SYNOPSIS

Name of Company: SkyePharma AG	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: SKP HFA pMDI	Volume:	
Name of Active Ingredient: Budesonide	Page:	

Title of Study:	A Randomized, Double-Blind, Active-Controlled, Parallel Group, Stratified, Multicenter, 12-Week Study to Evaluate the Safety and Efficacy after Multiple Dosing of Investigational Budesonide HFA Metered Dose Inhalers Compared with Conventional Budesonide CFC Metered Dose Inhalers (Pulmicort®) in Patients with Asthma
Study Centers:	Multicenter study – 49 sites in Europe (United Kingdom, France, Germany, Spain, Sweden, and Ukraine).
Publication (reference):	Not Applicable.
Studied period: FPFV: LPLV:	Phase of development: 04-Aug-2003 Phase III 07-May-2004
Objectives:	The primary objective of this study was: • To demonstrate the non-inferiority of the SkyePharma (SKP) hydrofluoroalkane (HFA) pressurized metered dose inhaler (pMDI) (SKP HFA pMDI; 100 µg and 200 µg budesonide per actuation) compared with conventional AstraZeneca (AZ) chlorofluorocarbon (CFC) pMDI (AZ CFC pMDI; 100 µg and 200 µg budesonide per actuation) at two dose levels (400 µg/day and 800 µg/day) over 12 weeks using spirometry (change in morning peak expiratory flow rate [AM PEFR]) in patients with asthma. The secondary objectives were: • To determine if the SKP HFA pMDIs (100 µg and 200 µg budesonide per actuation) are comparable to the AZ CFC pMDIs (100 µg and 200 µg budesonide per actuation) using other traditional clinical endpoints (i.e. pulmonary function tests [PFTs], frequency of asthma exacerbations, and patient derived data recorded daily on electronic diaries). • To compare the safety of SKP HFA pMDIs (100 µg and 200 µg budesonide per actuation) to AZ CFC

	pMDIs (100 µg and 200 µg budesonide per actuation), using incidence of treatment emergent adverse events (AEs), changes in oropharyngeal examinations, vital signs, and clinical laboratory tests.
Methods:	This Phase III, randomized, double-blind, active controlled, parallel group, stratified, multicenter study was designed to evaluate the safety and efficacy after multiple dosing of budesonide over 12 weeks delivered by SKP HFA pMDIs compared with AZ CFC pMDIs at two dose levels (400 µg/day and 800 µg/day). Prior to the Baseline Visit (Week 0), steroid-requiring patients (inhaled steroid regimen stable for at least 4 weeks prior to Screening Visit [at a dose not greater than 1000 µg/day budesonide or equivalent steroid]) underwent a Run-In Period of up to 2 weeks during which they received asthma maintenance therapy using budesonide CFC pMDI (200 µg/day or 400 µg/day, depending on their steroid dose prior to Screening Visit). Steroid-free patients (no history of steroid use for at least 12 weeks prior to Screening Visit) underwent a Run-In Period of up to 4 weeks prior to the Baseline Visit (Week 0) during which they received no controller medication. However, during the Run-In Period, the use of salbutamol pMDI was permitted for all patients as needed for the control of worsening asthma symptoms. At the Baseline Visit (Week 0) following the Run-In Period, eligible patients were assigned to dose levels according to their baseline forced expiratory volume (FEV_1). Patients with a baseline FEV_1 of 81% to 90% predicted were assigned to low-dose treatment (400 µg/day) with either HFA pMDI or CFC pMDI, whereas patients with a baseline FEV_1 of 50% to 80% predicted were assigned to medium-dose treatment (800 µg/day) with either HFA pMDI or CFC pMDI. At randomization, patients at each dose level were stratified within each treatment group according to their prior steroid use (steroid-requiring or steroid-free) and randomized to the treatment groups with SKP HFA pMDI or AZ CFC pMDI. Following the Baseline Visit (Week 0), study drug was administered twice daily (BID) over a 12-week period. Patient visits occurred at Weeks 2, 4, 8, and 12, during which assessments (including PFTs) were made. During the Treatment Period, patients were only permitted to take their blinded study medication for the treatment of their asthma. All other asthma medication was withheld for the duration of the Treatment Period. However, the use of rescue salbutamol pMDI was permitted as needed for the control of worsening asthma symptoms.

