2 STUDY SYNOPSIS

Name of Sponsor: HEXAL AG	**Individual Study Table Referring to Dossier Part**	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: Formoterol fumarate	**Report:**	
Title of the study:	Open-label, multi-center, non-controlled follow-up study over 3-months on the safety of Formoterol Easyhaler® in approximately 35 asthmatic pediatric patients initially treated in study 2003-51-DPI-2 Protocol No: 2003-72-DPI-6	
Date of final report:	Final Version, December 17, 2007	
Investigators:	Coordinating Investigator: [redacted] For a complete list of participating centers and investigators please refer to [redacted]	
Study Centers:	7 centers in Lithuania [redacted]	
Period of study:	First patient enrolled: 18 January 2005 Last patient completed: 11 July 2005	
Clinical phase:	Phase III (extension study)	
Objectives:	The objective of the present study was to evaluate the long-term safety of Formoterol Easyhaler® 12 µg formoterol/dose in asthmatic pediatric patients. In addition, efficacy of Formoterol Easyhaler® 12 µg formoterol/dose was under investigation.	
Methodology (design of study):	Open-label, multi-center, non-controlled follow-up study in children with moderate to severe persistent asthma.	
Number of patients:	Planned for enrollment: 35 patients Enrolled and treated: 31 patients Premature terminations: 2 patients (due to an adverse event [AE] and withdrawal of consent) Completed as per protocol: 27 patients Data set for safety analysis: 31 patients	

Diagnosis and main criteria for criteria for inclusion:	Patients who participated in the preceding study 2003-51-DPI-2 and who regularly terminated that study at Visit 6 after having received Formoterol Easyhaler® in Period 2 as randomized, and who were without any significant medical condition or laboratory profile during the study 2003-51-DPI-2 that might have compromised the patient's safety, compliance, or interfered with the evaluation or precluded completion of the present study.
Test product	• Name: Formoterol Easyhaler® • Formulation: Multidose powder inhaler (MPI) (containing 120 puffs) • Company responsible for placing product on the market: HEXAL AG, Germany • Unit dose: 12 µg/puff • Mode/route: Powder/inhaled through the mouth into the lung • Regimen: Multiple dose (1 puff twice daily for 3 months) • Batch no.: 1067664 • Retest date: 09/2006
Rescue medication	• Name: Salbutamol • Trade name: SalbuHEXAL® N Dosieraerosol • Formulation: Metered dose inhaler (MDI) (containing 200 puffs) • Company responsible for placing product on the market: Hexal AG, Holzkirchen, Germany • Unit dose: 100 µg per actuation • Mode/route: Powder/inhaled through the mouth into the lung • Regimen: Age <12 years: Multiple dose (1 puff when needed, maximum of 4 puffs/day) Age ≥12 years: Multiple dose (1-2 puffs when needed, maximum of 8 puffs/day) • Batch no.: 42TF14 • Retest date: 03/2006
Duration of treatment:	Treatment period: 3 months (patients had to be treated in the preceding crossover study 2003-51-DPI-2 with Foradil® Aerolizer™ during the first 3 months [Period 1] and Formoterol Easyhaler® during the second 3 months [Period 2]) After Visit 6 (start of study 2003-72-DPI-6 and end of study 2003-51-DPI-2), 3 further study visits followed, which were scheduled every 4 weeks.
Treatment assignment and administration	If the patient and his/her parents or legal guardian agreed to participate in the present follow-up study 2003-72-DPI-6, he/she kept the patient number which was assigned to him/her in the previous study 2003-51-DPI-2. All patients admitted to the present study received the same treatment, i.e. Formoterol Easyhaler® (12 µg formoterol/puff), from the first study visit (Visit 6) on for a further 3 months. Patients were asked to apply the medication/device twice daily, with an interval of about 12 hours between the puffs.

Assessment of efficacy / spirometry:	Spirometry parameters were assessed on each of the scheduled visits.
Assessment of safety / adverse drug reactions:	The investigators asked the patients every week either during the study visits or by phone calls for any symptom or AE which they might have experienced since the last visit or weekly phone call.
Criteria of evaluation:	*Primary safety parameter:* • For this safety study the incidence rate of adverse drug reactions (ADRs), i.e. all AEs for which the investigator judged the relationship to study medication as "suspected", was defined as the primary criterion. *Secondary safety parameters:* • (Serious) AEs • AEs leading to premature termination • Asthma exacerbations • Safety laboratory • Serum potassium • Vital signs (blood pressure and heart rate) • Electrocardiogram (ECG) • Physical examination/weight • Overall tolerability as assessed by investigator (5-point rating scale). In addition, patient's compliance was assessed. *Secondary efficacy parameters:* • Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC), FEV_1/FVC, Peak Expiratory Flow (PEF) at every visit • Asthma symptoms at every visit • Use of rescue medication • Premature termination due to unsatisfactory response • Changes in the corticosteroid therapy • Overall efficacy assessment by investigator (5-point rating scale)
Statistical methods:	Descriptive statistics were calculated and frequency tables were created for the incidence of ADRs and the number of ADRs per patient. These analyses were carried out overall and stratified by age group (age group 1: 6 to <12 years, age group 2: 12 to ≤17 years). All secondary safety and efficacy endpoints were analyzed descriptively using appropriate summary tables and/or statistics.

