



AZ Briefing document

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**AstraZeneca Briefing Materials: Review of the Benefits and Risks of
Formoterol-containing Products**

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
bid	Twice daily
BTS/SIGN	British Thoracic Society and Scottish Intercollegiate Guidelines Network
COPD	Chronic obstructive pulmonary disease
DSaRM	Drug Safety and Risk Management Advisory Committee
EPR III	Expert Panel Report III (NIH asthma treatment guideline)
EU	European Union
FEV ₁	Forced expiratory volume in one second
GINA	Global Initiative for Asthma
HRQL	Health-related quality of life
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICS	Inhaled corticosteroid
LABA	Long-acting β_2 -agonist
M-H	Mantel-Haenszel
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MID	Minimal important difference
od	Once daily
OHSU	Oregon Health and Science University
PAC	Pediatric Advisory Committee
PACQLQ	Pediatric asthma caregiver quality of life questionnaire
PADAC	Pulmonary/Allergy Drugs Advisory Committee
PAQLQ(S)	Pediatric Asthma Quality of Life Questionnaire (standardized)
PEF	Peak expiratory flow
PI	Prescribing Information
pMDI	Pressurized metered dose inhaler
% PN	Percent of predicted normal
PRO	Patient reported outcome
SABA	Short-acting β_2 -agonist
SAE	Serious adverse event

EXECUTIVE SUMMARY

Introduction

A joint meeting of the Pulmonary/Allergy Drugs Advisory Committee (PADAC), Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC) is scheduled for December 10 and 11, 2008 to review the benefits and risks of long-acting β_2 -agonists (LABAs) for the treatment of asthma.

The purpose of this document is to review the benefits and risks of formoterol in adult and pediatric patients with asthma. The document includes data generated in clinical trials and collected through post-marketing surveillance with AstraZeneca's formoterol-containing products in the US and the rest of world. The LABA marketed by AstraZeneca is formoterol fumarate dihydrate (hereafter formoterol), which is marketed in the US in a fixed combination with the inhaled corticosteroid (ICS) budesonide as SYMBICORT[®] Inhalation Aerosol (pMDI). Outside of the US, formoterol is marketed by AstraZeneca both as a monoproduct, OXIS[™] TURBUHALER[®], and in combination with budesonide as SYMBICORT TURBUHALER.

Overall assessment

Based on a comprehensive review of the efficacy and safety of its formoterol-containing products, AstraZeneca believes that SYMBICORT pMDI exhibits a favorable benefit-risk profile in patients 6 years of age and older. SYMBICORT pMDI offers an important therapeutic option for asthma patients who cannot be adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids (ICS)) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. AstraZeneca concurs with current evidence-based national and international asthma treatment guidelines, which recommend that patients with persistent asthma should always receive concomitant anti-inflammatory medication (eg, ICS) before considering adding maintenance treatment with a LABA.

As of December 2006, AstraZeneca had studied over 72,000 subjects with mild, moderate, and severe asthma in 64 clinical trials of 3-12 months duration. Of these subjects, approximately 50,000 were treated with formoterol-containing products. The safety data presented in this briefing document, a subset of that available from all clinical trials, was selected on the basis of criteria outlined by the FDA. In addition, as of 30 September 2008, the estimated postmarketing exposure to AstraZeneca formoterol-containing products approached 6 billion treatment days (SYMBICORT pMDI >48 million, SYMBICORT TURBUHALER >4.4 billion, OXIS TURBUHALER >1.4 billion).

Evolution of Guidelines and Unmet Need

Asthma is a complex chronic disorder characterized by airflow obstruction, bronchial hyper-responsiveness, and underlying airway inflammation. Clinically it is characterized by recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but

variable airflow obstruction that is often reversible either spontaneously or with treatment. The therapeutic approach to asthma is focused on addressing the 2 major components of the disease, namely inflammation and bronchoconstriction. Although bronchodilators alone can reduce symptoms, long-term control of asthma requires that the underlying inflammatory process also be addressed.

Asthma treatment is approached in a step-wise fashion based on level of symptomatology and response to therapy. The first National Asthma Education and Prevention Program (NAEPP) guidelines were published in 1991, and updates were made in 1997, 2002, and most recently in 2007 (EPR III 2007). The current guidelines reaffirm that ICS is the preferred long-term control therapy for all ages. LABAs used as an adjunct to ICS therapy are preferred in Steps 3 and higher to provide long-term control of asthma symptoms; the addition of LABA to low-dose ICS has equal weight with the option of increasing from a low- to a medium-dose of ICS for youths ≥ 12 years and adults who have moderate persistent asthma or asthma inadequately controlled on low-dose ICS. Similar to the guidelines for patients >12 years, at Step 3 in children 5 to 11 years, the option of adding LABA to low-dose ICS or increasing to a medium-dose of ICS are both preferred options, equally weighted. Unlike the guidelines for patients >12 years, where these 2 options are preferred over adding other adjunctive therapies such as theophylline or LTRAs to low-dose ICS, in children 5 to 11 these are equally recommended options at Step 3. At Steps 4 and 5 for children 5 to 11 years, ICS plus LABA are the preferred option. Therefore, it is expected that LABAs may be used less frequently in school-aged children with moderate asthma than they are in adolescents and adults (EPR III 2007, GINA 2007).

The guidelines also illustrate that there are a limited number of therapeutic options for asthma treatment beyond ICS. For patients whose asthma is not controlled on low-to-medium dose ICS treatment, the alternative treatment options other than the addition of LABAs are to increase the ICS dose or to use other adjunctive treatment such as theophylline or leukotriene modifiers. For the most severe patients, chronic therapy with injectables such as omalizumab or use of oral corticosteroids may also be considered. Most of these options are recognized to have limited additional effectiveness and in some cases incur the risk of significant short and long-term toxicity.

Development and Marketing Approvals of AstraZeneca formoterol-containing products

On 21 July 2006, the FDA approved SYMBICORT pMDI (New Drug Application [NDA] 21-929) for the long-term maintenance treatment of asthma in patients 12 years of age and older. SYMBICORT should be used for patients who are not adequately controlled on other asthma controller medications or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. The maximum daily recommended dose is 640/18 μg budesonide/formoterol (two inhalations of SYMBICORT pMDI 160/4.5 twice daily). SYMBICORT pMDI is currently available in 2 strengths, SYMBICORT 80/4.5 and SYMBICORT 160/4.5. Each dose (160/9 μg or 320/9 μg) is administered as 2 oral inhalations (of 80/4.5 and 160/4.5 μg , respectively) twice daily. A supplemental NDA (sNDA) was submitted in June 2008 supporting an indication of long-term maintenance treatment of asthma with SYMBICORT pMDI in pediatric patients 6 to <12 years of age.

SYMBICORT TURBUHALER contains budesonide and formoterol and is available in 3 strengths: 80/4.5, 160/4.5 and 320/9 µg/inhalation (budesonide/formoterol). It was first approved in Sweden in 2000, and as of August 2008, it had been approved in 101 countries for long-term maintenance treatment of asthma. Of these, 91 had also approved SYMBICORT for use as maintenance and reliever therapy for the treatment of asthma (ie, patients take a daily maintenance dose of SYMBICORT and in addition take SYMBICORT as needed in response to symptoms), and 88 had approved use in patients with COPD.

OXIS TURBUHALER contains formoterol only and is available in strengths of 4.5 and 9 µg/inhalation. OXIS TURBUHALER was first approved in Sweden in 1996 and as of August 2008 was approved in 79 countries. OXIS TURBUHALER is indicated as add-on therapy to maintenance treatment with inhaled corticosteroids, for the relief of broncho-obstructive symptoms and prevention of exercise-induced symptoms in patients with asthma when adequate treatment with corticosteroids is not sufficient. For asthma treatment, the normal maintenance dose is 4.5 to 9 µg once or twice daily.

Regulatory background

Prior to 2006, both Serevent (salmeterol) and Foradil (formoterol) US labeling allowed for these LABAs to be used alone or in combination with ICS for the maintenance treatment of asthma.

Initial concerns about the safety of LABAs were based on findings from the Salmeterol Nationwide Surveillance (SNS) and Salmeterol Multi-centre Asthma Research Trial (SMART) studies. Results of the GSK SMART study and 4 placebo-controlled studies conducted with Foradil Aerolizer were the primary focus of the PADAC meeting on 13 July 2005. The Committee recommended that all LABA containing products marketed in the US should have a boxed warning added to their prescribing information. On 18 November 2005, the FDA issued a public health advisory on Serevent, Advair[®] (fluticasone propionate/salmeterol xinafoate, GSK) and Foradil[®] (formoterol, Novartis) requesting that new warnings be added to the labels of these products. The updated labels warned that the drugs "may increase the chance of severe asthma episodes, and death when these episodes occur" and were changed to recommend that these products be used only as additional therapy for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Subsequently, the prescribing information for any LABA-containing product, including SYMBICORT, has included similar warnings and precautions.

Benefits of formoterol

The benefits of LABA treatment have been summarized in a large number of reviews and evidence-based analyses (eg, OHSU draft, 2008). In addition, the recognized benefits of LABA treatment form the basis for their preferred status as adjunctive therapy in treatment guidelines ([EPR III 2007](#), [GINA 2007](#)). In summary, there is consistent evidence:

- ICS is an effective monotherapy for the treatment of mild-to-moderate asthma. LABAs should only be used as additional therapy for patients not adequately controlled on other asthma controller medications, eg, low-to-medium dose ICS.
- The addition of a LABA to an ICS provides greater efficacy than continuing with the current dose of ICS alone for patients with poorly controlled persistent asthma, based on a variety of variables, including lung function, asthma symptoms, asthma exacerbations and health-related quality of life, and adjunctive medication requirements. For children, the demonstrated benefit has generally been limited to lung function variables.
- The addition of a LABA to an ICS provides greater efficacy than a higher dose of ICS for adults and adolescents with persistent asthma, based on symptom-related variables. There is also a trend towards fewer asthma exacerbations, but not statistically significant in meta-analyses. There are insufficient published data to draw similar conclusions in children under 12 years.

The introduction of LABAs provided important additional clinical benefit compared with ICS treatment alone. The clinical benefits of combination therapy with budesonide and formoterol were first demonstrated in the landmark Formoterol and Corticosteroids Establishing Therapy (FACET) and OXIS TURBUHALER and PULMICORT TURBUHALER In the Management of Asthma (OPTIMA) trials. In these studies, the overall effectiveness of ICS plus a LABA on measures of control was demonstrated for low and high doses of ICS in patients with a range of asthma severity. In patients already receiving ICS, adding formoterol was more effective than doubling the ICS dose (O'Byrne et al 2001). Formoterol also reduced severe asthma exacerbations in patients with moderate to severe asthma both when added to a low (100 µg bid) and to a higher (400 µg bid) dose of budesonide, in addition to improving lung function and symptoms (Pauwels et al 1997).

In patients age 12 years and above, the benefit of formoterol in combination with budesonide, has been unequivocally demonstrated in numerous AstraZeneca clinical trials. These benefits include improvements across a range of measures of asthma control such as lung function; asthma worsening and exacerbations; asthma symptoms, use of rescue medication, and asthma-related quality of life measures in patients with moderate and severe asthma. Many of these benefits are apparent even when compared to high doses of ICS monotherapy. These conclusions are consistent with current labeling and evidence-based treatment guidelines and demonstrate that SYMBICORT is an important therapeutic option for patients with asthma.

In children younger than 12 years of age, the benefits of an ICS such as budesonide have been well demonstrated in numerous clinical trials. In studies presented in this document, evaluating children between the age of 6 to <12, the additional benefits of adding formoterol to budesonide compared to budesonide alone have been clearly demonstrated on measures of control such as FEV₁ and PEF as well as in some measures of Health-related Quality of Life (HRQL) across a range of ICS doses, while parity on other measures of control was observed in patients with asthma previously treated with ICS. In light of potential systemic effects of

high-dose ICS (eg. adrenal axis suppression and effects on growth) an additional benefit of ICS/LABA in this population may be the ability to gain asthma control with a lower dose of ICS. In this regard, for children younger than 12 years of age, the addition of formoterol to budesonide provides a definitive benefit beyond that of ICS alone for patients not adequately controlled on ICS.

