Clinical Trial Study Synopsis: SKY2028-3-003

Disclaimer: *Information on this website is not intended to substitute for medical advice and / or treatment from a qualified healthcare professional. These studies may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups. Individual study results may not be representative of the complete results obtained from all studies on flutiform. Before prescribing flutiform, healthcare professionals should refer to the prescribing information approved in their country.*

Skyepharma AG	
Name of Study Drug: Flutiform®	
Name of Active Ingredient: Fluticasone propionate and formoterol fumarate	
Title of Study: Long-term Open-label Safety Study with SKP Flutiform®HFA pMDI (100/10 µg and 250/10 µg) in Adult and Adolescent Patients With Asthma	
Study Sites: Forty one (41) study sites in 5 European countries (Germany, Hungary, Poland, Romania, United Kingdom). There were 13 additional sites (in Ukraine, Germany, Romania and United Kingdom) that received IEC approval but did not enroll subjects.	
Publications: None	
Studied Period (Years): First Subject First Visit for Run-in Period: 03 March 2006 First Subject First Dose for Treatment Period: 27 March 2006 Last Subject Last Dose: 20 July 2007	**Phase of Development:** 3
Objectives: The primary objective was to assess long-term safety of SKP Flutiform HFA pMDI (100/10 µg and 250/10 µg) after BID treatment in adult and adolescent patients with mild to moderatesevere asthma over a period of up to 12 months. The secondary objective was to assess the efficacy of SKP Flutiform HFA pMDI (100/10 µg and 250/10 µg) after BID treatment in adult and adolescent subjects with mild to moderate-severe asthma over a period of up to 12 months.	

Methodology: This was an open-label, multicenter study to assess the long-term safety of SKP Flutiform HFA pMDI at dosages of 100/10 μg BID and 250/10 μg BID (hereafter referred to as Flutiform 100/10 μg BID and Flutiform 250/10 μg BID, respectively) for up to 12 months in adult and adolescent subjects with mild to moderate-severe asthma requiring treatment with inhaled steroids for at least 4 weeks prior to the Screening Visit at a dose that was no greater than 500 μg/day fluticasone propionate or equivalent. Approximately 400 subjects were planned for enrollment from approximately 50 centers in European Countries. This study consisted of a 2-week open-label Run-in Period followed by a 12-month open-label Treatment Period for approximately 160 subjects and a 6-month open-label Treatment Period for approximately 240 subjects.

Methodology (Continued):

Prior to enrollment, subjects underwent a Screening Visit and those who met all of the study entry criteria entered the Run-in Period for 14 (± 3) days. According to their steroid usage prior to screening, subjects were assigned to one of the following dosages of Flixotide™ Evohaler™ HFA pMDI (hereafter referred to as fluticasone) for asthma maintenance therapy during the Run-in Period:

- 100 μg/day fluticasone (50 μg/actuation; 1 inhalation BID) for subjects using 100 to 249 μg/day fluticasone or equivalent inhaled steroid.
- 250 μg/day fluticasone (125 μg/actuation; 1 inhalation BID) for subjects using 250 to 500 μg/day fluticasone or equivalent inhaled steroid.

Rescue salbutamol (albuterol) pMDI (hereafter referred to as salbutamol) was provided for the control of worsening asthma symptoms during both the Run-in Period and Treatment Period.

Following the Run-in Period, subjects returned to the clinic to complete the eligibility tests and procedures at the Baseline Visit (Week 0), at which time baseline assessments of pulmonary function and general asthma stability were evaluated. Eligible subjects were allocated into one of the two treatment groups based on their treatment assignment during the Run-in Period.

- Flutiform 100/10 μg BID for subjects assigned to 100 μg/day fluticasone during the Run-in Period.
- Flutiform 250/10 μg BID for subjects assigned to 250 μg/day fluticasone during the Run-in Period.

Following treatment group allocation, subjects were instructed to withhold all other asthma medications for the duration of the Treatment Period, with the exception of rescue salbutamol as needed for the control of worsening asthma symptoms. Study drug (including salbutamol) was withheld prior to pulmonary function testing for the appropriate duration.

