Clinical Trial Study Synopsis: SKY2028-3-005

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 and Abbott Respiratory LLC	
Name of Study Drug: Flutiform®	
Name of Active Ingredient: Fluticasone propionate and formoterol fumarate	
Title of Study: A Randomized, Double-blind, Active-controlled, Parallel Group, Stratified, Multicenter, 12-Week Study Comparing the Safety and Efficacy of Fluticasone and Formoterol Combination (Flutiform® 250/10 µg twice daily) in a Single Inhaler (Skyepharma HFA pMDI) with the Administration of Fluticasone (250 µg twice daily) Alone in Skyepharma HFA pMDI and Flovent® HFA pMDI in Adolescent and Adult Patients with Moderate to Severe Asthma	
Study Sites: Multicenter; the study was conducted at 68 sites in Europe, Latin America, and United States.	
Publications: None	
Studied Period (Years): First Subject First Visit: 18 March 2008 First Subject First Dose for Treatment Period: 03 April 2008 Last Subject Completed Dosing: 26 September 2008	**Phase of Development:** 3

Objectives: The primary objective of this study was to demonstrate the efficacy in terms of the formoterol fumarate component of SKP Flutiform HFA pMDI (250/10 μg) compared to SKP Fluticasone HFA pMDI (250 μg), when administered by inhalation twice daily (BID) over 12 weeks in adolescent and adult subjects with moderate to severe asthma, on the change in forced expiratory volume in 1 second (FEV_1) from morning predose at Baseline (Week 0) to 2 hours postdose at Week 12.

The primary endpoint must have demonstrated statistically significant efficacy in order for this study to be considered a positive study.

The secondary objectives of this study included:

- To demonstrate the efficacy of SKP Flutiform HFA pMDI (250/10 μg) compared to Flovent® Fluticasone pMDI (250 μg) on the change in FEV_1 from morning predose at Baseline (Week 0) to 2 hours postdose at Week 12.
- To demonstrate the efficacy of SKP Flutiform HFA pMDI (250/10 μg BID) using other pulmonary function tests (PFTs) (including FEV_1 percentage predicted normal and peak expiratory flow rate [PEFR]) and clinical endpoints (frequency of asthma exacerbations, discontinuation due to lack of efficacy, subject derived data recorded daily in telephone diary system including daily PEFR).

Objectives (Continued):

- To assess the safety profile of SKP Flutiform HFA pMDI (250/10 μg BID) using the incidence of adverse events and changes in electrocardiogram (ECGs), clinical laboratory tests, and vital signs.
- To assess the 12-hour serial FEV_1 area under the curve (AUC) in a subset population of at least 66 subjects.

Methodology:

This Phase 3, randomized, double-blind, active-controlled, parallel-group, stratified, multicenter, study evaluated the safety and efficacy of Flutiform 250/10 μg after twice daily dosing over 12 weeks delivered by SKP HFA pMDI compared with Fluticasone propionate 250 μg twice daily alone in adolescent and adult subjects with moderate to severe asthma. Only steroid-requiring subjects (inhaled steroid regimen for at least 4 weeks prior to the Screening Visit at a dose not greater than 500 μg/day Fluticasone propionate or equivalent) were eligible. All subjects entered a 2-week open-label Run-in Period. Subjects had a Run-in Period of 14 ± 3 days during which they received asthma maintenance therapy using 100 μg/day Flovent (1 inhalation BID) for subjects using ≤ 250 μg/day Fluticasone propionate or equivalent inhaled steroid, and 200 μg/day Flovent (2 inhalations BID) for subjects using > 250 μg/day Fluticasone propionate or equivalent inhaled steroid prior to the Screening Visit. Rescue albuterol was provided for the control of worsening asthma symptoms during the Run-in and Treatment Periods.