Assessment of risk profile of formoterol

The clinical program that specifically supported the 2006 FDA approval of SYMBICORT pMDI included data from 31 clinical studies (16 phase II/III trials) in which 9315 subjects aged 6 and above were evaluated; a total of 6434 of these subjects received SYMBICORT pMDI. No deaths were reported during randomized treatment and no findings of concern were observed regarding risk of asthma-related death, intubations, or hospitalizations; however, given the low incidence of these events, this program was of insufficient size to draw definitive conclusions.

The overall safety of formoterol is supported by extensive data from clinical trials and postmarketing use. As of December 2006, AstraZeneca had studied over 72,000 subjects with mild, moderate, and severe asthma in 64 clinical trials of 3-12 months duration. Of these subjects, approximately 50,000 were treated with formoterol-containing products. The safety data presented in this briefing document were selected on the basis of criteria outlined by the FDA in their requests for data from AstraZeneca with particular focus on asthma-related serious adverse events (deaths, hospitalizations, and intubations) occurring during randomized treatment.

The adjudicated data included a total of 23,510 patients, 13,542 exposed to formoterol (approximately 20% received SYMBICORT pMDI), and 9,968 exposed to non-LABA treatment. The vast majority of patients in this dataset were treated with ICS at baseline, and most were expected to have continued concomitant ICS during randomized treatment based on study protocol designs. In this large number of patients, the number of deaths from any cause during randomized treatment was low (7 of 23,510). There were 3 deaths in patients on formoterol-containing treatment and 4 deaths in patients on non-LABA treatment; none of these occurred in the clinical studies contained in the US NDA for SYMBICORT pMDI. No deaths were asthma-related and there was only 1 asthma-related intubation (in a formoterol-exposed patient). While the overall event rate is low, in this large population of over 23,000 patients, there is no evidence of any imbalance in deaths favoring non-LABA treatments.

There was also no indication of an increased risk of asthma-related hospitalizations during randomized formoterol-containing treatment compared with non-LABA treatment for patients receiving treatment for up to 1 year. In addition, time to first asthma-related hospitalization was prolonged in the formoterol-exposed group compared to the non-LABA-exposed group. Similar results were obtained for patients treated with ICS + formoterol compared to ICS alone. In this analysis, the benefit of ICS + formoterol, relative to ICS alone, was not only maintained but appeared to increase over time.

Of the 3670 patients <18 years treated with formoterol, there were no deaths during randomized treatment. For patients 12 to <18 years of age, the proportion of patients with an asthma-related hospitalization was numerically lower in the group exposed to formoterol-containing products than the group exposed to non-LABA treatment (0.92% vs 1.30%), whereas among patients below 12 years of age, the proportion was numerically higher in the formoterol-exposed patients (25 out of 2155 [1.16%]) compared to the non-LABA-exposed patients (14 out of 1268 [1.10%]). The slight imbalance against formoterol-treatment in the younger age group results from a high number of asthma-related hospitalizations in one arm of study SD-039-0673; in this arm, patients were treated with an exploratory low dose of SYMBICORT TURBUHALER (80/4.5 µg once daily) that proved to be subtherapeutic. When data from this arm of Study SD-039-0673 were excluded from the overall analysis, results were consistent with those for patients 12 years and older.

When analyzed by sex, race, severity (based on FEV₁), and dose there were no findings that suggested an increased risk in the formoterol-exposed group compared to non-LABA treatment.

Overall, there is no indication of increased risk of asthma-related deaths or hospitalizations in patients using formoterol-containing treatment compared with non-LABA treatment. Because AstraZeneca has relatively little data on the use of formoterol as monotherapy, the impact of adding ICS to formoterol alone on the risk of asthma-related deaths, intubations, or hospitalizations could not be adequately assessed.

Importantly, as per guidelines and recommended clinical practice, the clinically relevant question is whether there is increased risk of adding formoterol to maintenance ICS therapy. Analysis of AstraZeneca's data showed that the addition of formoterol to ICS compared with ICS treatment alone presented no additional risk of asthma-related deaths, intubations or hospitalizations. These data provide strong evidence that there is no additional risk of adding formoterol to maintenance therapy with ICS.

Post-treatment asthma-related deaths and asthma-related hospitalizations

In the post-treatment period, there were 1 asthma-related death and 5 asthma-related hospitalizations in 13,542 formoterol-exposed patients, and there were 5 asthma-related hospitalizations in 9,968 non-LABA-exposed patients. Hence, there were too few events reported following the randomized treatment period from which to draw definitive conclusions regarding asthma-related death. With regard to asthma-related hospitalizations, no apparent increased risk was observed for patients previously treated with formoterol vs non-LABA therapy.

Epidemiology of asthma since LABA introduction

LABAs were first introduced into the US market in 1994, when salmeterol was approved as a monotherapy. Initial concerns about the safety of LABAs were based on findings from the SNS and SMART studies. Subsequent to this, some meta-analyses heavily weighted by the SMART study attributed an increase in asthma-related mortality to the use of LABAs (eg,

Salpeter et al 2006). However, the rate of asthma deaths has decreased each year since 2000, despite increasing use of LABAs for asthma treatment. Concurrently, there has been no observed increase in rates of asthma-related hospitalizations or hospital out-patient and emergency department visits (Moorman et al 2007). Consistent with guideline changes, 85% of LABA use in the US is now in the form of combination ICS/LABA treatment (Wijesinghe et al 2008).

Similar epidemiological trends are apparent outside of the US. In Canada, asthma mortality and hospitalization rates have decreased continuously both before and after the 1999 implementation of the International Classification of Diseases Tenth Revision (ICD-10) (Public Health Agency of Canada 2007). In the UK, asthma mortality rates have gradually been declining since the late 1980s; current mortality rates are generally lower than those seen in 1960 (Anderson et al 2007). A case control study investigating the association between bronchodilator treatment and death from asthma in the UK between 1994 and 1998 (Anderson et al 2005) found that use of LABA was, if anything, associated with an inverse association with asthma mortality. Others have drawn similar conclusions (eg, DiSantostefano et al 2008).

Therefore, there is no evidence from epidemiological data that the introduction of LABAs has been associated with an increase in mortality or hospitalizations due to asthma; rather, there is some evidence to indicate that the introduction of LABAs and ICS/LABA combinations has been associated with a reduction in asthma-related mortality.

Pharmacogenetic effects on response to LABA

Considerable attention has been devoted to variation in response to β_2 agonist therapy and the impact of polymorphisms in the β_2 -adrenergic receptor gene (*ADRB2*) on the safety and efficacy profiles of these medications. However, since the July 2005 PADAC meeting, a substantial body of evidence has emerged including analyses derived from more than 4000 genotyped patients in SYMBICORT studies of 3 to 12 months duration. Analyses of this dataset, which included over 700 patients identified as Arg/Arg, those believed to be the most at risk, demonstrate no differential impact due to *ADRB2* polymorphisms on measures of lung function, asthma control, or exacerbations in patients maintained on LABA therapy taken with ICS. This conclusion applies to the amino acid 16 Arg/Gly polymorphisms as well as haplotype effects across the entire gene. These data strongly suggest that the findings in the GSK SMART study and 4 placebo-controlled studies conducted with Foradil Aerolizer are not related to known *ADRB2* polymorphisms. At this time, therapeutic recommendations based on known *ADRB2* polymorphisms are unfounded.

Post-marketing surveillance

As of 30 September 2008, the estimated postmarketing exposure to AstraZeneca formoterol containing products approached 6 billion treatment days (SYMBICORT pMDI >48 million, SYMBICORT TURBUHALER >4.4 billion, OXIS TURBUHALER >1.4 billion).

The post-marketing experience with SYMBICORT and OXIS includes isolated reports of possible asthma-related death and/or other SAEs due to asthma-related symptoms (including

hospitalizations). No new safety signals around asthma have emerged from the post-marketing data analysis, and AstraZeneca considers the current benefit/risk communication in the US Prescribing Information to be appropriate.

As a result of the FDA approval, AstraZeneca implemented a post-approval US Patient Risk Management Plan for SYMBICORT pMDI. In addition to the routine post-marketing surveillance activities (such as adverse event collection and assessment, reporting and analysis processes), this plan includes enhanced pharmacovigilance practices for specific adverse events of interest, including asthma and asthma-related deaths and other serious adverse events. AstraZeneca remains committed to keep these important adverse events under close surveillance and will continue to gather and assess information as new studies complete and additional information is reported.

Overall benefit to risk

AstraZeneca data is supportive of LABA usage as described in current evidence-based national and international asthma treatment guidelines, which recommend that patients with persistent asthma should always receive concomitant anti inflammatory medication (eg, inhaled corticosteroid) before considering starting maintenance treatment with a long-acting β_2 -agonist.

In patients age 12 and above, the benefit of formoterol in combination with budesonide, has been unequivocally demonstrated in numerous AstraZeneca clinical trials. These benefits include improvements across a range of measures of asthma control such as lung function; asthma worsening and exacerbations; asthma symptoms, use of rescue medication, and asthma-related quality of life measures in patients with moderate and severe asthma. Many of these benefits are apparent even when compared to high doses of ICS monotherapy.

In children younger than 12 years of age, the benefits of an ICS such as budesonide have been well demonstrated in numerous clinical trials. In studies presented in this document, evaluating children between the age of 6 to <12, the additional benefits of adding formoterol to budesonide compared to budesonide alone have been clearly demonstrated on measures of control such as FEV₁ and PEF as well as in some measures of Health-related Quality of Life (HRQL) across a range of ICS doses, while parity on other measures of control was observed in patients with asthma previously treated with ICS. In light of potential systemic effects of high-dose ICS (eg. adrenal axis suppression and effects on growth) an additional benefit of ICS/LABA in this population may be the ability to gain asthma control with a lower dose of ICS. In this regard, for children younger than 12 years of age, the addition of formoterol to budesonide provides a definitive benefit beyond that of ICS alone for patients not adequately controlled on ICS.

This document has reviewed asthma-related serious adverse events of possible concern using data specified by and provided to the FDA earlier this year. The adjudicated data included a total of 23,510 patients, 13,542 exposed to formoterol and 9,968 exposed to non-LABA treatment. There was no indication of any increased risk of asthma-related deaths, intubations or hospitalizations with formoterol compared with non-LABA treatment in this large number

of patients. In addition, the rate of asthma-related hospitalizations was lower for formoterol- vs non-LABA exposed patients.

Importantly, as per guidelines and recommended clinical practice, the clinically relevant question is whether there is increased risk of adding formoterol to maintenance ICS therapy. Analysis of AstraZeneca's data showed that the addition of formoterol to ICS compared with ICS treatment alone presented no additional risk of asthma-related deaths, intubations or hospitalizations. These data provide strong evidence that there is no additional risk of adding formoterol to maintenance therapy with ICS.

Based on a comprehensive review of the safety and efficacy of formoterol-containing products, AstraZeneca believes that SYMBICORT pMDI exhibits a favorable benefit-risk profile in patients 6 years of age and older. The currently approved SYMBICORT pMDI prescribing information and Medication Guide ([Appendix F](#)) for patients greater than 12 years of age appropriately convey any potential risks regarding the use of SYMBICORT. SYMBICORT pMDI offers an important therapeutic option for asthma patients who cannot be adequately controlled on other asthma-controller medications (eg, low- to medium-dose ICS) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

1. BACKGROUND

1.1 Purpose

The purpose of this document is to provide the Pulmonary/Allergy Drugs (PADAC), Drug Safety and Risk Management (DSaRM), and Pediatric (PAC) Advisory Committees with a review of the benefits and risks of the long-acting β_2 -adrenoceptor agonist (LABA) formoterol in adult and pediatric patients with asthma. The document focuses on data generated in clinical trials and collected through post-marketing surveillance with AstraZeneca's formoterol-containing products in both the US and the rest of world.

1.2 Product background

The LABA marketed by AstraZeneca is formoterol fumarate dihydrate (hereafter formoterol), which is marketed in the US in a fixed combination with the inhaled corticosteroid (ICS) budesonide as SYMBICORT[®] Inhalation Aerosol (pMDI). Outside of the US, formoterol is marketed by AstraZeneca both as a monoproduct, OXIS[™] TURBUHALER[®], and in combination with budesonide as SYMBICORT TURBUHALER.

Although there are physical differences in these formoterol-containing products manufactured by AstraZeneca (pMDI and TURBUHALER) the dose of formoterol provided by each is essentially similar. Therapeutic equivalence studies (SD 039-0681 and SD 039-0682) support these similarities in dose, therefore the data for all formoterol-containing products manufactured by AstraZeneca are felt to be relevant to the assessment of benefit/risk. A short description of each product follows.

