlled, dose-response, phase 2 study to assess the effects on bronchial hyperresponsiveness to AMP and other anti-inflammatory of FlutiForm low and high dose for 4 weeks in adult subjects with mild to moderate asthma.

The following scheme shows the schedule of events:



V1 = screening visit, V2, V5 = baseline visits of periods 1 and 2

The study consisted of a pre-randomisation phase, during which the screening visit and the first wash-out (from any existing controller medication) took place, and a double-blind treatment phase comprising two 28-day treatment periods (+/- 3 days), separated by a second wash-out period. Both wash-out periods lasted for 14 to 21 days (maximum 24 days). A follow-up telephone contact took place 7 to 10 days after last study drug dosing.

Subjects were evaluated for study eligibility at the screening visit (Visit 1). Subjects who complied with the inclusion/exclusion criteria and had a forced expiratory volume in the first second (FEV_1) ≥ 60% predicted entered the first wash-out period, during which they stopped taking their current asthma medication and were only allowed to take salbutamol, if required, as rescue medication. Use of rescue medication was recorded daily by the subject in a diary card, together with morning and evening peak expiratory flow rate (PEFR), asthma symptom scores, and sleep disturbance due to asthma.

At Visit 2, following the first wash-out period, a baseline AMP challenge test was performed. To be eligible to continue in the study, subjects had to show an AMP $PD_{20}FEV_1$ (provocative dose of AMP producing a 20% decline in FEV_1) of < 60 mg. If this threshold was not attained subjects could return for a repeat AMP test 7 days later, to attempt to satisfy this eligibility criterion. In addition to an AMP challenge, other measures were evaluated including eNO, sputum eosinophils, and lung function and diary data was reviewed. Subjects who met all entry criteria were randomised to receive 2 of the 3 study treatments; FlutiForm 500/20 µg BID, FlutiForm 10/10 µg BID, or placebo (via a dummy inhaler). The order in which the subjects were to receive treatment was determined using a Latin Square design.

Each treatment period was 28 (+/-3) days, during which study medication was inhaled twice a day via an AeroChamber® Plus spacer. On Day 27 of period 1 (Visit 3) sites contacted subjects to remind them that the last pre-visit dose of study medication should be taken that evening 12 hours prior to clinic assessments. Subjects returned to

the site the following day (Day 28 of treatment period 1, Visit 4) for an AMP challenge, and assessment of other efficacy and safety variables. These assessments for each subject had to take place at the same time of day (+/- 1.5 hours) throughout the study. Following Visit 4 subjects underwent the second washout period, lasting 14 – 21 days. At the end of the second wash-out period (Visit 5), subjects crossed over into the second treatment period, during which they were to receive one of the two alternative study medications. Prior to continuation into the second treatment period, the reproducibility of the AMP test was required to be within ± 1.5 doubling doses of that at the start of treatment period 1 [Visit 2]. If AMP PD_{20} reproducibility was not demonstrated the subject was re-assessed 7 days later to repeat the AMP challenge and either confirm the subject's eligibility to continue or discontinue them from the study. On Day 27 of treatment period 2 (Visit 6), sites again called subjects to remind them that the last dose of study medication was to be taken that evening. The final clinic visit took place the next day (Day 28 of treatment period 2, Visit 7).

During the pre-randomisation and treatment phases, subjects were allowed to take salbutamol (2 puffs, 100 µg per puff) on up to 4 occasions per day as rescue medication.

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 if they met prespecified withdrawal criteria.

Subjects were followed up by telephone 7-10 days (Visit 8) after completion or discontinuation from the study to assess ongoing or new adverse events that may have occurred.

At the end of the second treatment period (or post-withdrawal if the subject was discontinued from the study), subjects reverted to their pre-study asthma medication.

