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, Parallel Group, Stratified, Multicenter, 12-Week Safety and Efficacy Study of an Investigational Budesonide HFA Metered Dose Inhaler and a Conventional Budesonide CFC Metered Dose Inhaler (Pulmicort®) in Pediatric Patients with Asthma	
Study Centers:	Multicenter study - 38 study sites in Europe (France, Germany, Spain, Sweden and Ukraine).	
Publication (reference):	Not Applicable.	
Studied period: FPFV: LPLV:	 14-Oct-2003 11-May-2004	Phase of development: Phase III
Objectives:	The primary objective of the study was: ▪ To demonstrate the non-inferiority of the SkyePharma (SKP) hydrofluoroalkane (HFA) pressurized metered dose inhaler (pMDI) (SKP HFA pMDI) 100 µg per actuation at 400 µg/day (2 inhalations twice daily) compared with the conventional AstraZeneca (AZ) chlorofluorocarbon (CFC) pMDI (AZ CFC pMDI) 100 µg per actuation at 400 µg/day (2 inhalations twice daily) using mean percentage change in forced expiratory volume (FEV_1) from Baseline (Week 0) to Week 12 (or Final Visit for discontinued patients). The secondary objectives were: ▪ To compare the pharmacokinetics (PK) of budesonide at a single-dose level (200 µg) delivered by SKP HFA pMDI and AZ CFC pMDI in a subset population at selected study centers; ▪ To determine if the SKP HFA pMDI is comparable to the AZ CFC pMDI using other traditional clinical endpoints (pulmonary function tests [PFTs], frequency of asthma exacerbations, and patient derived data recorded daily on electronic diaries); ▪ To compare the systemic effects of the SKP HFA pMDI to the AZ CFC pMDI using 12-hour creatinine-corrected urinary cortisol levels in a subset	

	population at selected study centers; ▪ To evaluate the safety of the SKP HFA pMDI using incidence of treatment-emergent adverse events (AEs), changes in vital signs and oropharyngeal examinations.
Methods:	This was a Phase III, randomized, double blind, parallel group, stratified, multicenter study designed to compare the safety and efficacy of the SKP HFA pMDI 100 µg/actuation to the AZ CFC pMDI 100 µg/actuation at 400 µg/day dose level in pediatric patients with mild to moderate asthma. 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 800 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). 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 during which they received no asthma maintenance therapy. However, the use of salbutamol pMDI was permitted (as needed) for all patients during the Run-In Period for the control of worsening asthma symptoms. At the Baseline Visit (Week 0) following the Run-In Period, eligible patients were randomized to receive either SKP HFA pMDI or AZ CFC pMDI. Patients were stratified according to their prior inhaled steroid use (steroid-requiring versus steroid-free), Baseline FEV_1 % predicted (60% to 80% versus > 80%), and spacer use (spacer user versus no spacer). Clinical visits took place at Weeks 0, 2, 4, 8, and 12 for PFTs (spirometry), assessment of AEs, and review of electronic diary.
Number of patients (planned and analyzed):	It was planned to enroll approximately 160 patients (80 patients per group). A total of 159 patients were randomized (77 patients received SKP HFA pMDI and 82 patients received AZ CFC pMDI). There were 159 patients included in the Safety analysis, 157 patients included in the Full Analysis Set and 151 patients included in the Per-Protocol (PP) analysis.
Diagnosis and main criteria for inclusion:	Pediatric patients (6 to 12 years of age) with stable, mild to moderate, and symptomatic asthma; with a documented medical history of at least 6 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 800 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 > 60% (no upper

	limit) of predicted normal values after withholding inhaled β-agonists and corticosteroids 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 standard dose inhalations of salbutamol pMDI).
Test product, dose and mode of administration, batch number:	The investigational product was SKP HFA pMDI 100 μg/actuation (2 inhalations twice daily, 400 μg/day) with placebo CFC pMDI (2 inhalations twice daily). Patients were provided with a commercially available spacer from AZ, if needed. Batch Numbers: SKP HFA pMDI, 400 μg/day: S03C02I Placebo CFC pMDI: 3041729
Duration of treatment:	12 Weeks
Reference product, dose and mode of administration, batch number:	The reference product was AZ CFC pMDI 100 μg/actuation (2 inhalations twice daily, 400 μg/day) plus placebo HFA pMDI (2 inhalations twice daily). Patients were provided with a commercially available spacer from AZ, if needed. Batch Numbers: AZ CFC pMDI 400 μg/day: 41550 Placebo HFA pMDI: S03D02I
Criteria for evaluation:	
Efficacy:	The primary efficacy endpoint was the mean percentage change in FEV_1 from the Baseline Visit (Week 0) to Week 12 (or Final Visit for early discontinuations). Secondary efficacy endpoints included PFTs (FEV_1 percentage predicted normal, forced vital capacity [FVC] and forced expiratory flow 25% to 75% [$FEF_{25\%-75\%}$]), frequency of asthma exacerbations, and patient electronic diary data (morning [AM] and evening [PM] peak expiratory flow rate [PEFR], asthma symptom scores, sleep disturbance scores, and frequency of salbutamol pMDI used as rescue medication).
Pharmacokinetics:	Plasma samples were collected from a subset population (n=5) at pre-dose and at scheduled intervals for the 6 hours after the morning dose on one study day after randomization. The plasma concentrations of budesonide at a single dose level (200 μg) using the two inhaler devices were measured and the following PK parameters calculated: C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf} and $t_{1/2}$.
Safety:	The primary safety assessment was the change in 12-hour creatinine-corrected urinary cortisol levels from Baseline Visit (Week 0) to Week 12. Urine samples were collected from a subset population. The secondary safety endpoints included the incidence of