1.2.1 SYMBICORT pMDI

In the US, SYMBICORT Inhalation Aerosol is delivered with a pressurized metered-dose inhaler (hereafter referred to as SYMBICORT pMDI) and is available in 2 strengths, 80/4.5 and 160/4.5, delivering 80 and 160 µg of budesonide, respectively, and 4.5 µg of formoterol fumarate dihydrate per inhalation. Each dose (160/9 µg or 320/9 µg) is administered as 2 oral inhalations (of 80/4.5 and 160/4.5 µg, respectively) twice daily (bid). The FDA approved SYMBICORT pMDI (New Drug Application [NDA] 21-929) for the long-term maintenance treatment of asthma in patients 12 years of age and older on 21 July 2006. A supplemental NDA (sNDA) was submitted in June 2008 supporting an indication of long-term maintenance treatment of asthma with SYMBICORT pMDI in pediatric patients 6 to <12 years of age with a starting dose of 80/9 µg bid (40/4.5 µg, 2 inhalations). It should be noted that while there are differing doses of SYMBICORT pMDI available, it is only the ICS component that changes in each (ie, 80, 160 or 320 µg); the dose of formoterol remains constant (18 µg daily) regardless of patient population or ICS dose.

SYMBICORT pMDI should only be used for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT pMDI is not indicated for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled short-acting β₂-agonists (SABAs). The maximum daily recommended dose is 640/18 µg budesonide/formoterol (given as two inhalations of SYMBICORT pMDI 160/4.5 twice daily) for patients 12 years of age and older.

1.2.2 SYMBICORT TURBUHALER

SYMBICORT TURBUHALER is a dry-powder inhaler containing budesonide and formoterol, available in 3 strengths: 80/4.5, 160/4.5 and 320/9 µg/inhalation (budesonide/formoterol delivered doses). It was first approved in Sweden in 2000, and as of August 2008, it had been approved in 101 countries for long-term maintenance treatment of asthma. Of these, 91 had also approved SYMBICORT for use as maintenance and reliever therapy for the treatment of asthma (ie, patients take a daily maintenance dose of SYMBICORT and in addition take SYMBICORT as needed in response to symptoms), and 88 had approved use in patients with COPD.

SYMBICORT TURBUHALER is indicated in the regular treatment of asthma in patients 6 years of age and older where use of an ICS/LABA combination therapy is appropriate.

Recommended doses range from 80/4.5 µg one inhalation twice daily up to 320/9 µg two inhalations twice daily. As a maintenance and reliever therapy, SYMBICORT TURBUHALER can be used occasionally in doses up to 1920/54 µg/day for a limited period of time.

1.2.3 OXIS TURBUHALER

OXIS TURBUHALER is a dry-powder inhaler containing formoterol available in strengths of 4.5 and 9 µg/inhalation (delivered doses). OXIS TURBUHALER was first approved in Sweden in 1996 and as of August 2008 was approved in 79 countries. OXIS TURBUHALER is indicated as add-on therapy to maintenance treatment with inhaled corticosteroids, for the relief of broncho-obstructive symptoms and prevention of exercise-induced symptoms in patients with asthma when adequate treatment with corticosteroids is not sufficient. For asthma treatment, the normal dose is 4.5 to 9 µg once or twice daily. Regular daily doses should not exceed 36 µg (18 µg in children), although occasional doses up to 54 µg (36 µg in children) are allowed within a 24-hour period.

1.3 Regulatory background

1.3.1 LABA-related regulatory actions in the US

Salmeterol was the first LABA approved in the US. It was approved in 1994 as Serevent Inhalation Aerosol and in 1997 as Serevent Diskus. The first ICS/LABA combination, Advair (fluticasone propionate and salmeterol inhalation powder), was approved in 2000. Formoterol was first approved as the monotherapy, Foradil[®] (formoterol fumarate inhalation powder), in 2001, and as the ICS/LABA combination, SYMBICORT pMDI, in 2006. All of these products have an asthma indication. Prior to 2006, both Serevent (salmeterol) and Foradil (formoterol) US labeling allowed for these LABAs to be used alone or in combination with ICS for the maintenance treatment of asthma.

The Salmeterol Multi-Centre Asthma Research Trial (SMART) (Nelson et al 2006) was initiated by GlaxoSmithKline (GSK) in 1996 in consultation with the US Food and Drug Administration (FDA) as a large, controlled, prospective safety study to clarify signals from the Serevent Nationwide Surveillance (SNS) study (Castle et al 1993) that chronic use of Serevent[®] (salmeterol xinafoate) might be associated with severe, adverse asthma outcomes. SMART was halted prematurely in January 2003, when a planned interim analysis showed that salmeterol might be associated with an increased risk of severe asthma exacerbations, particularly in African Americans.

Novartis conducted three pivotal Phase 3 studies evaluating formoterol (Foradil) 12 µg bid and 24 µg bid as part of the original Foradil NDA. Due to concerns related to apparent dose-related serious asthma exacerbations, a Phase IV study similar in design to that of the Phase 3 studies was subsequently conducted by Novartis and reviewed by FDA. Although there were no deaths, and this study did not demonstrate a dose-related signal, the FDA did not believe this study contributed any important new information, as it was too small to definitively substantiate or refute the findings of the SMART study.

Results of the GSK SMART study of salmeterol and the 4 placebo-controlled studies conducted with formoterol (Foradil Aerolizer) were the primary focus of the PADAC meeting on 13 July 2005. The Committee recommended that all LABA-containing products marketed in the US should have a boxed warning added to their prescribing information.

On 18 November 2005, the FDA issued a public health advisory on Serevent, Advair[®] (fluticasone propionate/ salmeterol xinafoate, GSK) and Foradil[®] (formoterol, Novartis) requesting that new warnings be added to the labels of these products. The updated labels warned that the drugs "may increase the chance of severe asthma episodes, and death when these episodes occur" and were changed to recommend that these products be used only as additional therapy for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Subsequently, the prescribing information for any LABA-containing product has included similar warnings and precautions.

Therefore, when SYMBICORT pMDI was approved in the US in July 2006, the following boxed warning was included in the prescribing information:

WARNING

Long-acting beta2-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (eg, low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta2-adrenergic agonist), one of the active ingredients in SYMBICORT (see WARNINGS).

On 28 November 2007, a Pediatric Advisory Committee (PAC) meeting was held as a routine 1-year post-exclusivity review of the safety of salmeterol in children, as mandated by the Best Pharmaceuticals for Children Act (BPCA). The Office of Surveillance and Epidemiology, FDA, provided an analysis of observational and pharmacoepidemiology studies that had become available subsequent to the 2005 PADAC review, including a subgroup analysis of the pediatric populations in clinical trials.

The committee recommended updating the label for LABA-containing products to convey that the current warnings may also apply to pediatric patients and that data are not adequate to determine whether the concurrent use of inhaled corticosteroids or other asthma-controller therapy modifies this risk. The PAC agreed with an FDA recommendation to continue assessing the risks of LABAs and to seek advice from a future advisory committee.

Consequently, in January 2008, FDA requested manufacturers of LABA-containing products to provide information regarding controlled clinical studies to further evaluate the safety of LABAs in the treatment of asthma. Furthermore, the 10-11 December 2008 joint meeting of PADAC, DSaRM, and PAC, to which this briefing document relates, will review the benefits and risks of LABAs.

1.3.2 LABA-related regulatory actions and data reviews outside of the US

Health authorities outside of the US (eg, Canada, EU and some Asian countries) have also required changes in the labeling information for LABA-containing products as a result of the 2005 PADAC meeting. In addition, in 2007 the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK conducted a full review of the safety and efficacy of LABAs in the treatment of asthma and COPD. The MHRA concluded (as published in the 6 January 2008 MHRA Drug Safety Update) that:

- The available genetic data do not support making alternative recommendations for the use of LABA in patients of black or Asian ethnic origin
- Epidemiological data show that since the introduction of LABA, there has been a decrease in asthma-related hospitalizations in adolescents and a decrease in asthma-related mortality in all ages
- Data from randomized controlled clinical studies do not suggest a similar safety concern to that shown in postmarketing studies, probably because of more-consistent use of concomitant inhaled corticosteroids in randomized controlled settings. The data support the use of LABA in conjunction with inhaled corticosteroids in the treatment of moderate to severe asthma consistent with the guideline on the management of asthma from the British Thoracic Society and Scottish Intercollegiate Guidelines Network.
- To aid compliance with the concomitant use of inhaled corticosteroids and LABA, a combination inhaler should be used when appropriate

In 2008, the MHRA requested further information to support a therapeutic review of LABA use in the treatment of asthma in children under 12 years of age. AstraZeneca provided a response in June 2008; no conclusions have yet been published.

1.4 Disease background

1.4.1 Disease pathophysiology and prevalence

Asthma is a complex chronic disorder characterized by airflow obstruction, bronchial hyper-responsiveness, and underlying airway inflammation. Clinically it is characterized by recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

More than 22 million Americans have asthma, and it is one of the most common chronic diseases of childhood, affecting an estimated 6 million children ([EPR III 2007](#)). Over 30 million people in Europe are affected by asthma, with the UK having the highest prevalence in the world, occurring in 16% of the population ([GINA 2007](#)). The burden of asthma affects patients, their families, and society in terms of days lost from work and school, lessened

quality of life, and avoidable emergency department (ED) visits, hospitalizations, and even deaths.

Asthma increased in prevalence during 1980-1996 in the United States ([Moorman et al 2007](#)). Efforts have been made to address this trend by intervening at the individual patient/provider and the societal level to increase asthma awareness and improve adherence to asthma treatment guidelines. Although the exact etiology of asthma is unknown, adherence to an appropriate medical treatment regimen and environmental management should reduce the occurrence of exacerbations and lessen the hardship of this disease.

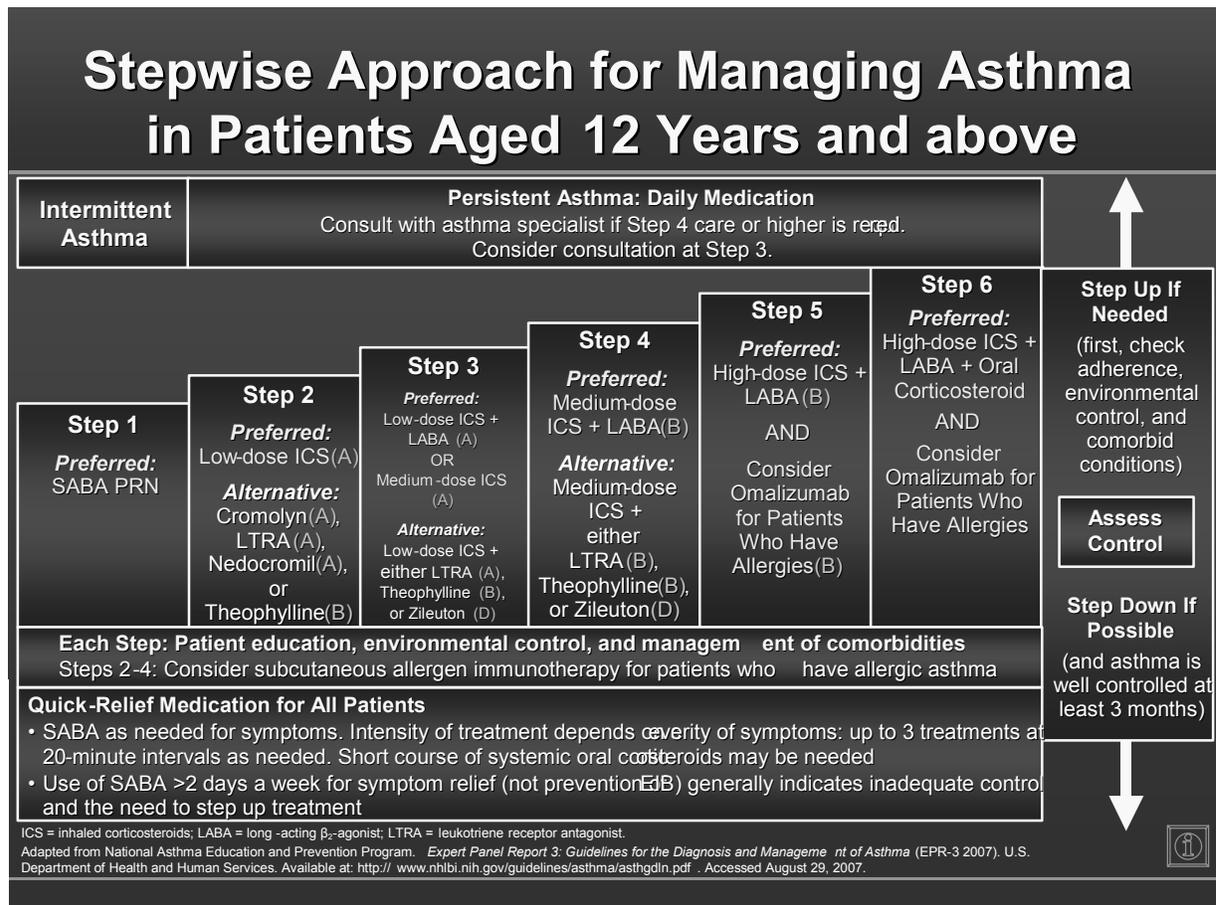
1.4.2 Therapeutic approach to asthma

The therapeutic approach to asthma is focused on addressing the 2 major components of the disease, namely inflammation and bronchoconstriction. Although bronchodilators alone can reduce symptoms, long-term control of asthma requires that the underlying inflammatory process also be addressed.