At the Baseline Visit (Week 0) following the Run-in Period, eligible subjects were stratified according to their Baseline FEV_1 % predicted (40% to 60% or > 60% to 80%) and randomized to 1 of 3 treatment groups, taking 2 inhalations BID from each inhaler:

Flutiform 250/10 μg HFA pMDI; or

SKP Fluticasone 250 μg HFA pMDI; or

Flovent (Fluticasone) 250 μg HFA pMDI

Study drug was administered BID over a 12-week period. Subject visits occurred at Weeks 2, 4, 8, and 12 during which assessments (including serial PFTs up to 4 hours) were made. In a subset of approximately 66 subjects from selected sites, postdose 12-hour serial PFTs were to be performed at Baseline, Week 2, and Week 12. During the Treatment Period, subjects could take only their blinded study drug; all other asthma medications were withheld for the duration of the Treatment Period, except the use of rescue albuterol was permitted as needed for the control of worsening asthma symptoms.

Number of Subjects (Planned and Analyzed):

Planned: approximately 375 subjects at screening in order to randomize 125 subjects per treatment group

	Flutiform 250/10 μg BID N = 146	SKP Fluticasone 250 μg BID N = 146	Flovent Fluticasone 250 μg BID N = 146
Full Analysis Set	146 (100.0)	146 (100.0)	146 (100.0)
Per Protocol Population	132 (90.4)	141 (96.6)	138 (94.5)
AUC Population	90 (61.6)	77 (52.7)	87 (59.6)
Safety Population	146 (100.0)	146 (100.0)	146 (100.0)

Diagnosis and Main Criteria for Inclusion:

Male and female subjects ≥ 12 years of age with a documented history of symptomatic asthma for at least 12 months; steroid-requiring (receiving inhaled steroid medication for at least 4 weeks prior to the Screening Visit at a dose not greater than 500 μg/day Fluticasone propionate or equivalent); an FEV_1 of 40% to 80% (inclusive) of predicted normal values at both the Screening and Baseline Visits; documented reversibility within 12 months of the Screening Visit, defined as a ≥ 15% (or ≥ 14.5%) increase from pre-albuterol FEV_1 levels 15 to 30 minutes following albuterol inhalation.

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

SKP Flutiform 250/10 μg HFA pMDI (fluticasone propionate 125 μg/actuation and formoterol fumarate 5 μg/actuation); Lot numbers A60086 and AA80010

Duration of Treatment:

The study consisted of a Screening Visit, a Run-in Period lasting 14 ± 3 days, a 12-week Treatment Period, and a Safety Follow-up Visit (initially by telephone unless a visit was considered necessary) that occurred approximately 2 weeks after the last day of dosing. The study duration for each subject was approximately 16 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

SKP Fluticasone propionate HFA pMDI 125 μg/actuation (Lot number AA70047), Flovent HFA pMDI 125 μg/actuation (Lot numbers 0374, 0377, 0419, 0421, and 0425[+])
Placebo SKP HFA pMDI and Placebo Fluticasone HFA pMDI (Lot numbers A50077, S05K70P1, S05K70P2, S08C01P11, S08D02P1, and S055K70P3[+])

\+ This lot was not dispensed to subjects.

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint was the change in FEV_1 from morning predose at Baseline (Week 0) to 2 hours post-dose at Week 12. If the primary endpoint was significant at the 2-sided 0.05 significance level, the secondary efficacy endpoints were evaluated with a hierarchical testing scheme. The secondary endpoints were ranked as follows for Flutiform versus SKP Fluticasone:

1. Change from Baseline to Final Week in morning (AM) PEFR
2. Change from Baseline to Final Week in evening (PM) PEFR
3. Change from Baseline to Final Week in rescue medication use
4. Change from Baseline to Final Week in asthma symptom scores
5. Change from Baseline to Final Week in symptom-free days
6. Change from Baseline to Final Week in rescue medication-free days
7. Change from Baseline to Final Week in asthma control days
8. Proportion of subjects with asthma exacerbations
9. Change from Baseline to Final Week in sleep disturbance scores
10. Change from Baseline to Final Week in awakening-free nights

Additional efficacy endpoints included PFTs (FEV_1 percentage predicted normal, FVC, and PEFR), 12hour FEV_1 AUC (in a subset of at least 66 subjects), frequency of asthma exacerbations, asthma symptom scores, sleep disturbance scores, frequency of albuterol pMDI used as rescue medication, and AM/PM PEFR.