Subjects were to continue Flutiform treatment for either 6 or 12 months. The first 80 subjects in each treatment group were to be considered for treatment for 12 months if they agreed to participate for this length of time. During the Treatment Period, study visits for clinical assessments were scheduled for Week 2, Week 4, and monthly thereafter. At each scheduled visit during the Treatment Period, subjects were assessed for asthma stability, adverse events, electrocardiograms (ECGs) and vital signs. Clinical laboratory assessments (chemistry, hematology, urinalysis) were performed at Screening, Baseline/ Week 0, Week 4 and Month 3, Month 6, and Month 12 (for subjects in the 12month subset). Efficacy assessments using spirometry (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC] and peak expiratory flow rate [PEFR]) were performed predose at each study visit and 1 hour (± 10 minutes) postdose at Week 2, Week 4, Month 2, and Month 3.

Number of Subjects (Planned and Analyzed):

Planned: 400 subjects

Enrolled and Treated with Flutiform: 472 subjects

Analyzed for Efficacy: 466 subjects

Analyzed for Safety: 472 subjects

Diagnosis and Main Criteria for Inclusion:

Male or female subjects at least 12 years of age with asthma requiring inhaled corticosteroid as maintenance therapy for at least 4 weeks prior to the Screening Visit and at a dose not greater than 500 μg/day fluticasone propionate inhalation HFA pMDI (or equivalent dose for other inhaled corticosteroids); an FEV_1 of 40% to 85% (inclusive) of predicted normal values following appropriate withholding of asthma medications; documented reversibility of at least 15% in FEV_1; during the Run-in Period, subjects had 2 or more inhalations per day of rescue salbutamol for at least 3 days and either 1) at least one night with sleep disturbance or 2) at least 3 days with asthma symptoms. Subjects were excluded if they had life-threatening asthma within the past year or during the Run-in Period; took systemic (oral or injectable) corticosteroid medication within 3 months before the Screening Visit or during the Run-in Period; took omalizumab within the previous 6 months; took a leukotriene receptor antagonist within the past week; had current evidence or history of any clinically significant disease or abnormality including uncontrolled coronary artery disease, congestive heart failure, myocardial infarction, or cardiac dysrhythmia; had an upper or lower respiratory infection within 4 weeks prior to the Screening Visit or during the Run-in Period; had significant, nonreversible, pulmonary disease (e.g., COPD, cystic fibrosis, bronchiectasis); had known HIV-positive status; had a smoking history equivalent to "10 pack years" (i.e., at least 1 pack of 20 cigarettes /day for 10 years or 10 packs/day for 1 year, etc.); had a current smoking history within 12 months prior to the Screening Visit; had current evidence or history of alcohol and/or substance abuse within 12 months prior to the Screening Visit; or had taken β-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole (Hismanal), quinidine type antiarrhythmics, or potent CYP3A4 inhibitors such as ketoconazole within the past week.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:

During the Run-in Period, subjects received fluticasone, either 50 μg BID or 125 μg BID, inhaled and selfadministered in the morning and evening. During the Treatment Period, subjects received Flutiform, either 100/10 μg BID or 250/10 μg BID, inhaled and self-administered in the morning and evening. Salbutamol was self-administered as needed as an asthma rescue medication during both the Run-in Period and the Treatment Period. Study lot numbers are listed as follows:

Study Period/ Treatment Assignment	Actuations per Dose (Morning and Evening)	Bulk Lot Number/Source
Run-in Period		
50 μg Flixotide Evohaler (fluticasone) HFA pMDI BID	1 actuation (50 μg/actuation)	9135, 2135, 8330/ GlaxoSmithKline
125 μg Flixotide Evohaler (fluticasone) HFA pMDI BID	1 actuation (125 μg/actuation)	9031, 1678, 6921/ GlaxoSmithKline
Treatment Period		
SKP Flutiform 100/10 μg HFA pMDI BID	2 actuations (fluticasone/formoterol, 50/5 μg per actuation)	A50080/ Skyepharma AG/sanofi-aventis
SKP Flutiform 250/10 μg HFA pMDI BID	2 actuations (fluticasone/formoterol, 125/5 μg per actuation)	A50081/ Skyepharma AG/sanofi-aventis
Rescue Medication for Both Study Periods		
Ventolin™ Evohaler™ (salbutamol/albuterol) HFA pMDI prn	prn (100 μg per actuation)	0667/ GlaxoSmithKline

Duration of Treatment: The Flutiform Treatment Period was 6 months in a subset of 256 subjects and 12 months in a subset of 216 subjects, or less if subjects discontinued prematurely.