Asthma treatment is approached in a step-wise fashion based on level of symptomatology and response to therapy. The first National Asthma Education and Prevention Program (NAEPP) guidelines were published in 1991, and updates were made in 1997, 2002, and most recently in 2007 [EPR III 2007](#). It is important to note that prior to 2006, both Serevent and Foradil US labeling allowed for these LABAs to be used as monotherapy or in combination with ICS for the maintenance treatment of asthma.

The current guidelines for adults and youths ≥ 12 years with asthma are shown in [Figure 1](#) below.

Figure 1 Stepwise approach to managing asthma in youths ≥ 12 years and adults, according to the EPR III treatment guidelines



The current guidelines reaffirm that ICS is the preferred long-term control therapy for all ages. As noted in the figure, LABAs used as an adjunct to ICS therapy are preferred in Steps 3 and higher to provide long-term control of asthma symptoms; the addition of LABA to low-dose ICS has equal weight with the option of increasing from a low- to a medium-dose of ICS for youths ≥ 12 years and adults who have moderate persistent asthma or asthma inadequately controlled on low-dose ICS. This Step 3 recommendation represents the most significant difference in the 2007 update of the guidelines with regard to LABA use; previously the addition of LABA to low-dose ICS in that patient population was the preferred treatment option.

The guidelines suggest that selection of a treatment option at Step 3 should weigh the “high quality evidence demonstrating the benefits of adding LABA to low-dose ICS against the potential risk of rare life-threatening or fatal exacerbations with the use of LABA.” They acknowledge that comparator studies demonstrate significantly greater improvements when

LABA is added to ICS compared to other adjunctive therapies. Furthermore, the addition of LABA to ICS more consistently results in improvements in the impairment domain and reduces the frequency of exacerbations to a greater degree than increasing the dose of ICS. If the risk domain is of particular concern, then a balance of potential risks needs to be considered. LABA in combination with ICS is the preferred treatment option in Steps 4 through 6, ie for patients with increasing asthma severity.

The Global Initiative for Asthma (GINA 2007) guidelines concur with the above, in that LABAs are not recommended as monotherapy, but when used in combination with ICS are the preferred treatment for asthma patients ≥ 5 years when a medium dose of ICS fails to achieve asthma control. The impact of the recent discussion on LABA safety was an increased emphasis in the 2007 update of the GINA guideline on the importance of only using LABA in combination with an appropriate dose of ICS.

These guidelines illustrate the limited number of therapeutic options for asthma treatment, especially for patients with more severe disease.

1.4.3 Epidemiology of asthma since introduction of inhaled β_2 -agonists

Initial concerns regarding the use of SABAs arose as a result of two “epidemics” of asthma deaths (for review, see Nelson 2006). The first (in the UK and other countries), lasting from 1959 to 1966, was temporally linked to the introduction of a new inhaler delivering a higher dose of isoproterenol than that used in other countries. The second, in the late 1970’s in New Zealand, was linked to use of fenoterol, a SABA dispensed at a higher relative dose than albuterol.

Salmeterol was introduced in the US as a monotherapy in 1994, and then as a single inhaler combination therapy with fluticasone in 2000. Foradil (formoterol fumarate inhalation powder) was introduced in US as a monotherapy in 2001, and as a single inhaler combination therapy with budesonide (SYMBICORT) in 2007.

Initial concerns about the safety of LABAs were based on findings from the SNS and SMART studies, which both evaluated salmeterol. Subsequent to this, some meta-analyses heavily weighted by the SMART study attributed an increase in asthma-related mortality to the use of LABAs (eg, Salpeter et al 2006). It should be noted that evaluation of mortality trends are complicated by methodological issues, specifically, the change from International Classification of Diseases Ninth Revision (ICD-9) to International Classification of Diseases Tenth Revision (ICD-10) coding for deaths in 1999 interrupted the previous mortality trend line. However, even taking this into account, the rate of asthma deaths has decreased each year since 2000, despite increasing use of LABAs for asthma treatment. Concurrently, there has been no observed increase in rates of asthma-related hospitalizations or hospital out-patient and emergency department visits (Moorman et al 2007). Consistent with guideline changes, 85% of LABA use in the US is now in the form of combination ICS/LABA treatment (Wijesinghe et al 2008).

In Canada, asthma mortality and hospitalization rates have decreased continuously both before and after the 1999 implementation of the ICD-10 ([Public Health Agency of Canada 2007](#)), and in the UK, asthma mortality rates have gradually been declining since the late 1980s; current mortality rates are generally lower than those seen in 1960 ([Anderson et al 2007](#)). A case control study investigating the association between bronchodilator treatment and death from asthma in the UK between 1994 and 1998 ([Anderson et al 2005](#)) found that use of LABA was, if anything, associated with an inverse association with asthma mortality. Others have drawn similar conclusions (eg, [DiSantostefano et al 2008](#)).

Therefore, there is no evidence from epidemiological data that the introduction of LABAs has been associated with an increase in mortality or hospitalizations due to asthma; rather, there is some evidence to indicate that the introduction of LABAs and ICS/LABA combinations has been associated with a reduction in asthma-related mortality.

1.5 Pharmacology of long-acting β_2 -agonists

Formoterol and salmeterol are classified as long-acting β_2 -agonist because they have a longer duration of effect than previously available short-acting β_2 -agonist, i.e., more than 12 hours. However, they have different chemical structures and resulting pharmacological profiles. For example, salmeterol is >20-fold more lipophilic than formoterol; the property of lipophilicity is reflected in how a molecule interacts with cells and tissues, its onset of action, clearance, and accumulation ([Anderson et al 1994](#)).

The LABA, formoterol, has a rapid onset of action, similar to that of SABAs ([Seberova and Andersson 2000](#)) and faster than that of salmeterol ([Palmqvist et al 1997](#)). This difference in onset of action is thought to result in part from the difference in lipophilicity, the more hydrophilic nature of formoterol resulting in rapid diffusion through the lipid bilayer and to the active site of the receptor ([Anderson et al 1994](#)). The clinical implication is that formoterol relieves bronchoconstriction as rapidly as SABAs. As a result there has been a change in nomenclature in the GINA guideline from “short-acting” to “rapid-acting” β_2 -agonist, recognizing that formoterol has both rapid-onset and long-acting characteristics.

Consistent with other β_2 -agonists, formoterol and salmeterol cause dose related changes in heart rate, diastolic blood pressure, and plasma glucose and potassium concentrations ([Guhan et al 2000](#)). For formoterol, it has been shown that tolerance develops to systemically mediated effects such as palpitations, tremor and effect on serum potassium during regular high or moderate dose treatment ([Rosenborg et al 2000](#), [Tötterman et al 1998](#)). Systemically mediated side effects have a short duration, comparable to that for SABAs. Simultaneously accounting for local bronchodilating and systemic effects indicated that the relative therapeutic index (i.e., the ratio of therapeutic indices) is favorable for formoterol in comparison with the rapid but short-acting salbutamol ([Rosenborg et al 2002](#)).

1.6 Published literature since the 2007 Advisory Committee meeting

A selection of meta-analyses related to the safety of LABAs, published after the Advisory Committee meeting in 2007, are briefly reviewed in [Appendix E](#). These publications include

data that contribute to the scientific debate regarding LABA safety. The data from pediatric patients are relatively limited in these publications. Because the meta-analysis by Salpeter and colleagues was central to the 2007 Advisory Committee discussion, it is also critiqued in [Appendix E](#).

2. BENEFIT/RISK OF FORMOTEROL IN ASTHMA PATIENTS

2.1 Benefits of formoterol

2.1.1 LABAs as a therapeutic option

Despite improvements in asthma control observed following initiation of ICS, a substantial proportion of asthma sufferers, both adult and pediatric, continue to have impairment of lung function, regular symptoms and occasional exacerbations leading to emergency room treatment or hospitalizations ([EPR III 2007](#)). Prior to the introduction of LABAs, therapeutic options for these patients were limited to increased use of SABAs in combination with high dose ICS, methylxanthines (eg, theophylline), or even oral corticosteroids.

The advent of LABAs provided important additional clinical benefit compared with ICS treatment alone. Formoterol reduced severe exacerbations both when added to a low (100 µg bid) and to a higher (400 µg bid) dose of budesonide in patients with moderate to severe asthma, in addition to improving lung function and symptoms ([Pauwels et al 1997](#)). In patients already receiving ICS, adding formoterol was more effective than doubling the ICS dose ([O'Byrne et al 2001](#)).

Today, there remain a limited number of therapeutic options for asthma treatment beyond ICS. For patients not controlled on ICS treatment alone (eg, low to medium dose), the alternative treatment options other than the addition of LABAs are to increase the ICS dose or to use other adjunctive treatment such as theophylline or leukotriene modifiers. For the most severe patients, consideration of chronic therapy with injectables such as omalizumab or use of oral corticosteroids may also be considered. Most of these options are recognized to have limited additional effectiveness and in some cases incur the risk of significant short and long-term toxicity. Ultimately, in patients inadequately controlled on maintenance therapy and experiencing asthma worsening, adjunctive medications with potential undesirable side effects, such as oral corticosteroids, may be necessary ([EPR III 2007](#)).

The benefits of LABA treatment have been summarized in a large number of reviews and evidence-based analyses (eg, OHSU draft, 2008). In addition, the recognized benefits of LABA treatment form the basis for their preferred status as adjunctive therapy in treatment guidelines ([EPR III 2007](#), [GINA 2007](#)). In summary, there is consistent evidence:

- ICS is an effective monotherapy for the treatment of mild-to-moderate asthma. LABAs should only be used as additional therapy for patients not adequately controlled on other asthma controller medications, eg, low-to-medium dose ICS.

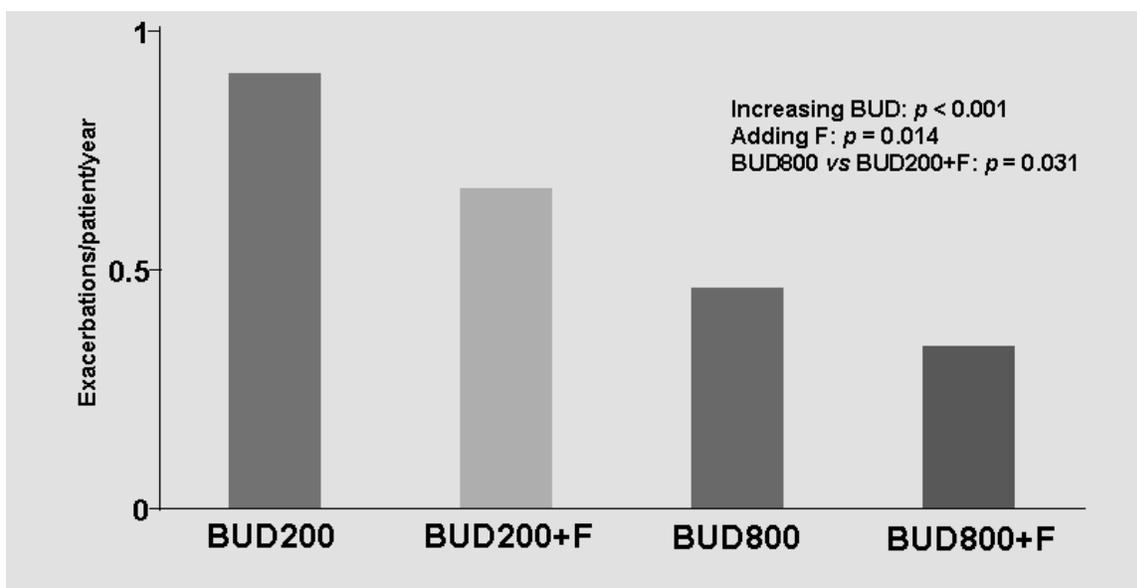
- The addition of a LABA to an ICS provides greater efficacy than continuing with the current dose of ICS alone for patients with poorly controlled persistent asthma, based on a variety of variables, including lung function, asthma symptoms, asthma exacerbations and health-related quality of life, and adjunctive medication requirements. For children, the demonstrated benefit has generally been limited to lung function variables.
- The addition of a LABA to an ICS provides greater efficacy than a higher dose of ICS for adults and adolescents with persistent asthma, based on symptom-related variables. There is also a trend towards fewer asthma exacerbations, but not statistically significant in meta-analyses. There are insufficient published data to draw similar conclusions in children under 12 years.