Safety:

The primary safety assessment was the incidence of treatment-emergent adverse events during the Treatment Period. Other safety endpoints included changes in clinical laboratory tests, vital signs, and ECGs.

Statistical Methods

Efficacy:

The primary efficacy endpoint was compared between treatment groups using an analysis of covariance (ANCOVA) with treatment group (all 3 treatment groups), site, and Baseline FEV_1 % predicted category (40% to 60% and > 60% to 80%) as main effects and Baseline value as a covariate. The change from Baseline to Final Week for the following secondary endpoints, AM/PM PEFR, asthma symptom scores, sleep disturbance scores, and rescue medication use was compared between treatment groups using a similar ANCOVA model as for the primary endpoint. Differences between treatment groups for the change from Baseline to Final Week for symptom-free days, rescue medication-free days, asthma control days, and awakening-free nights were assessed using van Elteren's method for combining Wilcoxon rank sum test results from independent strata, with Baseline FEV_1 % predicted category and site as the strata. Differences between treatment groups were assessed using logistic regression with effects for treatment groups (all 3 treatment groups) and Baseline FEV_1 % predicted category for the proportion of subjects experiencing at least 1 treatment-emergent asthma exacerbation.

Safety:

The incidence of treatment-emergent adverse events was summarized; incidence rates by severity and relationship, as well as incidence of serious adverse events, were also presented. Descriptive statistics were used to summarize laboratory data, vital signs, and ECG data, and change from Baseline values in these parameters. In addition, laboratory values were summarized with shift tables.

Summary/Conclusions

Efficacy Results:

The study included a single primary efficacy endpoint, change in FEV_1 from the morning predose value at Baseline (Week 0) to the 2 hour postdose value at Week 12. The contribution from the formoterol component of Flutiform 250/10 μg was demonstrated by the clinically important and statistically significant treatment group difference (LS mean difference = 0.161 L, $P < 0.001$) between the Flutiform 250/10 μg and SKP Fluticasone groups for mean change from predose at Baseline to 2 hours postdose at Week 12.

All sensitivity analyses supported the primary analyses for the primary endpoint.

In a subset of 254 subjects, 12-hour serial pulmonary function testing was performed at Baseline (Week 0), Week 2, and Week 12. The mean 12-hour FEV_1 AUC was numerically greater in the Flutiform 250/10 μg group compared to the SKP Fluticasone and Flovent Fluticasone groups at Week 0, Week 2, and Week 12.

Results for mean increases in FEV_1 from Baseline to 2 hours postdose were generally numerically greater for Flutiform 250/10 μg compared to SKP Fluticasone and Flovent Fluticasone beginning at Week 2 and were sustained throughout the 12-week Treatment Period.

Results from multiple secondary and tertiary efficacy endpoints assessing lung function, asthma symptoms and rescue medication use generally supported the superior efficacy of Flutiform 250/10 μg compared to SKP Fluticasone and Flovent Fluticasone. Numerically greater improvements with Flutiform 250/10 μg were noted as early as 1 day after the first dose and were maintained throughout the 12-week Treatment Period.

The results of this study which best supported the efficacy of Flutiform 250/10 μg as maintenance therapy included:

- Larger improvement in the percent of asthma control days (defined as days with asthma symptom score of 0, sleep disturbance score of 0 and no use of rescue medication).
- A low proportion of subjects experienced severe asthma exacerbations (defined as an exacerbation which required additional therapy (e.g., systemic steroid), emergency visit or hospitalization).
- Greater reduction in use of rescue medication.
- Larger improvements in AM PEFR and PM PEFR, self monitored daily by the subject using a peak flow meter.