Number of Subjects (Planned and Analysed):

Planned: 60
Enrolled: 129
Randomised: 62

		FlutiForm high dose	FlutiForm low dose	Placebo	Overall
Safety set (SS)	N	44	40	40	62
	N evaluable	39	32	37	62
Full analysis set (FAS)	N	39	37	34	55
	N evaluable	36	32	32	55
Per protocol set (PPS)	N	25	26	23	37
	N evaluable	25	26	23	37

N = number of randomised subjects in treatment group, N evaluable = number of subjects evaluable in treatment group (Note that some subjects received the first but not the second study treatment.) Therefore, these subjects were evaluable for the overall analysis set but for only one of the 2 treatment groups they were randomised to, for details see Section 10.3)

Diagnosis and Main Criteria for Inclusion / Exclusion:

Inclusion Criteria

- Male or female subjects aged 18 years and over.
- 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 in each treatment period, be non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study.
- Known history of mild to moderate asthma for≥ 6 months prior to the screening visit.
- Subject had not received systemic (injectable or oral) corticosteroid medication in the 12 weeks prior to the screening visit.
- Demonstrated a FEV_1 of ≥ 60% predicted FEV_1 [56] at the screening visit, following appropriate withholding of bronchodilators (no long-acting β_2-agonist or short-acting β_2-agonist/anticholinergic use 12 hours and 6 hours prior to screening, respectively).
- Demonstrated AMP $PD_{20}FEV_1$ < 60 mg following appropriate withholding of asthma medications (no short-acting bronchodilator use at least 6 hours prior to the AMP challenge test at Visit 2).
- Non-smoker for at least 12 months prior to study screening. Ex-smokers had to have a smoking history equivalent to less than “10 pack years” (*i.e.* at least

1 pack of 20 cigarettes per day for 10 years or 10 packs per day for 1 year, etc.).

- Demonstrated satisfactory technique in the use of the pressurised metered dose inhaler (pMDI).
- Willing and able to enter information in the diary card twice daily 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.

Exclusion Criteria

Subjects were excluded from the study if any of the following criteria applied:

- Near fatal or life-threatening (including intubation) asthma within the past year.
- Hospitalisation or an emergency visit for asthma within 4 weeks prior to the screening visit.
- History of omalizumab use within the past 6 months.
- Current evidence or history of any clinically significant disease or abnormality including uncontrolled coronary artery disease, congestive heart failure, myocardial infarction, or cardiac dysrhythmia. 'Clinically significant' was defined as any disease that, in the opinion of the investigator, would put the subject at risk through study participation, or which would affect the outcome of the study.
- In the investigator's opinion a clinically significant upper or lower respiratory infection within 4 weeks prior to the screening visit.
- Significant, non-reversible, active pulmonary disease (e.g. COPD, cystic fibrosis, bronchiectasis, tuberculosis).
- Known human immunodeficiency virus-positive status.
- Current evidence or history of alcohol and/or substance abuse within 12 months prior to the screening visit.
- Subjects who had taken β-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole (Hismanal), quinidine type antiarrhythmics, or potent CYP 3A4 inhibitors such as ketoconazole within one week prior to the screening visit.
- History of leukotriene receptor antagonist use, e.g. montelukast, within one week prior to the screening visit.
- Current use of medications other than those allowed in the protocol that will have an effect on bronchospasm and/or pulmonary function.
- Use of anti-histamines within 2 weeks prior to the screening visit; use of non-steroidal anti-inflammatory drugs, oral decongestants, inhaled cromolyn sodium, nedocromil sodium within 1 week prior to the screening visit.
- Current evidence or history of hypersensitivity or idiosyncratic reaction to test medications, rescue medication, or components.

- Use of an investigational drug within 30 days prior to the screening visit (12 weeks if an oral or injectable steroid).
- Current participation in a clinical study.

Test Product, Dose and Mode of Administration, Batch Number:

FlutiForm 250/10 µg pMDI, 2 puffs (i.e., 500/20 µg) every 12 hours (high dose), inhaled via AeroChamber® Plus

Batch number: PN3397

FlutiForm 50/5 µg pMDI, 2 puffs (i.e., 100/10 µg) every 12 hours (low dose), inhaled via AeroChamber® Plus

Batch number: PN3432

Duration of Treatment and Washout Periods:

Pre-treatment Phase: Screening and wash-out period of 14-21 days (maximum 24 days) duration.

