2. SYNOPSIS

Name of Company: Mundipharma Research Limited	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: FlutiForm®	Referring to Part … of the Dossier	
Name of Active Ingredient: Fluticasone propionate / formoterol fumarate	Volume: Page:	

Title of the Study: A double blind, double dummy, randomised, multicentre, two arm parallel group study to assess the efficacy and safety of FlutiForm® pMDI 125/5 µg (2 puffs bid) vs Symbicort® Turbohaler® 200/6 µg (2 puffs bid) in adolescent and adult subjects with moderate to severe persistent, reversible asthma.

Investigators: Prof. Anna Bodzenta-Lukaszyk, Bialystok, Poland, et al. A total of 26 centres recruited subjects: eight in Poland, seven in Bulgaria, six in Hungary, three in India and two in Romania.

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
16 April 2010 to 30 October 2010	Completed	Phase 3

Objectives: The primary objective of this study was to show non-inferiority in the efficacy of FlutiForm pressurised metered dose inhaler (pMDI) 125/5 µg (two puffs twice daily [bid]) versus Symbicort Turbohaler 200/6 µg (two puffs bid), based on the mean change in the morning pre-dose value of forced expiratory volume in the first second (FEV_1) from baseline (end of run-in period) to the end of the 12 week treatment period.

Additional efficacy assessments included subject-centred outcome assessments such as asthma quality of life questionnaire (AQLQ(S) ≥ 12 years), subject's assessment of study medication, amount of rescue medication use, asthma symptom scores, sleep disturbance due to asthma, discontinuations due to lack of efficacy, compliance with study medication use and asthma exacerbations (requiring oral/parenteral steroid use or medical intervention). Post-dose FEV_1, 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), vital signs, laboratory tests (including serum glucose and serum potassium), and 12-lead electrocardiograms (ECGs).

Methodology: This was a double-blind, double-dummy, two arm parallel group study. It consisted of a screening period, a 2 week run-in period, and a 12 week treatment period.

The screening period was approximately 7 days in duration, depending on the availability of laboratory results (Visit 1 to Visit 2). The routine laboratory results had to be reviewed and documented by the Investigator as not clinically significant before the subject could proceed with the run-in period.

The run-in period (Visit 2 to Visit 3) was of 14 (±3) days duration, but could have been extended to a maximum of 28 days duration if a subject failed to meet the entry criteria following the initial run-in period. During the run-in period, all subjects took fluticasone 50 µg (two puffs bid).

At Visit 3, subjects who had used rescue medication for at least 3 days and had had at least one night with sleep disturbance (i.e., sleep disturbance score of ≥ 1) OR had used rescue medication for at least 3 days and had had at least 3 days with asthma symptoms (i.e., a symptom score of ≥ 1) during the last 7 days of the run-in period and met the inclusion/exclusion criteria were randomised to receive FlutiForm pMDI 125/5 µg (2 puffs bid) or Symbicort Turbohaler 200/6 µg (2 puffs bid) in a 1:1 ratio, according to a random allocation schedule. Two different strata for the percentage of predicted normal FEV_1 values assessed at Visit 1 or Visit 2 (screening) were used (Stratum 1: FEV_1 ≥ 50 to ≤ 60% predicted, Stratum 2: FEV_1 > 60 to ≤ 80% predicted) to balance treatment allocation in each stratum. The FEV_1 predicted value used was from the screening period (Visit 1 or Visit 2) where both the FEV_1 and reversibility criteria were met in the same manoeuvre. Subjects received study medication for 12 weeks during the treatment period, with visits at 2 weeks (Visit 4), 6 weeks (Visit 5) and 12 weeks (end of study, Visit 6) after the start of treatment. During the treatment period the dose level of study medication remained the same. If the subject's asthma was not controlled with study medication and use of salbutamol rescue medication, they were withdrawn from the study.

Throughout the study, subjects were allowed to take salbutamol (two puffs, 100 µg per puff), on up to four occasions per day as rescue medication.