Reference Therapy, Dose/Strength/Concentration, and Mode of Administration and Lot Number: There was no reference therapy.

Criteria for Evaluation

Efficacy: The assessment of efficacy was a secondary objective and included the following variables from spirometry measurements: FEV_1, PEFR, and FVC. The predefined efficacy analysis sets are described as follows:

Full Analysis Set (FAS): the 466 subjects who received at least one inhalation of study drug during the Treatment Period and who had at least one Baseline/Week 0 and at least one postbaseline efficacy measurement.

Per Protocol (PP) Population: the 390 subjects in the FAS who did not have a major protocol violation.

Safety: All 472 subjects who received at least one inhalation of Flutiform were included in the safety analysis. The safety of Flutiform was assessed by evaluating study drug exposure, adverse events, serious adverse events, as well as changes in laboratory determinations, vital sign parameters, and ECGs.

Statistical Methods

Efficacy: Summary statistics were calculated for FEV_1, FVC, and PEFR at the following times:

- Predose measurements: Baseline/Week 0, Weeks 2 and 4, and Months 2 through 6 or Month 12
- Postdose measurements: Baseline/Week 0, Weeks 2 and 4 and Months 2 and 3

Summary statistics were also calculated for changes from Baseline/Week 0 to each visit. Changes within each dose group were analyzed using a paired t-test.

Safety: Incidence rates of adverse events emerging during treatment with Flutiform and the proportion of subjects prematurely withdrawn from the study due to adverse events were shown for each treatment group. Incidence rates of treatment-emergent adverse events were also displayed for each treatment group by severity and relationship to study drug, using the maximum severity and the most related categories. Incidence rates of serious adverse events were summarized separately.

Descriptive statistics (i.e., mean, standard deviation, minimum, median, and maximum) were used to summarize other safety data where appropriate. Laboratory and vital sign values were summarized with shift tables (i.e., low-normal-high at the Baseline/Week 0 versus low-normal-high at the other visits) to assess changes in laboratory values.

Summary/Conclusions

Efficacy Results:

Statistically significant improvements at the $\alpha = 0.001$ level were observed for all efficacy assessments (FEV_1, FEV_1% predicted, PEFR, and FVC) for Flutiform treatment overall and for each dose group (100/10 μg and 250/10 μg) at every time point. These assessments included mean changes from Baseline/Week 0 to the predose assessment at Week 2, Week 4, monthly thereafter, and at Final Visit, and mean changes from Baseline/Week 0 to the 1-hour postdose assessment at Week 2, Week 4, Month 2, and Month 3. The results from the Final Visit for mean change from Baseline/Week 0 to the predose assessment, and the results from Month 3 for the mean changes from Baseline/Week 0 to the 1hour postdose assessment are summarized as follows:

	Flutiform 100/10 μg BID N = 221	Flutiform 250/10 μg BID N = 245	Overall N = 466
	n Mean Change From Baseline (SD)[a]	n Mean Change From Baseline (SD)[a]	n Mean Change From Baseline (SD)[a]
Change From Baseline/Week 0 to Predose Assessment at Final Visit[b]			
FEV_1 (L)	220 0.381 (0.4875)***	242 0.236 (0.4336)***	462 0.305 (0.4652)***
FEV_1 % predicted	220 11.5 (13.84)***	242 7.4 (13.63)***	462 9.3 (13.87)
PEFR (L/min)	220 67.4 (81.62)***	242 51.0 (92.05)***	462 58.8 (87.52)***
FVC (L)	220 0.371 (0.5754)***	242 0.235 (0.5247)***	462 0.300 (0.5530)***
Change From Baseline/Week 0 to Postdose Assessment at Month 3			
FEV_1 (L)	215 0.526 (0.4880)***	233 0.392 (0.4378)***	448 0.456 (0.4669)***
FEV_1 % predicted	215 15.9 (13.45)***	233 12.5 (13.99)***	448 14.1 (13.82)***
PEFR (L/min)	215 80.9 (77.27)***	232 68.1 (94.90)***	447 74.3 (87.01)***
FVC (L)	215 0.467 (0.5664)***	233 0.336 (0.4986)***	448 0.399 (0.5356)***

a. Paired t-test performed on observed data for Full Analysis Set (FAS).

b. Final Visit was summarized using data captured on the Final Visit pages of the case report form (CRF). The Final Visit occurred at Month 6 or Month 12 for subjects who completed the study, depending on the study subset; or upon early discontinuation.