Treatment Phase: Two treatment periods, each of 28 days duration. A follow-up telephone contact took place 7 to 10 days after last study drug dosing.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo (dummy inhaler) FlutiForm pMDI, 2 puffs every 12 hours, inhaled via AeroChamber® Plus

Batch number: PN3399

Criteria for Evaluation:

Efficacy:

Primary Endpoint:

Change from baseline (Day 1) to end of treatment (Day 28) in AMP PD_{20} FEV_1

Secondary Endpoints:

- Change from baseline to end of treatment in percentage of eosinophils in induced sputum
- Change from baseline to end of treatment in exhaled nitric oxide (eNO) concentration
- Percentage of eosinophils in induced sputum at Day 1 and Day 28
- Exhaled nitric oxide (eNO) concentration at Day 1 and Day 28
- Lung function parameters at Day 1 and Day 28 and change from baseline: forced expiratory volume in the first second (FEV_1), peak expiratory flow rate (PEFR), forced vital capacity (FVC), forced expiratory flow at 25%, 50% and 75% of the volume to exhale (FEF_{25}, FEF_{50} and FEF_{75}) and forced expiratory flow in the middle portion of expiration (FEF_{25-75})
- Daily diary PEFR at Day 1 and Day 28 and change from baseline

- Asthma symptom scores at Day 1 and Day 28 and change from baseline
- Sleep disturbance scores at Day 1 and Day 28 and change from baseline
- Percentage of rescue medication-free days at Day 1 and Day 28 and change from baseline
- Number of uses of rescue medication use during treatment period
- Percentage of days with rescue medication use during treatment period
- Compliance with study medication
- Asthma exacerbations
- Discontinuations due to lack of efficacy

Safety:

- Adverse events (AEs)
- Clinical laboratory parameters for haematology, clinical chemistry and urinalysis
- Vital signs: blood pressure, pulse rate, respiration rate
- 12-lead ECG results

Statistical Methods:

Three analysis populations were defined: The Safety Set (SS), the Full Analysis Set (FAS) and Per Protocol Set (PPS).

The SS was defined as all randomised subjects who received study treatment at least once and had at least one post-dose safety assessment.

The FAS included all randomised subjects who received at least one dose of study treatment and had at least one post-dose primary efficacy (AMP $PD_{20}FEV_1$) measurement.

The PPS was defined as all FAS subjects who completed the study without major protocol violations affecting the primary efficacy endpoint.

The primary efficacy endpoint was the change in AMP $PD_{20}FEV_1$ from baseline (Day 1 of each treatment period, i.e. Visits 2 and 5, respectively) to end of treatment (Day 28 of each treatment period, i.e. Visits 4 and 7, respectively). The primary analysis was performed on the full analysis set (FAS) and was to only include those subjects with AMP $PD_{20}FEV_1$ values at end of treatment. The comparison of interest for the primary analysis on the FAS was between the FlutiForm high dose and FlutiForm low dose treatment groups. The AMP $PD_{20}FEV_1$ data recorded at each time point (baseline and end of treatment) and the change from baseline to end of treatment, were natural log-transformed in order to normalise the data distribution prior to analysis.

The null hypothesis was that there is no difference in the mean change in AMP $PD_{20}FEV_1$ from baseline to end of treatment between FlutiForm high dose and FlutiForm low dose and the alternative hypothesis was that there is a difference in the mean change in AMP $PD_{20}FEV_1$ from baseline to end of treatment between FlutiForm high dose and FlutiForm low dose. The hypothesis was tested on the FAS using an analysis of covariance (ANCOVA) with treatment, baseline AMP $PD_{20}FEV_1$ and

treatment period as fixed effects and centre as a random effect. The test was performed using a two-sided level of significance of α=0.05. After performing the statistical analysis, the treatment least square (LS) means and corresponding 95% confidence intervals (CIs), and the LS mean differences between the treatment groups and corresponding 95% CIs were back-transformed for presentation in the summary tables. The back-transformed LS mean differences and corresponding 95% CIs represent the absolute fold difference in AMP $PD_{20}FEV_1$ between the treatment groups. The p-values for the pairwise treatment comparisons (F-test from ANCOVA) were also displayed. A supportive analysis was provided for the per protocol set (PPS).