Subjects were followed up by telephone 14 days after completion or discontinuation of the study for reporting of ongoing AEs and any new AEs that may have occurred.

Number of Subjects: It was planned to randomise a total of 260 subjects to treatment (130 per treatment group), to ensure that 216 per protocol subjects were achieved (108 subjects per treatment group). A total of 334 subjects provided written informed consent and were screened, 279 subjects were randomised and treated (FlutiForm: 140; Symbicort: 139), and 261 subjects completed the study (FlutiForm: 133 [95.0%]; Symbicort: 128 [92.1%]). In the FlutiForm group, six subjects discontinued due to lack of therapeutic effect and one subject discontinued due to AEs. In the Symbicort group, four subjects discontinued due to lack of therapeutic effect, three subjects discontinued due to AEs, three subjects discontinued for administrative reasons, and one subject discontinued due to subject's choice. All 279 randomised and treated subjects were included in the full analysis set and safety set; 246 subjects (126 in the FlutiForm group and 120 in the Symbicort group) were included in the per-protocol set.

Indication and Criteria for Inclusion: Male or female subjects, aged ≥ 12 years, with moderate to severe persistent, reversible asthma for at least 6 months prior to Visit 1, characterised by treatment with an inhaled corticosteroid (ICS) at a dose of 250-1000 µg fluticasone or equivalent, or an ICS at a dose of 200-500 µg fluticasone or equivalent in combination with a long acting β_2-agonist (LABA) were screened for entry into the study. Potential subjects had to have ≥ 50% to ≤ 80% predicted FEV_1 (Quanjer et al., 1993 [adults], and 1995 [adolescents]) following appropriate withholding of asthma medications and show ≥ 15% reversibility of FEV_1 after salbutamol (four puffs, 100 µg per puff) inhalation at Visit 1 or Visit 2.

To be eligible for randomisation at Visit 3, subjects had to have used rescue medication for at least 3 days and had at least one night with sleep disturbance (i.e., sleep disturbance score of ≥ 1) OR had to have used rescue medication for at least 3 days and had at least 3 days with asthma symptoms (i.e., a symptom score of ≥ 1) during the last 7 days of the run-in period.

Pre-randomisation Treatment, Dose, and Mode of Administration:

Run-in Period

Flixotide (fluticasone) pMDI 50 µg, two puffs inhaled every 12 hours (batch number: PN3527).

Test Treatment, Dose, and Mode of Administration:

Treatment Period

FlutiForm (fluticasone/formoterol) pMDI 125/5 µg (batch numbers: PN3523 and PN3578).

Placebo (dummy inhaler) for Symbicort Turbohaler (budesonide/formoterol) 200/6 µg (batch number: PN3526).

Reference Treatment, Dose, and Mode of Administration:

Treatment Period

Symbicort Turbohaler (budesonide/formoterol) 200/6 µg (batch number: PN3525).

Placebo (dummy inhaler) for FlutiForm pMDI (fluticasone/formoterol) (batch numbers: PN3524 and PN3579).

Rescue Medication, Dose, and Mode of Administration:

Salbutamol (Ventolin®) 100 µg. Batch number: PN3528.

Duration of Treatment: The total expected duration of a study subject's participation was 17 – 19 weeks as follows:

Screening period: 7 days

Run-in period: 14 days (up to a maximum of 28 days)

Treatment period: 12 weeks

Follow-up period: 14 days

Treatment Schedule:

During the screening period, all subjects continued on their usual asthma medication.

During the run-in period, all subjects stopped their pre-study asthma medication and took fluticasone 50 µg (two puffs bid).

During the treatment period, subjects were dosed for 12 weeks as follows:

FlutiForm treatment group: FlutiForm (fluticasone/formoterol) pMDI 125/5 µg two puffs inhaled every 12 hours **plus** Placebo (dummy inhaler) for Symbicort Turbohaler (budesonide/ formoterol) 200/6 µg two puffs inhaled every 12 hours.