Number of patients (planned and analyzed):	It was planned to recruit approximately 320 patients (80 patients in each group). A total of 322 patients were randomized, with 321 patients included in both the Safety analysis and Full Analysis Set. One patient was withdrawn from the study without having taken any study medication following a randomization error. A total of 274 patients were included in the Per-Protocol (PP) analysis.
Diagnosis and main criteria for inclusion:	Eligible male or female patients, ≥ 12 years old at the Screening Visit. At the Screening Visit, eligible patients had to have a documented history of stable, symptomatic asthma (≥ 12 months); could be either steroid-requiring (receiving a constant dose and frequency of steroid asthma medication for at least 4 weeks prior to the Screening Visit [at a dose not greater than 1000 µg/day budesonide or equivalent steroid]) or steroid-free (no history of steroid asthma medication for at least 12 weeks prior to the Screening Visit). In addition, patients had to demonstrate an FEV_1 of 50% to 90% (inclusive) of predicted normal values at both Screening and Baseline Visits; documented reversibility within 6 months of the Screening Visit (defined as a ≥ 15% increase from pre-salbutamol FEV_1 levels within 30 minutes following two to four inhalations of salbutamol pMDI).
Test product, dose and mode of administration, batch number:	Patients assigned to SKP HFA pMDI received one of two treatments: Low Dose (400 µg/day) SKP HFA pMDI: SKP HFA pMDI 100 µg/actuation (two inhalations BID) and placebo CFC pMDI (two inhalations BID). Medium Dose (800 µg/day) SKP HFA pMDI: SKP HFA pMDI 200 µg/actuation (two inhalations BID) and placebo CFC pMDI (two inhalations BID). Batch Numbers: SKP HFA pMDI, 100 µg: S03C02I SKP HFA pMDI, 200 µg: S03C10I Placebo CFC pMDI: 3041729
Duration of treatment:	12 weeks
Reference product, dose and mode of administration, batch number:	Patients assigned to AZ CFC pMDI received one of two treatments: Low Dose (400 µg/day) AZ CFC pMDI: AZ CFC pMDI 100 µg/actuation (two inhalations BID) and placebo HFA pMDI (two inhalations BID). Medium Dose (800 µg/day) AZ CFC pMDI: AZ CFC pMDI 200 µg/actuation (two inhalations BID) and placebo HFA

	pMDI (two inhalations BID). Batch Numbers: AZ CFC pMDI, 100 µg: 41550 AZ CFC pMDI, 200 µg: 79950 Placebo HFA pMDI: S03D02I
Criteria for evaluation:	
Efficacy:	The primary efficacy endpoint was the change in AM PEFR from the Baseline Visit (Week 0) to Week 12 (or Final Visit for early discontinuations). Secondary endpoints included other PFTs (FEV_1, forced vital capacity [FVC], and forced expiratory flow 25%-75% [$FEF_{25\%-75\%}$]), frequency of asthma exacerbations, and patient electronic diary data (evening [PM] PEFR, asthma symptom scores, sleep disturbance scores, and frequency of salbutamol pMDI used as rescue medication).
Safety:	The primary safety assessment was the incidence of treatment-emergent AEs. Secondary safety endpoints included changes in vital signs, oropharyngeal examinations, and clinical laboratory tests during the Treatment Period.
Statistical Methods:	A non-inferiority analysis was used to demonstrate that SKP HFA pMDI was not inferior to AZ CFC pMDI in increasing AM PEFR. Analysis of variance (ANOVA), with effects for treatment (SKP HFA pMDI and AZ CFC pMDI), prior steroid use, and baseline PEFR, was used to construct the one-sided 97.5% (alpha = 0.025) confidence limit for the difference between SKP HFA pMDI and AZ CFC pMDI with respect to the change in AM PEFR from Baseline (Week 0) to Week 12 or Final Visit for patients who terminated early, for each dose (400 µg/day and 800 µg/day). The confidence intervals (CI) were constructed from the least squares means for the treatment effect of the ANOVA. Non-inferiority was demonstrated if the upper confidence limit of the difference (AZ CFC pMDI minus SKP HFA pMDI) was < 20 L/min for both dose levels (400 µg/day and 800 µg/day).

SUMMARY

EFFICACY RESULTS:

- Morning PEFR, the primary efficacy endpoint, increased from Baseline (Week 0) to Week 12/Final Visit in all treatment groups. In the 400 µg/day dose group, the mean change in the SKP HFA pMDI group and the AZ CFC pMDI group was +16.1 L/min and +18.4 L/min, respectively, in the PP population, and +16.3 L/min and +17.3 L/min, respectively, in the Full Analysis Set. Non-inferiority was demonstrated for the 400 µg/day dose as the upper limit of

the 95% CI for the least square mean difference between the SKP HFA pMDI and the AZ CFC pMDI groups was < 20 L/min (+18.9 L/min and +14.8 L/min in the PP population and Full Analysis Set, respectively).