The corresponding shift in the AMP dose-response curve was obtained by transforming the absolute fold difference of AMP $PD_{20}FEV_1$ between the treatment groups together with the corresponding 95% CIs using a base-2 logarithmic (log2) transformation. This reflects AMP $PD_{20}FEV_1$ doubling doses.

Descriptive statistics were provided for the AMP $PD_{20}FEV_1$ values at each time point, and for the change in AMP $PD_{20}FEV_1$ and change in AMP $PD_{20}FEV_1$ doubling doses from baseline to end of treatment by treatment group.

The secondary efficacy variables, percentage of eosinophils in induced sputum and eNO concentration, were analysed analogously using ANCOVA adjusting for treatment, baseline value and treatment period as fixed effects and centre as a random effect. Descriptive statistics were also provided. The analyses were performed primarily on the FAS, and supportively on the PPS.

The other efficacy variables, i.e. lung function parameters, daily PEFR, asthma symptom scores, sleep disturbance scores, asthma exacerbations, discontinuations due to lack of efficacy, rescue medication use, and compliance with study medication, were analysed using descriptive statistics for the FAS.

Safety variables, i.e. AEs, laboratory values, vital signs, and ECG data, were analysed using descriptive statistics for the safety set (SS).

Summary of Results:

Baseline Characteristics:

The median age of the subjects included in the SS ranged from 39.0 years in the FlutiForm low dose and placebo groups to 42.0 years in the FlutiForm high dose group. Approximately half the subjects were male in each FlutiForm dose group but almost two thirds of subjects were male in the placebo group. The vast majority of subjects were Caucasian in all analysis groups. There were no relevant differences between the groups regarding height, weight or BMI.

Baseline asthma characteristics these were generally comparable between treatment groups, except for AMP PD_{20} FEV1. Subjects treated with placebo had notably higher mean baseline AMP PD_{20} values, approximately 1 doubling dose higher than for subjects treated with FlutiForm and indicative of slightly lesser AHR in the former group.

Asthma Characteristics at Baseline - FAS

	FlutiForm high dose	FlutiForm low dose	Placebo	Overall
	N eval. = 36	N eval. = 32	N eval. = 32	N eval. = 55
FEV_1 % predicted [%]				
n	36	32	32	55
mean (SD)	88.93 (14.05)	87.21 (11.73)	87.96 (14.89)	89.03 (13.31)
median	88.09	90.04	88.09	89.49
Range	64.1-121.8	62.0-111.2	58.6-119.3	65.6-119.3
<80% [n (%)]	8 (22.2)	10 (31.3)	11 (34.4)	14 (25.5)
≥80□% [n (%)]	28 (77.8)	22 (68.8)	21 (65.6)	41 (74.5)
Exhaled nitric oxide [ppb]				
n	36	31	32	54
mean (SD)	36.6 (30.7)	46.5 (45.9)	44.5 (37.0)	41.3 (31.8)
median	26.5	33.0	38.5	33.5
Range	11-172	9-238	6-182	9-182
<25 [n (%)]	15 (41.7)	11 (35.5)	11 (34.4)	20 (37.0)
25 - <50 [n (%)]	17 (47.2)	13 (41.9)	12 (37.5)	22 (40.7)
≥50 [n (%)]	4 (11.1)	7 (22.6)	9 (28.1)	12 (22.2)
Eosinophils in induced sputum [%]				
n	30	28	25	49
mean (SD)	4.8 (4.4)	4.7 (4.0)	3.5 (3.6)	4.2 (3.7)
median	2.5	3.5	2.0	2.0
Range	0-16	0-13	0-11	0-13
≤2% [n (%)]	15 (50.0)	13 (46.4)	15 (60.0)	25 (51.0)
>2% [n (%)]	15 (50.0)	15 (53.6)	10 (40.0)	24 (49.0)
AMP PD_{20} FEV_1 [mg]				
n	36	31	32	-
geometric mean	7.90	6.64	15.34	-
95% CI	4.77, 13.08	3.86, 11.42	9.99, 23.56	-
Median	8.82	8.41	19.90	-
Range	0.4, 98.2[1]	0.5, 58.7	0.8, 59.8	-