Subjects used the inhalers in the following order:

1) FlutiForm® (125/5 µg)

2) Symbicort® Turbohaler® (placebo)

Symbicort treatment group: Symbicort Turbohaler (budesonide/formoterol) 200/6 µg two puffs inhaled every 12 hours **plus** Placebo (dummy inhaler) for FlutiForm pMDI (fluticasone/ formoterol) two puffs inhaled every 12 hours.

Subjects used the inhalers in the following order:

1) FlutiForm (placebo)

2) Symbicort Turbohaler 200/6 µg

Salbutamol 100 µg (two puffs on up to four occasions per day) was used as rescue medication throughout the run-in and treatment periods.

Criteria for Evaluation:

Efficacy assessments:

- FEV_1 morning pre-dose
- FEV_1 2 hours (± 15 min) morning post-dose
- PEFR recorded daily in the subject diaries
- Other lung function parameters such as forced vital capacity (FVC), forced expiratory flow (FEF) at 25, 50 and 75% of volume to exhale (FEF_{25}, FEF_{50}, FEF_{75}) and FEF_{25-75}.
- Asthma symptom scores
- Sleep disturbance due to asthma
- Study medication use (yes/no each day, recorded in electronic diary)
- Rescue medication use
- Asthma exacerbations (requiring oral/parenteral steroid use, medical intervention)
- Subject's assessment of study medication
- Discontinuations due to lack of efficacy
- Study medication compliance
- Asthma quality of life questionnaire (AQLQ(S) ≥ 12 years)

All pulmonary function parameters were captured using a centralised spirometry system.

Safety Assessments:

- Clinical laboratory test results including serum potassium and serum glucose
- AEs (learned through spontaneous reports)
- Vital signs
- 12-lead ECGs and heart rate morning pre-dose.

Statistical Methods:

Analysis Populations:

The **Enrolled Set** was defined as all subjects who provided informed consent for the study.

The **Safety Set** was defined as all randomised subjects who received study treatment and had at least one post-baseline safety assessment.

The **Full Analysis Set (FAS)** was defined as all randomised subjects who received study treatment and had at least one post-baseline primary efficacy (FEV_1) assessment.

The **Per Protocol Set (PPS)** was defined as all FAS subjects without any major protocol violations affecting the primary efficacy endpoint.

Efficacy Analyses:

Primary endpoint: The primary endpoint was the change in morning pre-dose FEV_1 values from baseline (Day 0, Visit 3) to the end of the 12 week treatment period (Day 84, Visit 6). The main objective of this study was to show non-inferiority of FlutiForm to Symbicort with respect to the mean change in morning pre-dose FEV_1 values from baseline to the end of the 12 week treatment period.

The null hypothesis was that the FlutiForm treatment group would be inferior to the Symbicort treatment group and the alternative hypothesis was that the FlutiForm treatment group would not be inferior to the Symbicort treatment group.

Pre-dose FEV_1 values recorded at each visit, and change from baseline to each visit were summarised by treatment group as continuous data for both the PPS and FAS.

The change in morning pre-dose FEV_1 values from baseline to Week 12 was analysed using an analysis of covariance (ANCOVA) with treatment as a factor, baseline morning pre-dose FEV_1 and asthma severity as covariates, and centre as a random effect. The statistical model was used to calculate the treatment difference (FlutiForm - Symbicort) and 95% confidence interval (CI). Non-inferiority was concluded if the lower limit of the 95% CI was greater than or equal to -0.2 L. A p-value for a non-inferiority test (corresponding to a null hypothesis that the difference in treatment means was -0.2 L) was also provided.

The main analysis was performed on the PPS. As a supportive analysis, the analysis was also performed on the FAS. A last observation carried forward (LOCF) approach was taken for the FAS.

The mean (95% CI) morning pre-dose FEV_1 values recorded at each visit were presented graphically for the PPS. In addition, the mean change from baseline to each visit were presented graphically for the PPS.