	treatment-emergent AEs, changes in vital signs and oropharyngeal examinations.
Statistical Methods:	A non-inferiority analysis was performed to demonstrate that SKP HFA pMDI was not inferior to AZ CFC pMDI in increasing FEV_1 (changes from Baseline [Week 0] to Week 12). Analysis of variance (ANOVA) with effects for treatment, prior steroid use, Baseline FEV_1 category, and spacer use 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 percentage change in FEV_1 from Baseline Visit (Week 0) to Week 12 (or Final Visit for patients who terminated early). The confidence limit was 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 of mean percentage change in FEV_1 (AZ CFC pMDI - SKP HFA pMDI) was < 10%. The primary efficacy analysis was based on the PP population and the Full Analysis Set.

SUMMARY

EFFICACY and PHARMACOKINETIC RESULTS:

- For the primary efficacy endpoint, percentage change in FEV_1 from the Baseline (Week 0) to Week 12 (or Final Visit for early discontinuations), the estimated difference between the treatments (AZ CFC pMDI minus SKP HFA pMDI) was -2.584 % for the PP population. The 95% confidence interval was -7.559 % to 2.392 % and therefore, non-inferiority of SKP HFA pMDI was demonstrated. In the Full Analysis Set, the estimated difference was -3.098 % and the 95% confidence interval was -7.956 % to 1.760 %, which also confirmed the non-inferiority of SKP HFA pMDI to AZ CFC pMDI.
- With respect to the secondary efficacy endpoints (including both spirometric PFTs, daily AM and PM PEFRs, the frequency of rescue salbutamol use, and the clinical asthma scores), no statistically significant differences were found between SKP HFA pMDI and AZ CFC pMDI.
- Maximum concentrations of budesonide were in the range of 0.193 to 0.397 ng/mL for the three evaluable patients dosed with AZ CFC pMDI. The C_{max} for the patient using the SKP HFA pMDI was also in the same range with a value of 0.302 ng/mL. Maximum concentrations were reached 10 to 20 minutes following drug administration. The range of AUC_{0-t} data representing the overall systemic exposure to budesonide was between 0.082 to 0.723 ng.h/mL for the patients dosed with the AZ CFC pMDI. The AUC_{0-t} for the patient dosed using the SKP HFA pMDI (0.293 ng.h/mL) was included within this range. Terminal phase half-life ranged from 0.69 to 2.50 hours in the four patients analyzed.

SAFETY RESULTS:

- Overall, the number of patients experiencing an AE during the course of the study was comparable between treatment groups (37.7% in the SKP HFA pMDI group and 39.0% in the AZ CFC pMDI group). The number of patients reporting an AE was not statistically different between treatment groups (p = 0.872).
- The majority of AEs were mild or moderate in severity and were largely due to

the patient's underlying condition. There were 2 patients in each treatment group who were discontinued from the study due to an AE (asthma exacerbation in each case). However, these events were not considered related to study medication.

- There were no SAEs during the study.
- Most of the AEs were judged by the Investigator to be unrelated to the study medication. However, 2 patients in each treatment group experienced AEs which were judged by the Investigator related to study medication: hoarseness (AZ CFC pMDI group), oral canker (AZ CFC pMDI group), headache (SKP HFA pMDI group), and bitterness in the mouth (both treatment groups). These AEs were all expected for this type of treatment in this population and were mild to moderate in severity.
- With respect to 12-hour creatinine-corrected urinary cortisol, mean values for the SKP HFA pMDI and AZ CFC pMDI groups were similar at Baseline (Week 0) (SKP HFA pMDI, 3.5 µmol/mol [n = 2] versus AZ CFC pMDI, 4.8 µmol/mol [n = 4]) but higher at Week 12 / Final Visit in the SKP HFA pMDI group (SKP HFA pMDI, 10.0 µmol/mol [n = 3] versus AZ CFC pMDI, 4.6 µmol/mol [n = 8]). Changes from Baseline could not be calculated in the SKP HFA pMDI group as there were no patients who had results both at Baseline (Week 0) and Week 12 / Final Visit.
- There were no clinically significant changes in vital signs (systolic/diastolic blood pressure and heart rate) during the study, and there was no evidence of oral candidiasis at Final Visit in either treatment group.

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