AMP PD_{20} FEV_1 = provocative dose of adenosine 5'-monophosphate producing a 20% decline in FEV_1, FAS = full analysis set, FEV_1 = forced expiratory volume in the first second, N eval. = number of subjects evaluable in treatment group, n = number of subjects, ppb = parts per billion, SD = standard deviation

[1] Please note: This value above the pre-defined limit of 60 mg refers to a subject score at Day 1 of period 2 (Visit 5), whereas the respective inclusion criterion was required only at Visit 2.

Efficacy Results:

Primary endpoint: Change in AMP PD_{20} FEV_1 from baseline to end of treatment (Day 1 to Day 28).

	N	N eval.	n	LS mean fold change[1]	95% CI
FlutiForm high dose	39	36	34	4.9	2.9, 8.3
FlutiForm low dose	37	32	31	3.9	2.3, 6.7
Placebo	34	32	31	1.1	0.6, 1.9

Absolute fold difference[2]

	LS mean fold difference	95% CI[3]	p-value[4]
FlutiForm high dose/low dose	1.3	0.7, 2.4	0.4891
FlutiForm high dose/placebo	4.4	2.2, 8.5	<0.0001
FlutiForm low dose/placebo	3.5	1.7, 7.0	0.0006

Doubling doses[5]

	LS mean fold difference	95% CI[3]
FlutiForm high dose/low dose	0.3	-0.6, 1.3
FlutiForm high dose/placebo	2.1	1.2, 3.1
FlutiForm low dose/placebo	1.8	0.8, 2.8

AMP PD_{20} FEV_1 = provocative dose of adenosine 5'-monophosphate producing a 20% decline in FEV_1, ANCOVA = analysis of covariance, CI = confidence interval, FAS = full analysis set, FEV_1 = forced expiratory flow in 1st second, LS mean = least square means (ANCOVA), N = number of subjects randomised to treatment group, N eval. = number of subjects evaluable in treatment group, n = number of subjects with data available

[1] LS mean from an ANCOVA with treatment, treatment period and baseline AMP PD_{20} as fixed effects and centre as a random effect. AMP PD_{20} FEV_1 data were naturally log transformed for analysis and results were back transformed for presentation in table.

[2] The absolute fold difference in AMP PD_{20} FEV_1 between 2 treatment groups is the ratio of the treatment means which is yielded after backtransformation of the difference estimator from the ANCOVA.

[3] 95% CI for LS mean difference.

[4] 2-sided p-value from ANCOVA F-test for pairwise treatment comparison.

[5] Results yielded after $\log_2$ transformation of the absolute fold difference and the respective confidence limits.

Source: Table 14.2.1.1.1

In the FlutiForm high and low dose groups there were 4.9-fold and 3.9-fold geometric mean increases in AMP PD_{20} from baseline while AMP PD_{20} remained essentially unchanged at Day 28 in the placebo group. The LS mean absolute fold difference and doubling dose difference between FlutiForm high and low dose were 1.3 (95% CI: 0.7, 2.4; p = 0.4891) and 0.3 (95% CI: -0.6, 1.3), respectively. Between-FlutiForm group differences were not statistically significant. Both FlutiForm doses were superior to placebo.

Inferential analysis of two further endpoints, the change in percentage sputum eosinophils and the change in eNO, was also performed.

Key secondary endpoints: Change in percent sputum eosinophils and change in exhaled nitric oxide from baseline to end of treatment (Day 1 to Day 28).