Secondary endpoints: The change from baseline to Week 12 post-dose FEV_1 values and discontinuations due to lack of efficacy were summarised and analysed for the PPS, with a supportive analysis performed on the FAS (a LOCF approach was taken for the FAS). All other secondary efficacy endpoints were analysed and summarised by treatment group for subjects in the FAS.

Change from baseline to Week 12 post-dose FEV_1 values, asthma symptom scores, symptom free days, sleep disturbance, awakening free nights, rescue medication free days, asthma control days, asthma quality of life questionnaire and peak flow were analysed analogously using ANCOVA. The difference in percentages and 95% CI were calculated for discontinuations due to lack of efficacy. Severe asthma exacerbations were analysed using Fisher's Exact Test. Study rescue medication use was analysed using the Hodges-Lehman method and a Wilcoxon Rank Sum Test. Subject's assessment of study medication was analysed using a proportional odds model. Other lung function parameters and compliance were summarised descriptively.

Safety Analyses:

Safety data were summarised descriptively for subjects in the Safety Set. Safety data that were evaluated included treatment exposure, AEs, laboratory values, vital signs, and ECGs.

Sample Size Rationale:

The sample size was based on the difference between the treatment groups in change from baseline to Week 12 in the morning pre-dose FEV_1 values analysed using an ANCOVA. Assuming an observed treatment difference of 0 (FlutiForm - Symbicort), a standard deviation of 0.45 L, a non-inferiority bound of -0.2 L, 90% power, and a two-sided alpha of 0.05, this could be achieved with 108 subjects per group in the PPS.

It was planned to randomise a total of 260 subjects. This was assuming that approximately 15% would not be part of the PPS. The sample size was calculated using the two-group t-test of equal means (equal variances) in nQuery Advisor 7.0.

Results:

The study population comprised 90 male and 189 female subjects: the ratio of female to male subjects was slightly higher for the Symbicort group (27%:73%) than the FlutiForm group (37%:63%). However, no effect of gender was observed in an ad hoc analysis of pre- and post-dose FEV_1 values at Day 84, performed for male and female subjects separately. Subjects had a mean age of 49 years (range: 14 to 79 years) and the majority (96%) were Caucasian. The median duration of asthma was 7.0 years (range: 1 to 45 years) for the FlutiForm group and 8.0 years (range: 1 to 40 years) for the Symbicort group. All subjects had an FEV_1 $\geq$ 50% to $\leq$ 80% predicted, and reversibility of $\geq$ 15% in FEV_1 at screening. At study entry, 98% of subjects were using an ICS and 90% of subjects were using a LABA.

Study medication compliance was high, with 96% of subjects in each treatment group being at least 75% compliant with study medication.

Efficacy:

Primary Endpoint

The primary efficacy analysis was performed on the PPS. The least square (LS) mean change in morning pre-dose FEV_1 from Day 0 to Day 84 (Week 12) was 0.164 L in the FlutiForm group and 0.207 L in the Symbicort group. The LS mean treatment difference (FlutiForm – Symbicort) was -0.044 L (95% CIs: -0.130, 0.043). Non-inferiority of FlutiForm to Symbicort was demonstrated as the lower limit of the 95% CIs for the treatment difference exceeded the pre-defined non-inferiority acceptance limit of -0.2 L ($p<0.001$). The analysis of the FAS confirmed this result (LS mean treatment difference: -0.030 L, 95% CIs: -0.115, 0.054 L, $p<0.001$). Non-inferiority of FlutiForm to Symbicort was also shown for the change from baseline to Day 14 and Day 42 for both the PPS and FAS in an ad hoc analysis.