2.1.2 AstraZeneca data demonstrating the clinical benefit of formoterol

2.1.2.1 Initial trials demonstrating benefit of budesonide + formoterol

The advent of LABAs provided important additional clinical benefit compared with ICS treatment alone. The clinical benefits of combination therapy with budesonide and formoterol were first demonstrated in the landmark FACET and OPTIMA trials. In these studies, the overall effectiveness of ICS plus a LABA on measures of control was demonstrated for low and high doses of ICS in patients with a range of asthma severity. In patients already receiving ICS, adding formoterol was more effective than doubling the ICS dose (O'Byrne et al 2001). As seen in Figure 2, the FACET study, which evaluated moderate-to-severe asthma patients, demonstrated that formoterol ("F" in Figure 2) reduced severe exacerbations both when added to a low (100 µg bid, "BUD200" in Figure 2) and to a higher (400 µg bid, "BUD800" in Figure 2) dose of budesonide, in addition to improving lung function and symptoms (Pauwels et al 1997).

Figure 2 Effect on severe asthma exacerbations of adding formoterol to both a low and a high dose of ICS in Study 37-3018



The AstraZeneca clinical trials database generally reflects the international asthma treatment guidelines and labeling for formoterol-containing products, ie, most subjects studied received concomitant anti-inflammatory medication along with a LABA.

As of December 2006, AstraZeneca had studied over 72,000 subjects with mild, moderate, and severe asthma in 64 clinical trials of 3-12 months duration. Of these subjects, approximately 50,000 were treated with formoterol-containing products. Overall, the population included subjects with a wide range of demographic characteristics and baseline asthma severity. These studies confirmed the benefit of treatment with LABA alone and in combination with ICS on clinical endpoints, including lung function, asthma symptoms, health-related quality of life, and asthma exacerbations.

2.1.2.2 Clinical benefits of SYMBICORT pMDI

The clinical program that specifically supported the 2006 FDA approval of SYMBICORT pMDI included data from 31 clinical studies (16 phase II/III trials) in which 9315 subjects aged 6 and above were evaluated; a total of 6434 of these subjects received SYMBICORT pMDI. The program evaluated the safety and efficacy of 3 doses of SYMBICORT pMDI (80/9 µg bid, 160/9 µg bid, and 320/9 µg bid) with the objective of demonstrating that SYMBICORT pMDI provides greater efficacy benefits than each of the individual components formoterol and budesonide and that there was no increased risks beyond that of the well established individual components. Overall, the population included subjects with a wide range of demographic characteristics and baseline asthma severity, with both sexes, various races, and subjects with mild, moderate, and severe asthma well represented.

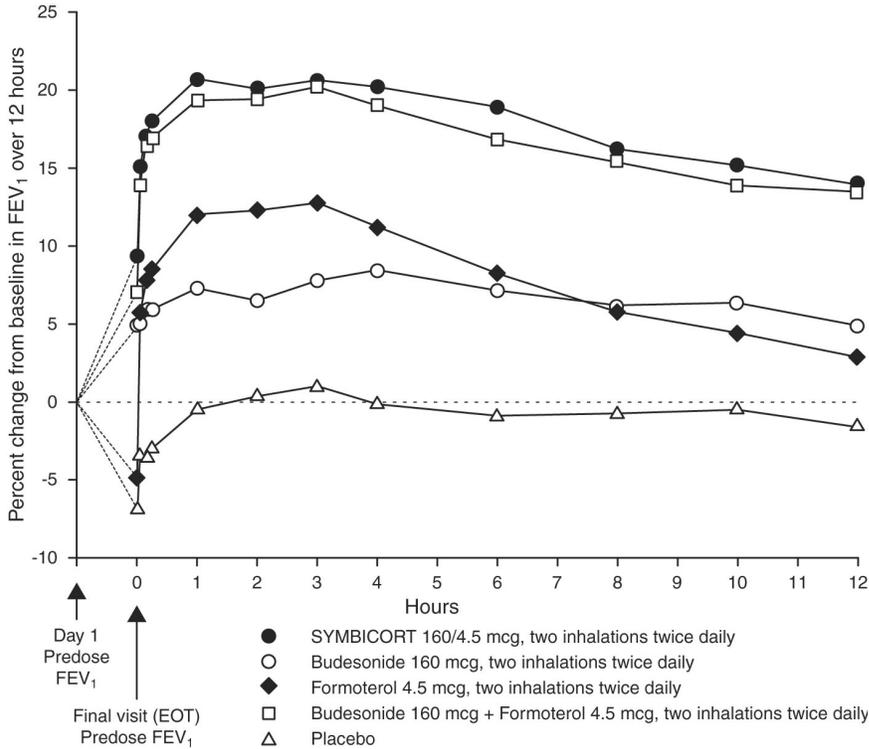
Findings from the 2 pivotal studies, SD-039-0716 and SD-039-0717 ([Corren et al 2007](#), [Noonan et al 2006](#)) that supported FDA approval are presented below. SYMBICORT pMDI

dosages of 160/9 µg, and 320/9 µg twice daily (each dose administered as 2 inhalations of the 80/4.5- and 160/4.5-µg strengths, respectively) were compared with the monocomponents (budesonide and formoterol) and placebo to provide information about appropriate dosing to cover a range of asthma severity. In these two clinical studies, improvements in key efficacy endpoints were greater with SYMBICORT pMDI than with the use of either budesonide or formoterol alone. In addition to these two pivotal studies, safety and effectiveness of SYMBICORT pMDI in patients 12 years of age and older were demonstrated in studies up to 12 months (Peters et al 2008, Morice et al 2008a, Busse et al 2008) that included long-term exposure to a high dose of SYMBICORT pMDI (1280/36 µg/day, twice that of the highest recommended dose).

An indication for twice-daily use in pediatric subjects (6 to <12 years of age) was not sought in the original NDA because chemistry manufacturing and control (CMC) information was still being generated to support the approval of the 40/4.5 µg formulation strength (80/9 µg dose). However, an sNDA is currently under FDA review to support approval of SYMBICORT pMDI for the long-term maintenance treatment of asthma in patients 6 years of age and older; see Section 3.1.2 for additional details.

Study SD-039-0717 was a randomized, double-blind, parallel-group, 12-week study comparing SYMBICORT pMDI with placebo and with each of its components as monoproducts in asthma patients 12 years and older. The co-primary efficacy variables were predose FEV₁ and baseline-adjusted average 12-hour postdose FEV₁. Figure 3 demonstrates the change in predose FEV₁ from baseline (“Day 1 predose FEV₁” in the figure) to end of treatment (up to 12 weeks, identified as “Final visit [EOT] predose FEV₁” in the figure). In addition, 12-hour postdose FEV₁ is shown at end of treatment. With regard to both co-primary endpoints, the ICS/LABA combination showed superiority over placebo and each monoproduct.

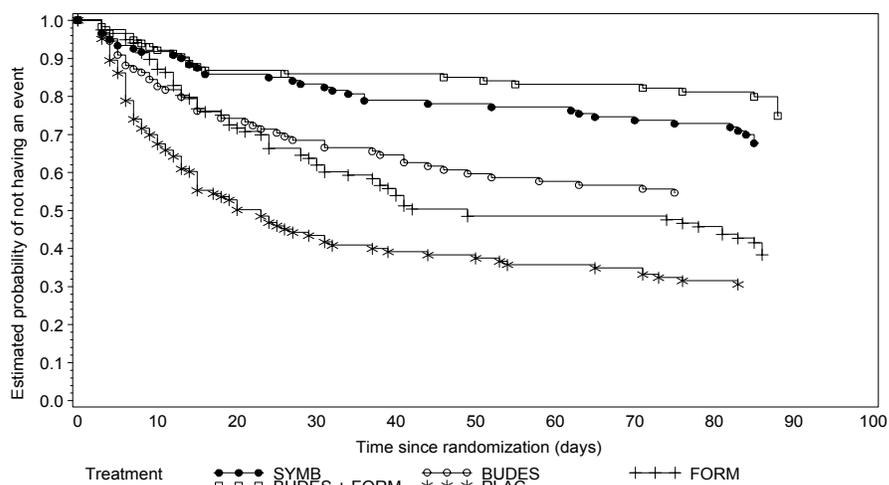
Figure 3 Change from baseline in FEV₁ at end of treatment in Study SD-039-0717



In addition, for key secondary endpoints (percentage of subjects who had a predefined asthma event; asthma symptoms as measured by percentage of symptom-free days; and health-related quality of life as assessed by the overall AQLQ[S] score), SYMBICORT pMDI also showed superiority over both placebo and over the monoproducts.

Time to first predefined asthma event was assessed as a measure of asthma control, and was longer for patients treated with combination of budesonide and formoterol compared to those treated with placebo, formoterol, and budesonide (see [Figure 4](#)).

Figure 4 Time (days) to first CRF predefined asthma event in Study SD-039-0717: Kaplan-Meier survival curves



For the second pivotal study, SD-039-0716 (figures not included in this document), results for the co-primary and most secondary efficacy variables were similar to the findings presented above. However, because the patient population had somewhat less severe disease, parity to ICS was observed for some secondary measures of asthma control.

In both pivotal studies, following the initial dose of SYMBICORT, FEV₁ improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and was maintained through Week 12.

No diminution in the 12-hour bronchodilator effect was observed with either SYMBICORT 160/9 µg or SYMBICORT 320/9 µg twice daily, as assessed by FEV₁, following 12 weeks of therapy or at the last available visit.

Reduction in asthma symptoms and in albuterol rescue use, as well as improvement in morning and evening PEF, occurred within 1 day of the first dose of SYMBICORT; improvement in these variables was maintained over the 12 weeks of therapy.

In addition to the US clinical program, a clinical trial program bridging the SYMBICORT pMDI to the SYMBICORT TURBUHALER was conducted to support approval of SYMBICORT pMDI in the EU. All therapeutic equivalence studies in this program achieved their primary and secondary objectives of showing superiority over budesonide as monotherapy and therapeutic equivalence of SYMBICORT pMDI to SYMBICORT TURBUHALER. These results further support the relevance of the OXIS and SYMBICORT TURBUHALER data to the benefit/risk assessment of formoterol.

2.1.3 Summary of clinical benefit

In patients 12 years and above, the benefit of formoterol in combination with budesonide over ICS or LABA monotherapy, has been unequivocally demonstrated in numerous AstraZeneca

clinical trials. These benefits include improvements across a range of measures of asthma control such as lung function; asthma worsening and exacerbations; asthma symptoms, use of rescue medication, and asthma-related quality of life measures in patients with moderate and severe asthma. Many of these benefits are apparent even when compared to high-dose ICS monotherapy. These conclusions are consistent with approved labeling and current evidence-based treatment guidelines, and demonstrate that SYMBICORT is an important therapeutic option for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies.

2.2 Assessment of risk profile of formoterol during randomized treatment in clinical trials

The safety of formoterol is supported by extensive data from clinical trials and postmarketing use. As of December 2006, AstraZeneca had studied over 72,000 subjects with mild, moderate, and severe asthma in 64 clinical trials of 3-12 months duration. Of these subjects, approximately 50,000 were treated with formoterol-containing products. In addition, as of 30 September 2008, the estimated postmarketing exposure to AstraZeneca formoterol-containing products approached 6 billion treatment days (SYMBICORT pMDI >48 million, SYMBICORT TURBUHALER >4.4 billion, OXIS TURBUHALER >1.4 billion).