Percentage of Eosinophils in Induced Sputum: Change from Baseline to End of Treatment - FAS

	N	N eval.	n	LS mean[1]	95% CI
FlutiForm high dose	39	36	25	-0.9	-2.1, 0.3
FlutiForm low dose	37	32	26	-0.5	-1.7, 0.7
Placebo	34	32	20	-0.2	-1.6, 1.1

	LS mean difference	95% CI[2]	p-value[3]
FlutiForm high dose - low dose	-0.4	-2.0, 1.3	0.6655
FlutiForm high dose - placebo	-0.6	-2.4, 1.2	0.4769
FlutiForm low dose - placebo	-0.3	-2.1, 1.5	0.7561

ANCOVA = analysis of covariance, CI = confidence interval, FAS = full analysis set, LS mean = least square means (ANCOVA), N = number of subjects randomised to treatment group, N eval. = number of subjects evaluable in treatment group, n = number of subjects with data available
[1] LS Mean from an ANCOVA with treatment, baseline percentage of eosinophils in induced sputum and treatment period as fixed effects and centre as a random effect.
[2] 95% CI for LS mean difference.
[3] p-value from ANCOVA F-test for pairwise treatment comparison.
Source: Table 14.2.2.1.1

Exhaled Nitric Oxide [ppb]: Data Analysis - Change from Baseline to End of Treatment - FAS

	N	N eval.	n	LS mean[1]	95% CI
FlutiForm high dose	39	36	36	-18.1	-24.3, -11.8
FlutiForm low dose	37	32	31	-21.3	-28.0, -14.7
Placebo	34	32	32	-5.5	-12.0, 1.1

	LS mean difference	95% CI[2]	p-value[3]
FlutiForm high dose - low dose	3.3	-5.8, 12.4	0.4770
FlutiForm high dose - placebo	-12.6	-21.6, -3.6	0.0067
FlutiForm low dose - placebo	-15.9	-25.2, -6.6	0.0010

ANCOVA = analysis of covariance, CI = confidence interval, FAS = full analysis set, LS mean = least square means (ANCOVA), N = number of subjects randomised to treatment group, N eval. = number of subjects evaluable in treatment group, n = number of subjects with data available, ppb = parts per billion
[1] LS Mean from an ANCOVA with treatment, baseline exhaled nitric oxide and treatment period as fixed effects and centre as a random effect.
[2] 95% CI for LS mean difference.
[3] p-value from ANCOVA F-test for pairwise treatment comparison.
Source: Table 14.2.3.1.1

The percentage of eosinophils in induced sputum decreased in all 3 treatment groups from baseline to end of treatment although the changes were non-significant. The

decrease in sputum eosinophils exhibited a dose-dependent pattern. However, none of the between-treatment differences were statistically significant.

In the FlutiForm dose groups the eNO concentrations decreased to a similar extent (approximately 20 ppb), i.e., no dose dependency was evident between the 2 FlutiForm doses. The eNO concentration also decreased numerically in the placebo group although the decrease was non-significant. Both FlutiForm dose groups elicited significantly greater reductions in eNO compared to placebo.

For the remaining efficacy variables only descriptive statistics were summarised and are presented below.

Secondary Endpoints (continued)		FlutiForm high dose	FlutiForm low dose	Placebo
Change from baseline (Day1) to end treatment (Day 28)				
FEV_1 [L]	Mean (SD)	0.293 (0.343)	0.274 (0. 270)	0.018 (0.248)
PEFR [L/min]	Mean (SD)	53.47 (66.65)	52.52 (55.89)	-3.6 (60.37)
FVC [L]	Mean (SD)	0.107 (0.297)	0.142 (0.223)	-0.006 (0.248)
FEF_{75} [L/sec]	Mean (SD)	0.215 (0.300)	0.150 (0.334)	0.029 (0.204)
FEF_{50} [L/sec]	Mean (SD)	0.773 (0.756)	0.586 (0.620)	0.018 (0.450)
FEF_{25} [L/sec]	Mean (SD)	1.165 (1.013)	0.923 (1.161)	-0.031 (0.765)
FEF_{25-75} [L/sec]	Mean (SD)	0.549 (0.555)	0.402 (0.624)	0.051 (0.370)
Morning daily PEFR [L/min]	Mean (SD)	58.11 (59.17)	42.19 (40.99)	-17.6 (57.90)
Evening daily PEFR [L/min]	Mean (SD)	52.72 (51.55)	42.36 (41.32)	-18.03 (54.58)
Asthma symptom scores	Mean (SD)	-0.43 (0.71)	-0.25 (0.42)	-0.10 (0.25)
Sleep disturbance scores	Mean (SD)	-0.27 (0.58)	-0.19 (0.33)	-0.08 (0.28)
Percentage of rescue medication-free days	Mean (SD)	36.16 (42.16)	29.95 (34.87)	3.33 (24.51)
Severe exacerbations of asthma	n (%)	0 (0.0)	1 (3.1)	0 (0.0)
Discontinuations due to lack of efficacy	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Rescue medication: number of uses per day[1]	Mean (SD)	0.44 (0.9)	0.60 (1.0)	0.87 (1.2)
Rescue medication: percentage of study days[2]	Mean (SD)	18.9 (30.1)	23.8 (30.6)	34.8 (37.9)