Summary/Conclusions

Efficacy Results (Continued):

For the telephone diary based assessments, greater numerical improvements in AM and PM PEFR, reductions in asthma symptom score, and rescue medication use occurred within 1 day of the first dose of Flutiform 250/10 μg compared to the SKP Fluticasone and Flovent Fluticasone groups.

These findings demonstrate that Flutiform 250/10 μg provides greater efficacy compared to SKP Fluticasone and Flovent Fluticasone for the management of moderate to severe asthma.

Results from primary, secondary, and tertiary efficacy endpoints were generally clinically indistinguishable for SKP Fluticasone 250 μg and Flovent Fluticasone 250 μg which supports the use of Flovent Fluticasone as a monotherapy comparator in the other Phase 3 studies.

Safety Results:

Flutiform was generally safe and well tolerated in adolescent and adult subjects with moderate to severe asthma. Of note, 12.6% of subjects in the safety population were between 12 and 17 years of age.

The overall incidence of treatment-emergent adverse events was 32.9%, 39.7%, and 40.4% in the Flutiform, SKP Fluticasone, and Flovent Fluticasone groups, respectively. The most frequently reported (≥ 5.0% of subjects in any treatment group) treatment-emergent adverse events by MedDRA preferred term were influenza, nasopharyngitis, and rhinitis allergic.

Treatment-emergent adverse events were predominantly mild to moderate in severity. The only treatment-emergent adverse event considered severe in more than 1 subject was asthma (1 [0.7%] in the Flutiform treatment group, 1 [0.7%] in the SKP Fluticasone treatment group, and 2 [1.4%] in the Flovent Fluticasone treatment group).

No deaths were reported. Serious adverse events were experienced by 2 Flovent Fluticasone subjects (abortion spontaneous and asthma), both of which were considered by the investigator to be not related to study drug. Study drug was prematurely discontinued at least in part due to adverse events in 10 subjects: 1 Flutiform, 5 SKP Fluticasone, and 4 Flovent Fluticasone. The only treatment-emergent adverse events leading to discontinuation in more than 1 subject were asthma (1 Flutiform, 1 SKP Fluticasone, and 2 Flovent Fluticasone), insomnia (2 SKP Fluticasone), and tension (2 SKP Fluticasone).

No clinically meaningful changes from Baseline in laboratory parameters were observed in any treatment group. Overall, the most common shift was from normal to high eosinophils (9.3% Flutiform, 8.9% SKP Fluticasone, 10.5% Flovent Fluticasone). Of note, increases in eosinophils are associated with asthma.

Two subjects (1 Flutiform and 1 Flovent Fluticasone) had high serum glucose levels at Baseline that shifted to low at the Final Visit. The Flovent Fluticasone subject had a history of type I diabetes. There were 9 subjects with an elevated (1 Flutiform, 2 SKP Fluticasone, and 4 Flovent Fluticasone), decreased (1 SKP Fluticasone), or both elevated and decreased (1 Flutiform) PCS serum glucose values. Of note, 7 (2 Flutiform, 1 SKP Fluticasone, and 4 Flovent Fluticasone) of the 9 subjects with a PCS serum glucose value had a history of diabetes, type I diabetes, type II diabetes, or noninsulin-dependent diabetes. The protocol did not require fasting blood samples for clinical laboratory assessments. Of note, increases in glucose levels have been reported in patients receiving betaagonists.

There were no clinically concerning trends in vital signs or ECG results in any treatment group. Of note, there were no clinically important findings for QTcF in any treatment group.

Conclusions:

In this study, Flutiform 250/10 µg was safe and efficacious in the management of moderate to severe asthma in adolescent and adult subjects. Flutiform 250/10 µg demonstrated superior efficacy compared to SKP Fluticasone 250 µg. The safety profile of this combination product was consistent with the safety profiles of its component, fluticasone.