The following sections review the safety information requested by the FDA, with particular focus on asthma-related serious adverse events (deaths, hospitalizations, and intubations). AstraZeneca has also provided additional analyses that we believe are relevant in the discussion of the safety of formoterol.

2.2.1 Methodology

2.2.1.1 Selection of data

The safety data presented in this briefing document were selected on the basis of criteria outlined by the FDA in their requests for data from AstraZeneca and other pharmaceutical sponsors. As previously noted, safety information for all formoterol-containing products marketed by AstraZeneca was considered relevant although only SYMBICORT pMDI is currently approved in the US.

The criteria for inclusion were as follows:

- All blinded, parallel-arm, randomized, controlled trials conducted with LABA in treatment of asthma
- Trials in which the compound was administered as randomized treatment with or without ICS or other adjunctive therapy
- Both placebo and active-controlled trials

- Trials in which there was a randomized, blinded phase followed by an open-label extension, but only including the blinded phases of the trial
- Randomized, double-blind, cross-over trials, but only the first period
- Trials in which unblinded and unlocked data were available 1 January 2008

The criteria for exclusion were as follows:

- Trials in indications other than asthma, uncontrolled trials, or trials primarily to obtain clinical pharmacology data

Note that according to the FDA request, only events occurring during randomized treatment are included in the primary analyses in this briefing document. Thus, events with an onset date after the date of last dose are not included in analyses. However, for the sake of completeness, deaths (any cause), intubations, and asthma-related hospitalizations with an onset date after the date of last dose are also briefly discussed.

2.2.1.2 Adjudication of data

The FDA gave recommendations for the following standardized procedure for adjudicating all serious adverse events for the selected trials: “All serious adverse events reported in the trials should be reviewed, in a manner blind to treatment, to determine whether the event involved death, hospitalization or intubation. For events involving one or more of these outcomes, it should be determined whether the event occurred in the setting of an acute asthma exacerbation or was otherwise asthma-related. The determination of asthma-relatedness should be based on the clinical judgment of at least one physician (blind to treatment) it may be useful to have more than one physician review the events for asthma-relatedness, especially if the determination is not obvious. Please do not rely upon the coded adverse event term to determine asthma-relatedness, as the reliability and validity of the specific terms for asthma may be variable.”

AstraZeneca identified 1357 SAEs from clinical trials meeting the outlined inclusion criteria. The narratives for these SAEs were re-blinded prior to the implementation of the following 3-step adjudication procedure, conducted by physicians who were blinded to treatment.

1. An AstraZeneca Patient Safety physician deselected all SAEs from the 1357 that clearly did not belong to any of the relevant categories (all-cause death, asthma-related death, asthma-related intubation, or asthma-related hospitalization).
2. Two AstraZeneca physicians with training as specialists in pulmonology independently adjudicated all remaining narratives (n=477).
3. A third AstraZeneca specialist in pulmonology assessed and adjudicated any cases where agreement between the physicians was not reached in Step 2 (n=3).

Only adjudicated data are presented here, and thus the results are not necessarily identical with previously published results. For example, the recently published summary of AstraZeneca formoterol safety data (Sears et al 2008) includes open-label studies (eg the RELIEF study with approximately 18,000 participants [Pauwels et al 2003]) and SAEs that did not require hospital admission that were excluded from the adjudicated data. However, the conclusions reached based on the adjudicated data do not differ substantially from those previously published based on unadjudicated data.

2.2.1.3 Disposition of safety results

The following presentations show results for the combined adjudicated population, including patients of all ages, by randomization to formoterol-containing treatment vs non-LABA treatment; these groups will hereafter be referred to as “formoterol-exposed” and “non-LABA-exposed,” as outlined in Table 1. A later section (Section 3) will show corresponding results for the pediatric population (ie, a subset of the above). An overview of the design of included trials can be found in Appendix A and safety results are summarized by trial in Appendix B. Only studies including a non-LABA comparator are included in the summary presentations; however, for the sake of completeness, Appendix B includes a by-study presentation of results for studies in which all treatment arms included a LABA (not including open label studies).

Furthermore, asthma-related adverse events as presented in the SYMBICORT pMDI 4-month safety update and the pediatric sNDA are included as Appendix D. In these submissions asthma events or potentially asthma-related events were defined and categorized consistent with data from another clinical program with the same LABA (formoterol delivered as Foradil Aerolizer, Novartis Pharmaceuticals) in the 13 July 2005 PADAC meeting. In the SYMBICORT pMDI clinical program, there were no deaths or findings of concern; however, the study population was of insufficient magnitude to draw definitive conclusions.

In addition to analyses based on the data provided to the FDA, certain analyses considered to be of interest have been done (within the same population) which are not directly verifiable from the database provided to the FDA. These include asthma-related SAEs, total number of asthma-related hospitalizations, and discontinuations due to any cause. The analysis of discontinuations is based on summaries in the individual clinical study reports. These analyses will be presented in Section 2.2.7.

2.2.1.4 Statistical analysis

In addition to a descriptive presentation of results, the risks of all-cause mortality and asthma-related events have been analyzed. This has been done in two ways, one using a simple pooled unstratified analysis and one using stratification by study (Mantel-Haenszel approach adjusted for exposure). The pooled analysis simply combines treatment arms across trials and compares event totals between LABA and non-LABA containing groups; all trials are included, even those with no events, though no allowance is made for possible differences between trials in this analysis which could lessen the comparability between groups and possibly introduce a degree bias. The stratified analysis combines the data differently, allowing for possible differences between trials and thus reduces the likelihood of bias. For

the assessment of relative risk, this approach only includes trials with at least one event, though the related and subsidiary risk difference analysis is stratified by trial and includes all trials, even those with no events. Among the 23,510 patients included in this dataset there was no asthma-related deaths and only 1 intubation during randomized treatment; thus too few events to perform a statistical analysis.

In the pooled unstratified analysis, differences in risks were expressed by the odds ratio (OR) with the associated 95% confidence interval and p-value calculated with an exact method (StatXact[®] version 8.0.0; Cytel[®] Inc., Cambridge, USA). Due to the low frequency of events in these analyses the odds ratio is a good approximation of relative risk (RR). Therefore the presented odds ratios may well be interpreted as relative risks.

Because some patients may experience multiple asthma-related hospitalizations, a description of the rate of asthma-related hospitalizations allowing for multiple events within a patient was calculated via a Poisson regression adjusting for exposure time (StatXact[®]).

Mantel-Haenszel estimates of relative risk

For each event of interest, data were combined across trials using the Mantel-Haenszel approach to estimate the overall relative risk via Breslow and Day ([Breslow and Day 1987](#)). This approach allows for differing exposure times between groups. Confidence intervals were provided using the method described by Robins et al ([Robins et al 1986](#)). Note that only trials with at least one event will contribute to this overall RR estimate. A subsidiary Mantel-Haenszel risk difference analysis was therefore performed, which includes all trials ([Greenland and Robins 1985](#)). As expected, these results were in line with Mantel-Haenszel relative risk analysis and thus only the relative risk results are presented in this document.

Overall event rates for formoterol-containing and non-LABA treatments across trials were provided using a weighted average corresponding to the Mantel-Haenszel estimate of the common relative risk. In this way, incidence rates for formoterol-containing and non-LABA treatments were consistent with the overall Mantel-Haenszel relative risk estimate in that the ratio of incidence rates (formoterol-containing/non-LABA) would exactly equal the overall relative risk. Confidence intervals (CIs) for within treatment events rates were calculated using a normal approximation ([Greenland and Robins 1985](#)).

For individual studies, a descriptive 95% credibility interval for the RR was provided using the method of Barker and Cadwell ([Barker and Cadwell 2008](#)) with an uninformative uniform prior; the median of the posterior distribution was used to provide a point estimate for the relative risk. These were provided to account for individual studies in which no events were observed, as this interval is calculable even when the number of events within each treatment group is equal to 0. The credibility interval quickly converges with the conventional asymptotic CI for the event rate ratio as the number of events increases.

Visual display of individual trial and overall relative risk estimates

Throughout this document, where the overall Mantel-Haenszel relative risk for a given event has been calculated, the results are displayed visually along with individual trial data in a forest plot format. The individual trial data are plotted with the point estimate represented by a box symbol for which the relative size is governed by the total number of events observed in that trial, ie the smaller the box size the fewer events occurred in that trial. Each trial in the forest plot is labelled by both the study number and the number of events/total exposure in patient-years in the formoterol-exposed group versus the number of events/total exposure in years in the non-LABA-exposed group. For the individual studies, 95% credibility intervals are presented to ensure all trials are accounted for, including those in which no events were observed.

Kaplan Meier survival curves

Survival curves of the Kaplan Meier type were used to describe the time pattern of the occurrences of the events.

2.2.1.5 Overview of dataset

The data for formoterol-containing products is derived from SYMBICORT pMDI, SYMBICORT TURBUHALER and OXIS TURBUHALER trials. The contribution of each product to the “formoterol-exposed” treatment group as well as the “non-LABA” treatment group are summarized in [Table 1](#). Note that in the majority of cases, the formoterol was received in conjunction with ICS. The dataset included a total of 23,510 patients, whereof 13,542 received formoterol-containing products. Of the patients in the formoterol-exposed group, approximately 20% received SYMBICORT pMDI.

Table 1 Overview of dataset (adjudicated data, all ages)

Treatment	Patients (N)	Total exposure (1000 treatment years)	Dose
Formoterol-exposed patients			
OXIS TURBUHALER	2690	1.33	9, 18, 36 µg; prn
OXIS TURBUHALER + PULMICORT TURBUHALER/pMDI	2328	0.96	Range 160/9 to 1280/36 µg
SYMBICORT TURBUHALER	5861	3.24	Range 80/4.5 to 1280/36 µg; maintenance and prn: adjustable dosing
SYMBICORT pMDI	2663	0.95	Range 160/9 µg to 1280/36 µg
Total	13542	6.49	
Non-LABA-exposed patients			
PULMICORT TURBUHALER/pMDI	6913	3.74	Range 160 µg to 1280 µg
Terbutaline	1285	0.71	2000 µg; prn
Placebo	1374	0.43	

Table 1 Overview of dataset (adjudicated data, all ages)

Treatment	Patients (N)	Total exposure (1000 treatment years)	Dose
Fluticasone	396	0.05	500 µg
Total	9968	4.92	
Total – all trials	23510	11.41	

2.2.2 Baseline characteristics of the adjudicated population (all ages)

Baseline characteristics for the entire adjudicated population (all ages) are shown in [Table 2](#).

Table 2 Baseline characteristics (adjudicated population, all ages)

Parameter	Class	Treatment group		
		Formoterol-exposed (N=13542)	Non-LABA-exposed (N=9968)	Total (N=23510)
Age (years)	N	13542	9968	23 510
	Mean	33.9	34.8	34.2
	Range	4.0-87.0	4.0-87.0	4.0-87.0
Age group	4-11 years	2155 (15.9%)	1268 (12.7%)	3423 (14.6%)
	12-17 years	1515 (11.2%)	1155 (11.6%)	2670 (11.4%)
	≥18 years	9872 (72.9%)	7545 (75.7%)	17417 (74.1%)
Sex	Female	7175 (53.0%)	5264 (52.8%)	12439 (52.9%)
	Male	6367 (47.0%)	4704 (47.2%)	11071 (47.1%)
Race	Asian	1026 (7.6%)	678 (6.8%)	1704 (7.2%)
	Black or African American	436 (3.2%)	252 (2.5%)	688 (2.9%)
	White	11 355 (83.9%)	8567 (85.9%)	19 922 (84.7%)
	Other	711 (5.3%)	464 (4.7%)	1175 (5.0%)
	Unknown	14 (0.1%)	7 (0.1%)	21 (0.1%)
BMI at entry (kg/m ²)	N	13 385	9908	23 293
	Mean	24.7	24.8	24.7
	Range	11.1-64.7	11.7-58.8	11.1-64.7
FEV ₁ at baseline (%PN)	N	13 011	9537	22 548
	Mean	79.9	79.9	79.9
	Range	19.0-180.0	18.0-175.0	18.0-180.0
ICS use at baseline	No	1775 (13.1%)	1980 (19.9%)	3755 (16.0%)
	Yes	11 767 (86.9%)	7988 (80.1%)	19 755 (84.0%)
Smoker at baseline	No	7604 (56.2%)	6199 (62.2%)	13 803 (58.7%)
	Yes	689 (5.1%)	693 (7.0%)	1382 (5.9%)
	Unknown	5249 (38.8%)	3076 (30.9%)	8325 (35.4%)
Region	US	2849 (21.0%)	1432 (14.4%)	4281 (18.2%)
	Non-US	10 693 (79.0%)	8536 (85.6%)	19 229 (81.8%)

2.2.3 All-cause mortality in the adjudicated population

2.2.3.1 All-cause mortality in trials comparing formoterol-exposed vs non-LABA

Table 3 presents the number of patients who died due to any cause (including asthma) during randomized treatment. Overall the number of deaths from any cause was low (7 of 23,510). There were 3 deaths in patients on formoterol-containing treatment and 4 deaths in patients on non-LABA treatment. For Subject SD-037-0345/181/30801 of the formoterol-containing group, the original cause of death was reported as status asthmaticus; however, adjudication determined that cause of death was septic shock. A short description of the 7 deaths is presented in Table 4 and narrative descriptions can be found in Appendix C. There were no deaths during randomized treatment for any treatment group in the clinical studies contained in the US NDA for SYMBICORT pMDI.