FEV_1 = forced expiratory flow in 1st second, $FEF_{25, 50, 75}$ = forced expiratory flow at 25%, 50%, 75% of the volume to exhale, FEF_{25-75} = forced expiratory flow in the middle portion of expiration, FVC = forced vital capacity, SD = standard deviation.

[1] Refers to use throughout the treatment period: time between Visit 2 and Visit 4 (i.e. from day of randomisation to last dose in period 1) and the time between Visit 5 and Visit 7 (i.e. from first dose in period 2 to last dose in period 2.

[2] The percentage of study days on which rescue medication was used during the study period.

Source: Table 14.2.4.1, 14.2.4.2, 14.2.4.3, 14.2.4.4, 14.2.4.5, 14.2.4.6, 14.2.4.7, 14.2.5.1, 14.2.5.2, 14.2.6.1, 14.2.6.2, 14.2.7, 14.2.8, 14.2.9.1, 14.2.9.2,

For almost all the secondary endpoints in the table above numerically greater effects were observed with high versus low dose FlutiForm. This directional consistency supports the greater numerical effects observed with high versus low dose FlutiForm for the primary endpoint, the change in AMP PD_{20}, and for one of the two key secondary endpoints, the change in percentage sputum eosinophils, even though the study did not meet its primary objective and demonstrate a significant difference between FlutiForm doses for the change in AMP PD_{20}.

Results for the secondary endpoints above which demonstrated consistently greater effects with both FlutiForm doses than placebo also provide support for the results of the primary and key secondary endpoint analyses: The latter demonstrated significantly greater effects with both doses of FlutiForm over placebo for the change in AMP PD_{20} and eNO, and numerically greater effects compared to placebo upon the change in percentage of sputum eosinophils.

Safety Results:

In the safety set (SS), the overall percentage of subjects experiencing an AE was 23.1% in the FlutiForm high dose group, 37.5% in the FlutiForm low dose group and 32.4% of subjects in the placebo group. At system organ class and preferred term level no definitive statement regarding between-group differences can be made due to the low incidences of AEs. The profile of AEs in the FlutiForm high dose and low dose groups did not indicate any dose-response relationship. In all 3 treatment groups AEs classed as 'respiratory, thoracic and mediastinal disorders' were most common. Most AEs occurred only in individual subjects. Only dysphonia (FlutiForm low dose group), asthma (FlutiForm low dose and placebo groups) and nasopharyngitis (placebo group) were observed in 2 subjects in any given treatment arm.

The vast majority of AEs were mild or moderate in severity; severe AEs were reported for 1 subject (3.1%) in the FlutiForm low dose group (asthma, urticaria) and 1 subject in the placebo group (2.7%, asthma). No subjects in the FlutiForm high dose group experienced a severe AE.

There were no deaths and no serious AEs (SAEs) during the study.

AEs leading to withdrawal from treatment were reported for 1 subject in the FlutiForm low dose (3.1%) and 1 subject in the placebo group (2.7%). The subject in the FlutiForm low dose group was withdrawn due to severe urticaria (unlikely related to study medication) and severe exacerbation of asthma (not related). The subject in the placebo group had a moderate exacerbation of asthma that led to study discontinuation during the first treatment period. The AE was deemed not related to study medication by the investigator.