Secondary Endpoints

The key secondary endpoint change in FEV_1 from morning pre-dose on Day 0 to 2 hours post-morning dose on Day 84 was subjected to the same non-inferiority analysis as for the primary endpoint in the PPS. The LS mean change in FEV_1 from morning pre-dose on Day 0 to 2 hours post-morning dose on Day 84 was 0.319 L in the FlutiForm group and 0.406 L in the Symbicort group. The LS mean treatment difference (FlutiForm – Symbicort) was -0.087 L (95% CIs: -0.173 to -0.001 L). Non-inferiority of FlutiForm to Symbicort was concluded as the lower limit of the 95% CI for the treatment difference exceeded the pre-defined non-inferiority acceptance limit of -0.2 L ($p=0.010$). The analysis of the FAS confirmed this result (LS mean treatment difference: -0.087 L; 95% CIs: -0.172, -0.001 L; $p=0.010$). However, the 95% CIs for the treatment difference did not encompass zero (upper 95% CI: -0.001 L for both the PPS and FAS), favouring Symbicort over FlutiForm in terms of the change in FEV_1 from morning pre-dose on Day 0 to 2 hours post-morning dose on Day 84. Ad hoc analyses were therefore performed on the Day 14 and Day 42 data using the same analysis method as for the Day 84 analysis. The Day 14 and Day 42 data showed treatment differences of -0.018 L (95% CIs: -0.093, 0.057 L) and -0.038 L (95% CIs: -0.120, 0.044 L), respectively, demonstrating substantially lesser point estimate differences between treatments than at Day 84 with CIs for the treatment differences clearly suggesting that there are no clinically relevant differences between treatments.

Non-inferiority of FlutiForm compared to Symbicort was shown for the secondary endpoint, discontinuations due to lack of efficacy. In the PPS, six subjects (4.8%) in the FlutiForm group and two subjects (1.7%) in the Symbicort group discontinued during the treatment period due to lack of efficacy, giving a treatment difference (FlutiForm – Symbicort) of 3.1%. The upper limit of the 95% CI for the treatment difference was below the pre-defined non-inferiority limit of 10% (95% CIs: -1.3, 7.5%). The supportive analysis of the FAS confirmed this result (treatment difference: 1.4%; 95% CIs: -2.9, 5.8%).

Treatment with FlutiForm was comparable to treatment with Symbicort for the remaining secondary efficacy endpoints with statistical tests performed on the FAS.

Morning and evening pre-dose peak flow rates were obtained from subject diaries for the 7 days prior to each visit. The LS mean morning peak flow rates increased by 33.1 L/min in the FlutiForm group and 26.9 L/min in the Symbicort group from Day 0 to Day 84. The LS mean treatment difference was 6.2 L/min (95% CIs: -0.70, 19.5 L/min). The LS mean evening peak flow rates increased by 25.8 L/min in the FlutiForm group and 23.8 L/min in the Symbicort group from Day 0 to Day 84. The LS mean treatment difference was 2.0 L/min (95% CIs: -10.3, 14.3 L/min).

There was a similar decrease (i.e., improvement) in mean asthma symptom scores from Day 0 to Day 84 in both treatment groups. The LS mean change was -0.86 in the FlutiForm group and -0.85 in the Symbicort group, giving a LS mean treatment difference of -0.01 (95% CIs: -0.13, 0.12). The percentage of symptom-free days increased by a LS mean of 55.55% in the FlutiForm group and 56.10% in the Symbicort group from Day 0 to Day 84. The LS mean treatment difference for the change in percentage of symptom-free days was -0.54% (95% CIs: -8.36, 7.27%).

The mean sleep disturbance scores also decreased (i.e., improved) over the course of the study in both treatment groups. The LS mean change from Day 0 to Day 84 was -0.61 in the FlutiForm group and -0.65 in the Symbicort group. There was virtually no difference between treatments (LS mean treatment difference: 0.03; 95% CIs: -0.04, 0.11). The percentage of awakening-free nights increased by a LS mean of 43.66% in the FlutiForm group and 48.74% in the Symbicort group from Day 0 to Day 84. The LS mean treatment difference for the change in percentage of awakening-free nights was -5.08% (95% CIs: -11.15, 0.99%).