Table 3 All-cause mortality during randomized treatment (adjudicated population, all ages)

	Formoterol-exposed	Non-LABA-exposed	Total
Patients (N)	13542	9968	23510
Total exposure (1000 treatment years)	6.49	4.92	11.41
Number (%) of deaths	3 (0.02%)	4 (0.04%)	7 (0.03%)
Deaths / 1000 treatment years	0.46	0.81	0.61

Table 4 Brief description of all-cause deaths during randomized treatment

Study code/ Centre/ Patient No	Age/ Sex/ Race	Randomized treatment (daily dose)	ENDTR TDY	EVENT DAY	ENDTRTDY -EVENTDAY	Onset in relation to last dose	Days since randomization when death occurred	Cause of death
Formoterol-exposed patients								
SD-037-0345/181/30801	35/F/X	PULMICORT_OXIS_TBH (160/9)	241	237	4	Before	247	Status asthmaticus ^a Septic shock; Pneumonia
SD-039-0349/401/578070	36/M/C	SYMBICORT_TBH (640/18)	1	1	0	Same day	1	Completed suicide
SD-039-0668/286/248	73/F/C	SYMBICORT_TBH_SYMBICORT_TB H_pm (320/9/160/4.5 pm)	229	214	15	Before	330 ^b	Metastases to peritoneum
Non-LABA -exposed patients								
BU-543-0681A/1/1304	67/F/C	PULMICORT_TBH (640)	3	3	0	Same day	4	Cerebral hemorrhage
SD-039-0668/153/945	55/M/C	PULMICORT_TBH_BRICANYL_TBH _pm (640/400 pm)	91	91	0	Same day	91	Myocardial infarction
SD-039-0668/153/946	46/F/C	PULMICORT_TBH_BRICANYL_TBH _pm (640/400 pm)	362	316	46	Before	347	Hypertropic cardiomyopathy
SD-039-0673/572/1742	66/M/O	PULMICORT_TBH_BRICANYL_TBH _pm (640/400 pm)	304	304	0	Same day	308	Death ^c

^a Adjudication determined that cause of death was not status asthmaticus. Patient was intubated for severe asthma which deteriorated to an antibiotic-resistant nosocomial infection. Patient developed pneumonia and sepsis. Probable cause of death was septic shock. See [Appendix C](#) for narrative.

^b Cancer diagnosed during treatment. Study drug stopped on day 229. Patient subsequently died due to the cancer.

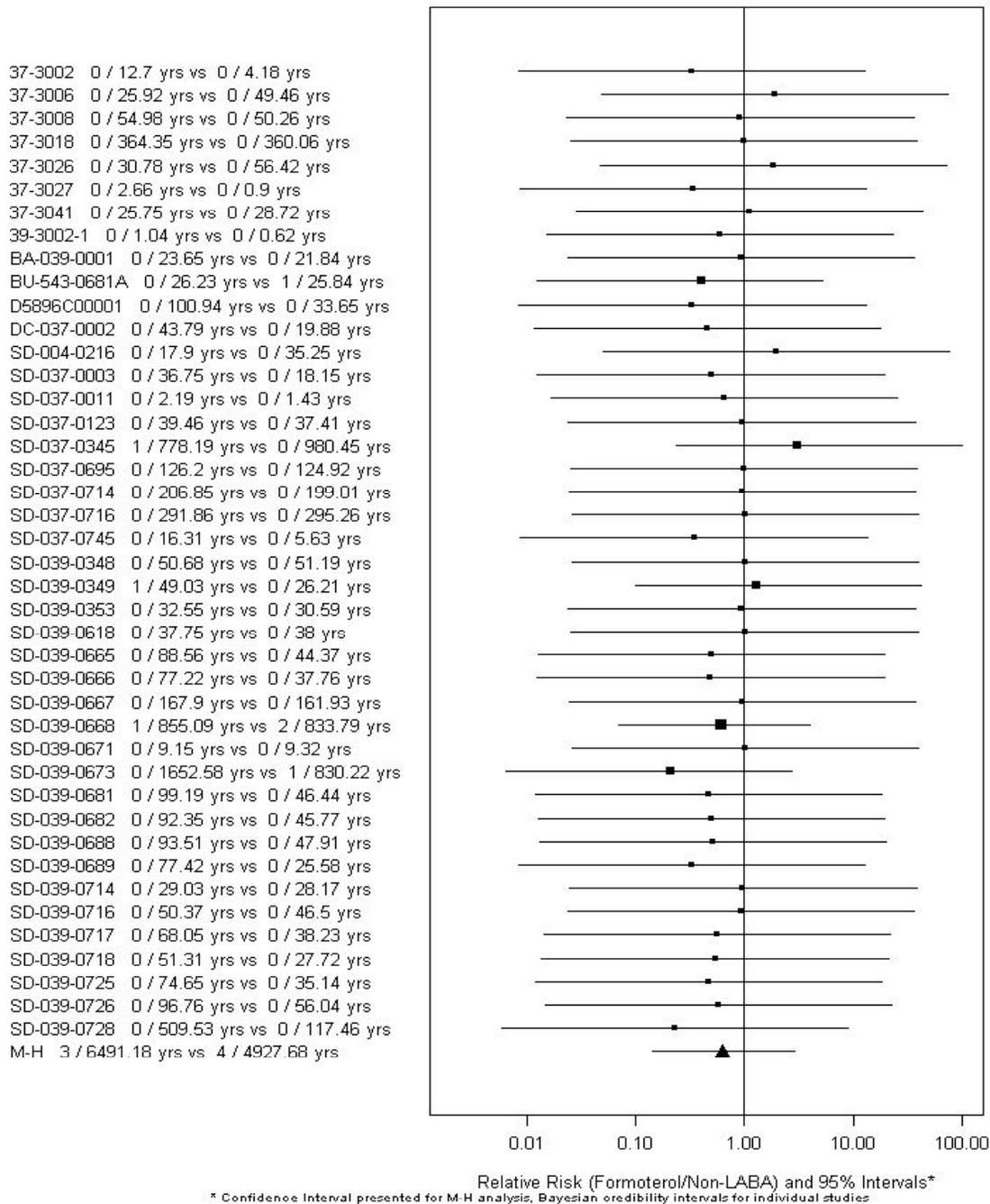
^c Cause of death unknown. Patient experienced loss of consciousness and cyanosis and died 4 days later.

ENDTRTDY Days on randomized treatment; EVENTDAY Day of onset of event leading to death.

Figure 5 displays the overall Mantel-Haenszel (M-H) relative risk estimate and 95% CI of all-cause mortality, stratified by study and adjusted for total exposure times between the treatment groups. Note that although estimates of relative risk (RR) within individual studies are also presented (solid boxes), only studies with at least one event have contributed to the overall M-H estimate (solid triangle).

The relative size of each point estimate has been weighted as a function of the total number of events observed, ie the smallest solid boxes represent studies in which no events occurred. Each study in the analysis has been labelled by both the study number and the number of events/total exposure in years in the formoterol-exposed group versus the number of events/total exposure in years in the non-LABA group. For the individual studies, 95% credibility intervals are presented to also include studies in which no events were observed.

Figure 5 Relative risk estimates of all-cause mortality during randomized treatment, overall (Mantel-Haenszel) and by individual trial



In general, RR estimates among individual studies are generally centered around the left of the line of unity, representing no increased risk for formoterol- versus non-LABA-exposed patients.

The overall M-H estimate of RR (shown as the solid triangle at the bottom of Figure 5 and presented in Table 5) stratified by study and adjusting for total exposure time, was 0.64 (95% CI: 0.14 to 2.92), again indicating no increase in risk for formoterol- versus non-LABA-exposed patients. Note that only the 5 studies with at least 1 event contributed to this estimate. Potential differences in risk across individual studies were examined using a chi-square test for homogeneity (p=0.311), indicating no evidence of heterogeneity of relative risk across the studies.

Table 5 presents summary output for the overall M-H analysis of RR for all-cause mortality. Crude event rates (calculated as number of events divided by total exposure) within treatment are presented. Event rates using a weighted average corresponding to the M-H estimate of the common relative risk, ie, adjusting for differences in size and duration of individual trials are similar to the crude rates. Event rates are lower for formoterol- versus non-LABA-exposed patients by either estimate.

Table 5 Stratified Mantel-Haenszel analysis for all-cause mortality during randomized treatment

Treatment	No. of events	Total exposure (years)	Crude event rate ^a	Mantel-Haenszel analysis	
				Weighted event rate ^a (95% CI)	RR (95% CI)
Formoterol	3	6491.2	0.5	0.53 (0.17, 1.66)	0.64 (0.14, 2.92)
Non-LABA	4	4927.7	0.8	0.82 (0.31, 2.20)	

^a Event rate per 1000 treatment years

In conclusion, regardless of the method used, there was no evidence of an increase in all-cause mortality in patients receiving formoterol-containing products compared with patients receiving non-LABA treatment.

2.2.3.2 All cause mortality in trials comparing ICS + formoterol vs ICS alone

This section evaluates all cause mortality during randomized treatment in patients receiving ICS + formoterol compared with ICS alone. Only trials with treatment arms in which patients received both ICS and either formoterol or non-LABA treatment as randomized treatment are included. Treatment arms that did not include an ICS are excluded from this analysis, eg, formoterol-only or placebo arms. The actual comparisons consist of budesonide + formoterol as monoproducts vs budesonide, or SYMBICORT (either formulation) vs budesonide. ICS doses were either equivalent or, in some cases, up to 4 times higher in the non-LABA

treatment arms as in the ICS + formoterol treatment arms. A total of 28 trials were included in this analysis.

Figure 6 displays the overall Mantel-Haenszel (M-H) relative risk estimate and 95% CI of all-cause mortality, stratified by study and adjusted for total exposure times between the treatment groups, for clinical trials comparing ICS + formoterol versus ICS alone.

In general, relative risk estimates among individual studies are generally centered around the line of unity, representing no increased risk for ICS + formoterol versus ICS monotherapy patients.

The overall pooled M-H estimate of RR (shown as the solid triangle at the bottom of **Figure 6** and presented in **Table 6**) stratified by study and adjusting for total exposure time, was 0.61 (95% CI: 0.14 to 2.79), again indicating no increase in risk for ICS + formoterol versus ICS monotherapy patients. Note that only the 5 studies with at least one event have contributed to this estimate. Potential differences in risk across individual studies were examined using a chi-square test for homogeneity ($p=0.358$), thus indicating no evidence of heterogeneity of relative risk across the studies.

