AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Formoterol pMDI
Study Code	D589GC00002
Edition Number	1
Date	16 October 2012

A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study of single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via Symbicort pMDI and Foradil® Aerolizer® 12 µg evaluating the bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg bid

Study dates: First patient enrolled: 07 October 2010
Last patient last visit: 03 January 2012

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was conducted at 19 centers in the United States of America (USA).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the bronchodilating effects of 3 doses of formoterol given in combination with budesonide as Symbicort pMDI in a population of asthmatic children demonstrated to be stable on a medium dose range of ICS therapy	Average 12-hour FEV_1	Efficacy
Secondary	**Secondary**	
To evaluate the bronchodilating effect of Foradil Aerolizer (formoterol fumarate inhalation powder; Merck) 12 µg	Maximum 12-hour FEV_1	Efficacy
	FEV_1 at each time point	
	FEV_1 value at 12 hours	
To determine the systemic exposure to formoterol following administration of formoterol 2.25 µg, 4.5 µg, and 9 µg, given in combination with budesonide as Symbicort pMDI or Foradil Aerolizer 12 µg	Amount of formoterol excreted in the urine over a 12-hour period after administration (Ae[0-12h])	Pharmacokinetic
	Fraction of the formoterol dose excreted in the urine over a 12-hour period after administration (fe[0-12h])	
To evaluate the safety of formoterol, given in combination with budesonide, in a population of asthmatic children demonstrated to be stable on a medium dose range of ICS therapy	Treatment-emergent adverse events	Safety
	Other significant adverse events	
	Number of withdrawals due to predefined criteria for worsening of asthma, physical examinations, and vital signs	

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid.

Study design

This was a Phase 2, single-dose, randomized, double-blind, 5-way cross-over, active- and placebo-controlled, multicenter study comparing single doses of 2.25 µg, 4.5 µg, and 9 µg of inhaled formoterol given as Symbicort pMDI and Foradil Aerolizer 12 µg dry powder inhaler with placebo treatment, given in combination with budesonide pMDI 160 µg, in pediatric patients with asthma.

Target subject population and sample size

Male and female patients (ages 6 to <12 years inclusive) who have a documented clinical diagnosis of asthma as defined by the American Thoracic Society for at least 6 months prior to Visit 1 and have required daily inhaled glucocorticosteroid therapy in the medium dose range (as defined by 2007 National Asthma Education and Prevention Program guidelines) for at least 4 weeks prior to Visit 1. Patients must demonstrate sufficient reversibility to bronchodilators and meet lung-function criteria.

An adequate number of patients were to be randomized to obtain 50 completed patients; 54 patients were randomized to obtain 50 completed patients.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Details of investigational product and any other study treatments

Treatment	Dosage and mode of administration	Manufacturer/ Batch number
Investigational Product		
Symbicort 80/2.25 µg	pMDI for oral inhalation, 80/2.25 µg	10-002603AZ, 10-002603AZ, 5000002C00
Symbicort 80/4.5 µg	pMDI for oral inhalation, 80/4.5 µg	2000097D00, 2000105D00, 2000125D00, 2000091G00
Comparator		
Foradil® Aerolizer® 12 µg	Aerolizer® dry powder inhaler for oral inhalation, 12 µg	S0226, S0256AB, F8002, S0226
Placebo	pMDI (HFA) for oral inhalation	10-002586AZ, 10-002586AZ, 3000319E00
Maintenance medication		
Budesonide HFA pMDI 40 µg	pMDI (HFA) for oral inhalation, 40 µg	10-002584AZ, 10-002584AZ, 1000014C00
Budesonide HFA pMDI 80 µg	pMDI (HFA) for oral inhalation, 80 µg	10-002604AZ, 10-002604AZ, 2000122C00

HFA = hydrofluoroalkane; pMDI = pressurized metered dose inhaler.

Duration of treatment

The cross-over study consisted of 5 single-day treatment periods, preceded by a 1- to 2-week run-in standardization period and separated by 3- to 14-day washout periods.

Statistical methods

The primary efficacy endpoint was analyzed with an additive analysis of covariance (ANCOVA) model appropriate for a cross-over design, adjusting for the fixed factors of patient, period, and treatment, and for the covariate of pre-dose FEV_1 from each visit.

The secondary efficacy endpoints were analyzed in the same manner; using the FEV_1 values at each time point, descriptive statistics were presented to show the pattern of FEV_1 responses over time from the 12-hour serial FEV_1 assessments.

Multiplicity for the 3 doses of formoterol was addressed by using a hierarchical testing procedure starting with the highest dose. If statistical significance was not achieved at the 0.05 level for a given dose, formal statistical testing was stopped.

Nominal p-values were reported for the comparison of Foradil and placebo.