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 to Day 84, the LS mean percentage of asthma control days increased by 46.75% in the FlutiForm group and 49.02% in the Symbicort group (LS mean treatment difference: -2.27%; 95% CIs: -10.29, 5.75%).

One subject (0.7%) in the FlutiForm group and two subjects (1.4%) in the Symbicort group had an exacerbation of asthma requiring treatment with oral or parenteral steroids or medical intervention. There was no significant difference between the treatment groups in the number of exacerbations of asthma (p=0.6223, Fisher's exact test).

The median percentage of study days on which salbutamol rescue medication was used was similar for the FlutiForm and Symbicort groups (median: 35.50% and 30.20%, respectively; treatment difference: 0.40; 95% CIs: -4.70 to 6.60%, Hodges-Lehmann method). The median number of uses of rescue medication per day was very low in both treatment groups (0.325 for the FlutiForm group and 0.270 for the Symbicort group). There was no difference between the treatment groups in the median number of uses of rescue medication per day (treatment difference: 0.000, 95% CIs: -0.070, 0.080, Hodges-Lehmann method). The percentage of rescue medication-free days increased by a LS mean of 52.76% in the FlutiForm group and 50.18% in the Symbicort group from Day 0 to Day 84 (LS mean treatment difference: 2.58%; 95% CIs: -5.09, 10.25%).

The odds ratio for the subject's overall assessment of study medication at study completion was 0.750 (95% CIs: 0.476, 1.183), indicating no difference between the treatment groups since the 95% CI for the odds ratio encompassed 1. Subject's overall assessment of study medication at Day 84 was 'very good' or 'good' for 90% of subjects in the FlutiForm group and 88% of subjects in the Symbicort group.

The AQLQ overall score increased by a LS mean of 0.8 units in both treatment groups from Day 0 to Day 84 (LS mean treatment difference: 0.0; 95% CIs: -0.01 to 0.2).

Increases were also observed in both treatment groups for arithmetic mean 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. Numerically larger changes from Day 0 to Day 84 were observed in the Symbicort group compared with the FlutiForm group for FVC and all FEF parameters; however, no statistical tests were performed on outcomes for these variables.

Safety: The median duration of treatment was 84.0 days in both treatment groups, which was equivalent to the protocol-planned duration of treatment (i.e., 12 weeks). The duration of treatment ranged from 14 to 101 days for subjects in the FlutiForm group and 7 to 92 days for subjects in the Symbicort group.

Adverse events were reported by a similar number of subjects in the FlutiForm group (29 subjects [20.7%]) and the Symbicort group (26 subjects [18.7%]). Adverse events in the 'infections and infestations' System Organ Class were the most common in both treatment groups. At the preferred term level, the most common AEs (reported by ≥ 2% of subjects in either treatment group) were headache (FlutiForm: 2.9%, Symbicort: 5.8%), pharyngitis (FlutiForm: 2.1%; Symbicort: 3.6%), viral infection (FlutiForm: 2.9%; Symbicort: 2.2%), bronchitis (FlutiForm: 2.9%; Symbicort: 1.4%) and dysphonia (FlutiForm: 3.6%; Symbicort: 0%). The absence of any reported cases of dysphonia in the Symbicort group is somewhat surprising given that dysphonia is plausibly related to oropharyngeal drug deposition, as is pharyngitis that in contrast affected 3.6% of subjects in the Symbicort group. Hoarseness (a type of dysphonia) is listed as an AE in the Symbicort Summary of Product Characteristics. Furthermore, no difference in the occurrence of local AEs (such as dysphonia) has previously been reported between the corticosteroids in the Symbicort and FlutiForm formulations (budesonide and fluticasone, respectively), whilst oropharyngeal drug deposition resulting from the use of a Turbohaler (i.e., the Symbicort device) and a pMDI (i.e., the FlutiForm device) is quite similar. Headache was reported for twice as many subjects in the Symbicort group (5.8%) compared with the FlutiForm group (2.9%), but this is not considered to be clinically relevant since the incidence was low in both treatment groups and it is a common AE that can be expected for both treatments. There were no other notable differences between the treatment groups in the incidence of AEs.