*** Indicates a statistically significant change from Baseline/Week 0 at the $\alpha = 0.001$ level.

Results for the PP population were similar to those presented above for the FAS, with statistically significant mean changes for every assessment time for each dose group and for both dose groups combined.

The results for all efficacy endpoints demonstrated statistically significant and clinically important improvements over Baseline/Week 0 for subjects who received Flutiform therapy for up to 12 months.

Safety Results:

The overall incidence of adverse events for all subjects treated with Flutiform was 36.9% (174/472): 29.9% (67/224) for the low dose group (100/10 μg BID) and 43.1% (107/248) for the high dose group (250/10 μg BID). The most common adverse events (> 2%) overall were nasopharyngitis (9.5%), dyspnea (5.1%), pharyngitis (2.8%), headache (2.8%), lower respiratory tract infection (2.5%), upper respiratory tract infection (2.5%), asthma (2.5%), and cough (2.1%). Only 17 (3.6%) subjects experienced adverse events that were reported as severe. The only severe adverse event that was reported for more than one subject was asthma, which was reported for 6 subjects in the high dose group and 3 subjects in the low dose group.

Adverse events that occurred with at least a 2% higher incidence in the high dose group compared with the low dose group were related to the respiratory system: nasopharyngitis (11.3% versus 7.6%), dyspnea (7.7% versus 2.2%), asthma (3.6% versus 1.3%), cough (3.2% versus 0.9%), and dysphonia (2.4% versus 0.4%). The increased incidence of these adverse events in the higher dose group may be due to more severe underlying asthma in this dose group (subjects assigned to the high dose group were taking a higher dosage of inhaled corticosteroids prior to study enrollment).

Safety Results (Continued):

Only 18 (3.8%) of subjects had adverse events related to study drug (i.e., reported as possibly or probably related to study drug by the investigator. The only related adverse events reported for more than one subject were asthma (n = 2) and dysphonia (n =5). Dysphonia is a known side effect of inhaled corticosteroids and may be related to the higher steroid exposure, because all events were reported in the Flutiform 250/10 μg BID dose group.

No deaths were reported. Ten subjects (5 in each dose group) experienced a total of 12 serious adverse events, and none of the serious events were considered related to study drug by the investigator. Serious adverse events associated with the respiratory system were reported for 2 subjects in the low dose group (pneumonia and anxiety-induced respiratory syndrome) and 1 subject in the high dose group (asthma exacerbation). One serious adverse event associated with the cardiovascular system (myocardial infarction) was reported for a subject in the high dose group who had cardiovascular risk factors.

Fourteen subjects were prematurely discontinued from study drug, at least in part, due to adverse events, including 8 subjects due to events that were related to the respiratory system (2 Flutiform 100/10 μg BID, 6 Flutiform 250/10 μg BID).

Asthma exacerbations were reported for 11.2% (53/472) of subjects. Overall, 46 (9.7%) of subjects experienced mild to moderate exacerbations and only 9 (1.9%) subjects experienced severe exacerbations. Only one event of asthma exacerbation was reported as a serious adverse event. The incidence of mild to moderate exacerbations was similar between the 100/10 μg BID and the 250/10 μg BID dose groups (9.8% versus 9.7%, respectively), and the incidence of severe exacerbations was approximately 1% higher in the high dose group (2.4%) than in the low dose group (1.3%).

Clinical laboratory results showed no abnormal trends or dose-response related changes. Of note, there were 4 subjects who met the high criterion for glucose levels. Three of these subjects had a prior history of diabetes and all of the subjects had elevated values at every visit, including Screening and Baseline/ Week 0. Vital signs assessments showed no abnormal trends or dose-response related changes.

Overall no clinically important ECG changes were observed. There were 4 subjects who developed QTcF intervals that were greater than 500 ms during the study. These subjects each had one postbaseline QTcF interval that was greater than 500 ms and they continued on study drug with no subsequent QTcF intervals greater than 500 ms. There were no cardiovascular or dysrhythmia events associated with the QT prolongation. Of note, betaagonists are known to be associated with QT prolongation.

Conclusions:

Flutiform was generally safe and well tolerated and demonstrated efficacy in the treatment of mild to severe asthma when administered by inhalation at doses of 100/10 μg and 250/10 μg BID for up to 12 months to the 472 subjects requiring inhaled corticosteroids in this study.