Urinary excretion of formoterol was summarized descriptively for each treatment, including a summary of the number of values below the limit of detection for each treatment. A multiplicative ANOVA model with patient, period, and treatment as fixed factors was fitted to the data.

All statistical comparisons were based on a 2-sided test using an alpha (α) level of significance of 5%, unless otherwise specified. Secondary analyses reported nominal 5% levels of significance. No other correction to the reported p-values was made for the analysis of secondary measures.

The SAS® software, version 8.2 or higher, was used to produce all statistical outputs.

Subject population

A total of 169 patients were enrolled in the study from 19 centers in the USA. Fifty-four patients from 14 centers were randomized and 50 patients completed the study. Four patients discontinued the study, 2 due to patient/caregiver decision and 2 due to adverse events. The target population was captured for the study. Of the patients randomized, 57.4% (31 patients) were male. The majority of subjects were either white (57.4%, 31 patients) or black/African American (40.7%, 22 patients). Mean age was 9.2 years (ranging from 6 to 11 years), with 20.4% (11 patients) of all patients randomized between the ages of 6 to <8 years. On average, patients entered the study with a 73.2-month history of asthma.

Summary of efficacy results

- The primary objective evaluated the bronchodilating effects of 3 doses of formoterol given in combination with budesonide as Symbicort pMDI in a population of asthmatic children. Formoterol 4.5 µg and 9 µg, administered as single doses via Symbicort pMDI, were statistically significantly superior to placebo in improving average FEV_1 over the 12-hour time period ($p<0.0001$), maximum FEV_1 ($p<0.0001$), and FEV_1 at 12 hours ($p = 0.009$ and $p< 0.0001$ respectively), in asthmatic children aged 6-11 years.

- Formoterol 2.25 µg, administered as a single dose via Symbicort pMDI, was statistically significantly superior to placebo in improving average FEV_1 over the 12-hour time period ($p = 0.0001$) and maximum FEV_1 ($p = 0.0011$), while no difference could be detected 12 hours after dosing ($p = 0.5509$).

- Formoterol 4.5 µg and 9 µg, administered as single doses via Symbicort pMDI, were statistically significantly superior to formoterol 2.25 µg administered as a single dose via Symbicort pMDI, as measured by improvements in average FEV_1 over 12 hours ($p = 0.0007$ and $p = 0.0001$, respectively), maximum FEV_1 ($p = 0.0011$ and $p = 0.0035$, respectively), and FEV_1 at 12 hours ($p = 0.0400$ and $p = 0.0004$, respectively).

- There were no statistically significant differences between the formoterol 4.5 µg and 9 µg doses for the 3 FEV_1 endpoints, although FEV_1 at 12 hours after dose differed numerically in favor of the 9 µg dose.

Secondary objectives (to evaluate the bronchodilating effect of the Foradil Aerolizer 12 µg dose; and to determine the systemic exposure to formoterol following administration of formoterol 2.25 µg, 4.5 µg, and 9 µg given in combination with budesonide as Symbicort pMDI or Foradil Aerolizer 12 µg):

- Foradil 12 µg demonstrated statistically significant bronchodilation over the formoterol 2.25 µg dose. Both the formoterol 9 µg and 4.5 µg doses demonstrated comparable bronchodilation with Foradil 12 µg.

Summary of pharmacokinetic results

The amount of formoterol in the urine increased with dose across the range of 2.25 µg, 4.5 µg, and 9 µg, suggesting generally dose-proportional PK with approximately 5% of the dose excreted unchanged. The amount of formoterol in urine after treatment with Foradil 12 µg was comparable to that after treatment with formoterol 9 µg.

Summary of safety results

After randomization, there were a total of 42 adverse events (AEs) reported by 13 patients. Sixteen AEs were reported by 7 patients on the same day that treatment medication was received; 9 AEs were reported by 8 patients 1 to 2 days after treatment medication was received; 3 AEs were reported by 3 patients 3 to 4 days after treatment medication was received; and 14 AEs were reported by 9 patients 5 or more days after treatment medication was received.

The most common AE was headache (12 incidences in 5 patients) and occurred after all treatments except budesonide 160 µg/Foradil 12.0 µg. The second most common AE was oropharyngeal pain (4 incidences in 3 patients) and occurred after all treatments except formoterol 2.25 µg and placebo.

Two patients discontinued study treatment due to AEs (an 8-year-old with acute sinusitis and asthma who had received 2.25 µg formoterol and a 10-year-old with headache who had received 9 µg formoterol). The event of headache was considered related to study treatment and was the only AE during the study that was considered related to study treatment. There were no SAEs or deaths reported during the study. Vital sign and physical examination findings did not raise any safety concerns.