Analyses of laboratory parameters were unremarkable. Potential systemic effects of FlutiForm, based on the known safety pharmacology of both actives, were as follows:

- One subject of the FlutiFom high dose group experienced an AE of arrhythmia (mild, probably related), another subject an AE of tachycardia (mild, definitely related). Both resolved without intervention. No clinically significant ECG findings were documented in any subjects throughout the study.
- One subject in each of the FlutiForm high and low dose groups presented with markedly abnormal high glucose values at Day 28 (9.7 mmol/L and 9.4 mmol/L, respectively), which were also documented as AEs (both mild, one unlikely related, one not related). Both subjects had glucose concentrations above normal range at

screening (7.4 mmol/L and 7.1 mmol/L, respectively), the subject in the high dose group being a known diabetic at study entry.

- One subject treated with FlutiForm low dose and subsequently with FlutiForm high dose, presented with low serum potassium levels at Day 28 of both treatment periods (3.4 mmol/L in both periods) which satisfied the criterion for a markedly abnormal result. Note that the subject's screening potassium levels had been at the lower limit of normal (3.5 mmol/L). However, as the pre-specified level of a markedly abnormal potassium was attained 2 AEs of "hypokalaemia" (mild and possibly related) were documented for his subject (one in each treatment period).

There were no noteworthy findings regarding vital signs and no clinically significant ECG abnormalities in any of the treatment groups.

Overall Conclusions:

A significant difference between high (500/20 µg bid) and low dose FlutiForm (100/10 µg bid) was not observed for the primary endpoint (the change in PD_{20} AMP), hence the study did not meet its primary objective. However, there was a numerical difference in favour of high dose FlutiForm for the primary endpoint which was supported by a dose-dependent trend for the large majority (15 of 19) of secondary endpoints in the study for the overall FAS. This directional consistency suggested a dose-response relationship. Meaningful exceptions to this dose-response trend were noted only for two endpoints, the change in eNO, and the change in FVC; for discontinuations due to lack of efficacy there were no events in either group.The evidence from this trial therefore supports that of an earlier 12-week, parallel group study in severe asthma patients (FLT3503) in which the same FlutiForm doses were compared. Although the latter trial was not primarily intended to evaluate dose-response there was a trend towards greater symptomatic benefit, improved health status and a lower exacerbation rate with high dose FlutiForm. A point of difference between FLT3503 and the present study is that there was no evidence of spirometric dose-response in the former.

The failure to demonstrate a statistically significant difference between FlutiForm doses for AMP PD_{20} (and for the change in sputum eosinophils) is likely due to the incomplete block design of the study, as a result of which between-patient variability may have obscured between-treatment differences. This hypothesis is supported by the *post-hoc* analysis of 15 FlutiForm-only subjects. In this population who received both FlutiForm treatments and had available data for both treatment periods a significant dose-response for AMP PD_{20} was seen and between-dose differences for effects upon sputum eosinophils were magnified compared to the overall FAS, albeit remained non-significant. Other aspects of study design which may have limited the ability of the study to discriminate the effects of the two FlutiForm dose levels are the fact that elevated baseline levels of eNO and sputum eosinophils were not required to enter the study, and the multicentre nature of the study which introduced a further source of variability, perhaps most relevant to the more technically demanding variables assessed, i.e., AMP PD_{20}, sputum eosophils and eNO.

Compared to placebo both FlutiForm doses showed statistically and/or numerically greater effects for the primary and almost all secondary endpoints. The exception among endpoints tested inferentially was the change in sputum eosinophils for which the differences between FlutiForm and placebo were in favour of active treatment but non-significant (which may relate to aspects of study design described above). The only other exceptions were severe asthma exacerbations and discontinuations due to lack of efficacy although, given the very low event rates for these outcomes, these data are not meaningful.

The study did not reveal any safety concerns regarding administration of FlutiForm in adult subjects with mild to moderate persistent asthma, or any evidence of dose-dependent safety. The treatment was safe and well tolerated.

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