The majority of AEs were mild or moderate in nature, with only one severe AE reported in each treatment group (asthma [exacerbation] in the FlutiForm group and acute sinusitis in the Symbicort group). An additional subject in the Symbicort group had an AE of asthma for which the verbatim term was 'severe asthma exacerbation' but that the Investigator considered was of moderate severity. The incidence of treatment-related AEs was low and similar for both treatment groups (FlutiForm: 6.4%, Symbicort: 5.0%). The only treatment-related AEs reported for more than one subject in either treatment group were dysphonia (reported for five subjects [3.6%] in the FlutiForm group), headache (reported for one subject [0.7%] in the FlutiForm group and two subjects [1.4%] in the Symbicort group) and blood glucose increased (reported for two subjects [1.4%] in the Symbicort group).

One subject died during the run-in period due to suspected myocardial infarction or pulmonary embolism, but the death was not considered to be related to study medication by the Investigator. Three subjects reported SAEs: rib fracture in the FlutiForm group and acute sinusitis and asthma (exacerbation) in the Symbicort group. None of the SAEs were considered to be related to study medication by the Investigator. The SAEs of acute sinusitis and asthma (exacerbation) in the Symbicort group led to discontinuation of study medication. Two further subjects (one in each treatment group) discontinued due to asthma (exacerbation). All AEs leading to discontinuation resolved.

Analyses of haematology, biochemistry, urinalysis and vital signs parameters did not reveal any clinically notable changes over the course of the study in either treatment group. Systemic effects of long-acting β_2-agonists (LABAs) in terms of reduction in serum potassium or cardiac arrhythmias were not observed. Although several out of range values were observed for serum cholesterol, glucose and triclycerides, with mean values for these parameters around the upper limit of the reference range, there were no notable changes in mean values or the number of out of range values from baseline (Day 0) to end of study (Day 84). Two AEs associated with laboratory parameters were reported (both blood glucose increased in the Symbicort group). It should be noted that blood samples for laboratory safety evaluation did not have to be drawn under lasting conditions, which is relevant to the glucose, cholesterol and triglyceride results. There were no clinically significant ECG findings during the study.

Conclusions:

This study demonstrated similar efficacy of FlutiForm (fluticasone/formoterol) to Symbicort (budesonide/formoterol). Non-inferiority was formally demonstrated, per the non-inferiority margin defined *a priori*, in terms of the primary endpoint: mean change in morning pre-dose FEV_1 from baseline to Week 12. The primary efficacy endpoint result was supported by similar efficacy results for FlutiForm and Symbicort for multiple secondary endpoints: discontinuations due to lack of efficacy, diary peak flow (morning and evening), asthma exacerbations, rescue medication use, asthma symptom scores, sleep disturbances scores, asthma control days and AQLQ results were very similar between treatments. Regarding the change from baseline pre-dose FEV_1 to 2 hours post-dose FEV_1 at Week 12, non-inferiority between treatments was formally demonstrated in that the lower limit of the 95% confidence interval for Flutiform - Symbicort was within the 0.2 L margin specified *a priori*. However, the confidence interval did not include zero and thereby favoured Symbicort. It is plausible that the requisite differences in device usage technique may have contributed to the unexpected 2 hour FEV_1 result at Week 12, and this study suggests the need for particularly rigorous and repeated device use instructions in Orally Inhaled Product studies where two or more very different device inhaler devices are used by the same subjects. Reassuringly, post-hoc analysis performed to investigate this result demonstrated no differences between treatments for the 2 hour endpoint at Week 6, i.e., when treatment effects would be expected to be maximal.

With regards to safety, the profile of FlutiForm was consistent with the safety profiles of its individual components, fluticasone and formoterol. Treatment with FlutiForm was safe, well tolerated, and safety data were similar to those observed in the Symbicort treatment arm.

Date of the Report: 6 July 2011