- In the 800 µg/day dose group, the mean change in the SKP HFA pMDI group and the AZ CFC pMDI group was +15.4 L/min and +16.6 L/min, respectively, in the PP population, and +14.8 L/min and +17.4 L/min, respectively, in the Full Analysis Set population. Non-inferiority was demonstrated for the 800 µg/day dose as the upper limit of 95% CI for the least square mean difference between the SKP HFA pMDI and the AZ CFC pMDI groups was < 20 L/min (+13.7 L/min and +14.0 L/min in the PP and Full Analysis Set populations, respectively).
- All treatment groups showed an increase in FEV_1 from Baseline (Week 0) to Week 12, with the greatest increases occurring in the 800 µg/day dose groups. Similarly, all treatment groups showed an increase in FVC and $FEF_{25\%-75\%}$ from Baseline (Week 0) to Week 12. Although the mean increase from Baseline was greater in the SKP HFA pMDI group, there was no clinically significant difference between the groups for both the 400 µg/day and 800 µg/day dose groups by Week 12.
- In both the 400 µg/day and 800 µg/day dose groups, the percentage of patients with at least one asthma exacerbation was similar between the AZ CFC pMDI and SKP HFA pMDI groups at each visit. Two patients in the AZ CFC pMDI 800 µg/day group and one patient in the SKP HFA pMDI 800 µg/day group had a severe asthma exacerbation, which required concomitant medication.
- The AZ CFC pMDI 400 µg/day dose group showed a greater increase in PM PEFR from Baseline (Week 0) to Week 12 than the SKP HFA pMDI 400 µg/day group (+17.6 L/min versus +5.0 L/min). However, the difference was not statistically significant (95% CI: -32.9 to 7.1 L/min). Increases in PM PEFR were similar for the 800 µg/day dose groups (+9.1 L/min versus +10.2 L/min).
- Mean change in asthma symptoms scores and sleep disturbance scores were similar between treatment groups at the same dose level.

SAFETY RESULTS:

- Adverse events were reported by 151 of 321 patients (47.0%). There were slightly more patients with an AE in the combined SKP HFA pMDI group (51.2%) compared to the AZ CFC pMDI group (42.8%). However, the difference was not statistically significant (p=0.146).
- For each treatment group, the most common AE system organ class was Respiratory, Thoracic, and Mediastinal Disorders. The most common AE was nasopharyngitis in the SKP HFA pMDI group (12.3%), whereas headache was the most common AE in the AZ CFC pMDI group (8.2%). Other common AEs (> 2% in both groups) were upper respiratory tract infection, respiratory tract infection, asthma, and lower respiratory tract infection.
- Most AEs were mild or moderate in severity. There were a total of 8 severe AEs in 7 patients (4.3%) in the combined SKP HFA pMDI group and a total of 8 severe AEs in 6 patients (3.8%) in the combined AZ CFC pMDI group.
- Most AEs were not judged by the Investigator to be related to the study drug. There were a total of 11 AEs in 10 patients (6.2%) judged by the Investigator to be related in the combined SKP HFA pMDI group and a total of 6 AEs in 5

patients (3.1%) judged by the Investigator to be related in the combined AZ CFC pMDI group.

- There were 3 serious adverse events (SAEs) in the SKP HFA pMDI group compared to one SAE in the AZ CFC pMDI group. However, none of the SAEs in the study were judged by the Investigator to be related to the study drug. Three of the 4 patients with an SAE went on to complete the study; 1 patient in the SKP HFA pMDI 400 µg/day group, who had a severe exacerbation of asthma, was discontinued from the study.
- There were no clinically significant differences between AZ CFC pMDI and SKP HFA pMDI groups for any of the hematology or blood chemistry parameters. Three clinically significant abnormal laboratory evaluations (high alanine aminotransferase [ALT] values), were recorded in two patients in the SKP HFA pMDI 800 µg/day group and one patient in the AZ CFC pMDI 400 µg/day group. These abnormal evaluations were not resolved in two patients at the end of the study.
- There were no clinically significant differences in vital signs (systolic and diastolic blood pressure and heart rate) between treatment groups during the Treatment Period.
- There were 3 patients in the study who had evidence of oral candidiasis at Final Visit; 2 patients (2.3%) in the SKP HFA pMDI 800 µg/day group and 1 patient (1.3%) in the AZ CFC pMDI 400 µg/day group.

Date of the report: **13-Jan-2005 (Final CSR)**