Summary and conclusions:

Efficacy:

The present study 2003-72-DPI-6 was a 3-month follow-up study conducted in pediatric patients who had been pretreated with formoterol in the initial crossover study 2003-51-DPI-2 for 6 months in total, including 3 months of treatment with Formoterol Easyhaler® in Period 2 of study 2003-51-DPI-2. Thus, the present follow-up study demonstrated the long-term efficacy of Formoterol Easyhaler® for a total of 6 months. The efficacy results showed that the good efficacy results obtained at the end of the initial crossover study 2003-51-DPI-2 were maintained throughout the present extension study 2003-72-DPI-6.

The main efficacy results were as follows:

- Spirometric data: In the PP population, mean FEV_1 and PEF were stable with slight increases during the present study by 0.08 L (FEV_1) and by 2.6 L/min (PEF), respectively. Similarly, small increases were seen for $\%FEV_1$ predicted and for FVC, while FEV_1/FVC decreased marginally. There were no relevant differences between the 2 age groups.
- Asthma symptoms: Only few patients (no more than 6 patients per symptom at any time point) reported asthma symptoms during the study, which were all of mild intensity. Mean scores minimally decreased, i.e. improved, during the present study from Visit 6 to Visit 9.
- Use of rescue medication: In the PP population, 15 patients (55.6%) used rescue medication during the study and the mean number of daily puffs was 0.2 puffs/day with a range of 0 to 2 puffs/day.
- Assessment of overall efficacy: For all patients the investigators judged the overall efficacy of Formoterol Easyhaler® to be "very good" (81.5% of patients) or "good" (18.5%).

None of the patients terminated the study due to unsatisfactory response to study medication.

Results were consistent between the ITT population and the PP population.

Safety:

Formoterol Easyhaler® was demonstrated to be safe and well-tolerated in the present 3-month follow-up study 2003-72-DPI-6 conducted in pediatric patients who completed treatment with Formoterol Easyhaler® in the second 3-month period (Period 2) of the initial study 2003-51-DPI-2. Thus, patients who completed the present study had been exposed to formoterol for a total of 9 months including treatment with Formoterol Easyhaler® for 6 consecutive months. Overall there were no findings leading to any safety concerns during the present follow-up study.

Safety results were as follows:

- Primary safety variable ADR: Two patients (6.5%) reported 1 ADR each. Both patients belonged to age group 2 (12 - <18 years). Two additional patients reported AEs with unassessable relationship to study medication. All these events were not considered as serious or related to asthma. Three events were of mild intensity and 1 of moderate intensity.
- AEs: 10 AEs were reported in 8 patients (25.8%). The most frequent AEs were viral infection (3 patients [9.7%]) and ventricular extrasystoles (2 [6.5%]). None of the AEs were considered related to asthma or severe in intensity.
- SAEs: No SAEs occurred during the study.
- AEs leading to premature termination of the study: Only 1 patient (3.2%) terminated the study prematurely due to an AE (mild ventricular extrasystoles).
- Asthma exacerbations documented as an AE: No asthma exacerbations were documented as AE.
- Laboratory data (except serum potassium): No findings of concern were found in the analysis of hematology and clinical chemistry data. All abnormal values that occurred during the study were judged by the investigator as not clinically relevant.
- Serum potassium: At the end of this 3-month follow-up study, median serum potassium levels had slightly decreased compared to Visit 6. No abnormal serum potassium values were reported at Visit 9. At Visits 7 or 8, no abnormally low and only 3 abnormally high potassium values that occurred were considered clinically relevant and for 1 patient a corresponding AE was reported. All other abnormal serum potassium values were considered as not clinically relevant by the investigator.
- Other safety data: No findings of concern were observed in the analysis of other safety data (vital signs, physical examination, and body weight). Overall tolerability was considered by the investigator as good or very good. During the present study, mean QTc only marginally changed by –2 ms and individual changes ranged from –60 to 70 ms. Abnormal ECG findings were observed for 5 patients (16.1%) at Visit 9. For 3 of these patients a corresponding AE was reported, all of which led to discontinuation of the study medication.

Conclusions:

The data obtained in this 3-month follow-up study conducted in pediatric patients who had been treated with formoterol for 6 months prior to the present study show that Formoterol Easyhaler® is an efficacious, safe, and well-tolerated long-term treatment of moderate to severe persistent asthma in children.