Figure 6 Relative risk estimates of all-cause mortality overall (M-H) and by individual trial, among patients in ICS/LABA vs. ICS trial designs

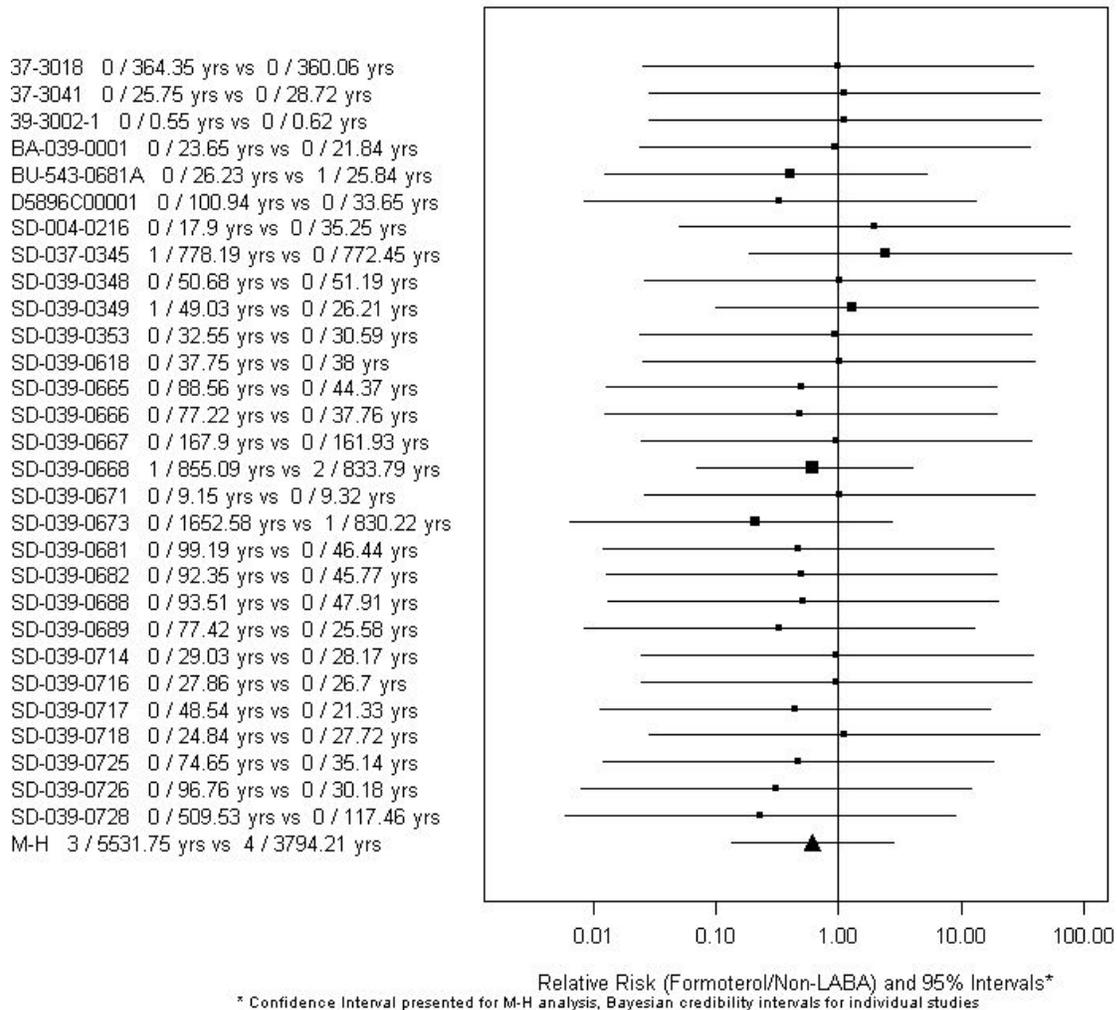


Table 6 presents summary output for the overall M-H analysis of RR for all cause mortality. As before, both simple event rates and event rates using stratification corresponding to the M-H relative risk estimate are provided. Event rates are lower for ICS + formoterol versus ICS monotherapy patients by either estimate.

Table 6 Stratified M-H analysis for all-cause mortality during randomized treatment, among patients in ICS + formoterol vs. ICS trial designs

Treatment	No. of events	Total exposure (years)	Crude event rate ^a	M-H analysis	
				Weighted event rate ^a (95% CI)	RR (95% CI)
ICS + formoterol	3	5531.8	0.5	0.62 (0.20, 1.96)	0.61 (0.14, 2.79)
ICS	4	3794.2	1.1	1.02 (0.38, 2.73)	

^a Event rate per 1000 treatment years.

2.2.4 Asthma-related deaths in the adjudicated population

There were no asthma-related deaths during randomized treatment among the 23,510 patients included in the adjudicated population.

2.2.5 Asthma-related intubations in the adjudicated population

There was 1 asthma-related intubation (SD-037-0345/181/30801) during randomized treatment in the adjudicated population (n=23,510) (see [Table 7](#)); the patient was randomized to formoterol-containing treatment. It should be noted that the final outcome of this event was death due to septic shock. This case was not assessed as an asthma-related death during the adjudication procedure. A short description is presented in [Table 4](#) and a narrative in [Appendix C](#). Given that there was only 1 asthma-related intubation, it is not possible to establish any relationship between formoterol and asthma-related intubations.

Table 7 Asthma-related intubations during randomized treatment (adjudicated population, all ages)

	Formoterol-exposed	Non-LABA-exposed	Total
Patients (N)	13542	9968	23510
Total exposure (1000 treatment years)	6.49	4.92	11.41
Number (%) of patients with intubation	1 (0.01%)	0	1 (0%)
Intubations / 1000 treatment years	0.15	0	0.09

2.2.6 Asthma-related hospitalizations in the adjudicated population

2.2.6.1 Number of patients with at least 1 asthma-related hospitalization

[Table 8](#) presents the number of patients who were hospitalized at least once for asthma during randomized treatment, and also presents an estimate of the rate in relation to the duration of the exposure.

Table 8 Patients with at least 1 asthma-related hospitalization during randomized treatment (adjudicated population, all ages)

	Formoterol-exposed	Non-LABA-exposed	Total
Patients (N)	13542	9968	23510
Total exposure (1000 treatment years)	6.49	4.92	11.41
Number (%) of patients with ≥ 1 asthma-related hospitalization	78 (0.58%)	83 (0.83%)	161 (0.68%)
Asthma-related hospitalizations/ 1000 treatment years ^a	12.02	16.87	14.11

^a Note that a patient who was hospitalized on more than one occasion has only been presented once in this calculation.

In the formoterol-exposed group, there were 78 (0.58%) patients with at least 1 asthma-related hospitalization, compared with 83 (0.83%) in the non-LABA-exposed groups. The number and percentage of patients with ≥ 1 asthma-related hospitalization was lower in the formoterol-exposed patients than in the non-LABA-exposed patients.

2.2.6.2 Asthma-related hospitalizations for formoterol vs non-LABA exposed patients

Table 9 presents the unstratified relative risk, as approximated by the odds ratio using the total number of patients (23,510) and the number of patients experiencing at least one asthma hospitalization among formoterol-exposed (78 of 13,542) vs non-LABA-exposed (83 of 9,968) patients.

Table 9 Odds ratio for asthma-related hospitalization during randomized treatment (adjudicated population, all ages)

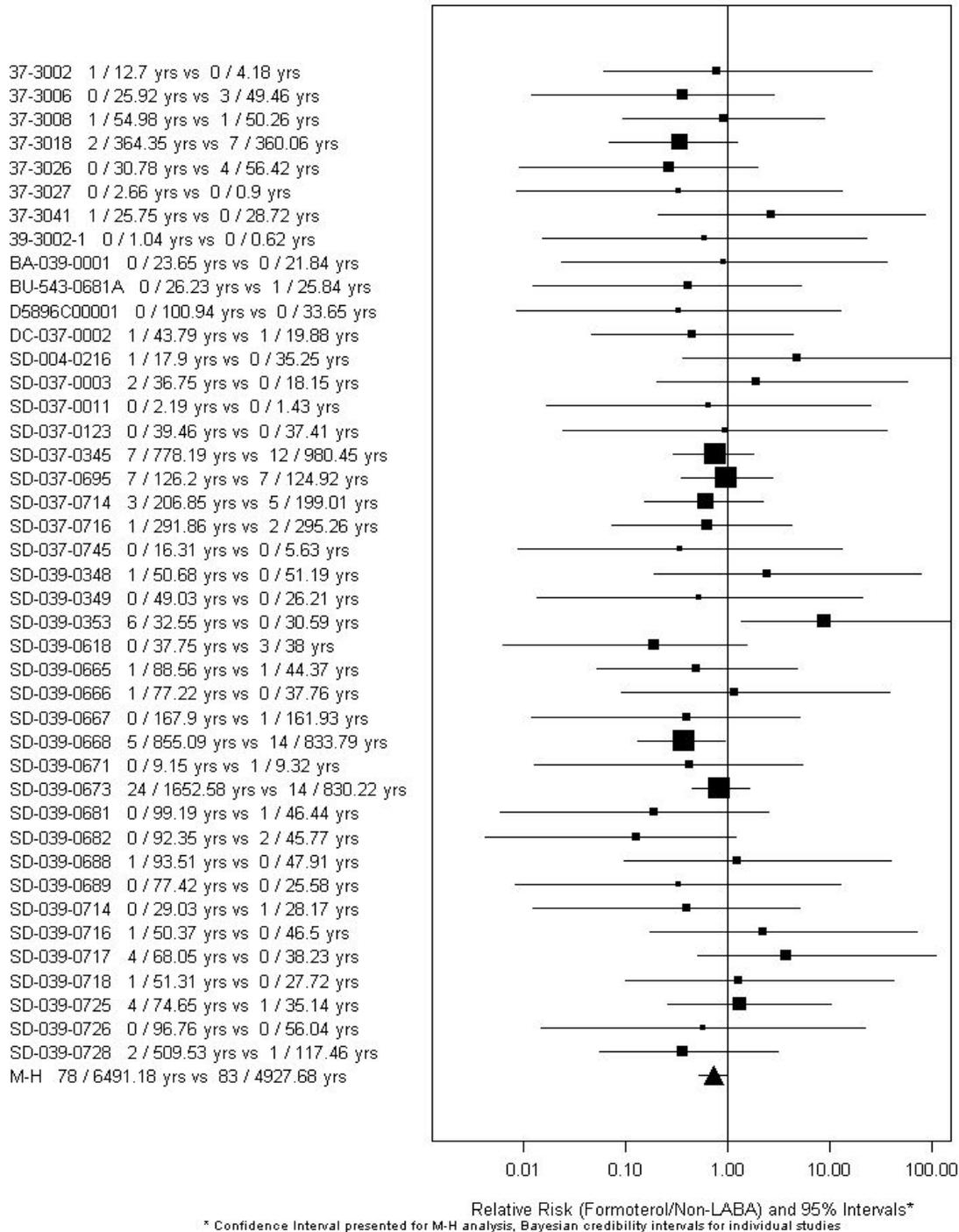
Formoterol-exposed		Non-LABA-exposed		Comparison formoterol-exposed vs non-LABA-exposed	
N	No. (%) with ≥ 1 hosp	N	No. (%) with ≥ 1 hosp	OR	95% CI
13542	78 (0.58%)	9968	83 (0.83%)	0.69	(0.50-0.95)

Hosp Hospitalization; OR Odds ratio.

These data indicate there were fewer patients with an asthma-related hospitalization in the formoterol-containing treatment group than the non-LABA treatment group.

Figure 7 displays the overall M-H relative risk estimate and 95% CI of asthma-related hospitalizations, stratified by study and adjusted for total exposure times between the treatment groups (see Section 2.2.1.4).

Figure 7 Relative risk estimates of asthma-related hospitalizations during randomized treatment, overall (Mantel-Haenszel) and by individual trial for formoterol vs non-LABA exposed patients



In general, RR estimates among individual studies are generally centered around the line of unity, with more studies to the left of this line than to the right, representing no increased risk and possibly a reduction in risk for formoterol versus non-LABA exposed patients.

The overall pooled M-H estimate of RR (shown as the solid triangle at the bottom of [Figure 7](#) and [Table 10](#)) stratified by study and adjusting for total exposure time, was 0.73 (95% CI: 0.54 to 1.01), again indicating no increase in risk for formoterol versus non-LABA exposed patients. Note that only 32 studies with at least 1 event contributed to this estimate. Potential differences in risk across individual studies were examined using a chi-square test for homogeneity (p=0.141), indicating no evidence of heterogeneity of relative risk across the studies.

[Table 10](#) presents summary output for the M-H analysis of relative risk for asthma-related hospitalizations. As before, both simple event rates and event rates using stratification corresponding to the M-H relative risk estimate are provided. Event rates are lower for formoterol versus non-LABA exposed patients by either estimate.

Table 10 **Stratified M-H analysis for asthma-related hospitalizations during randomized treatment for formoterol vs non-LABA exposed patients**

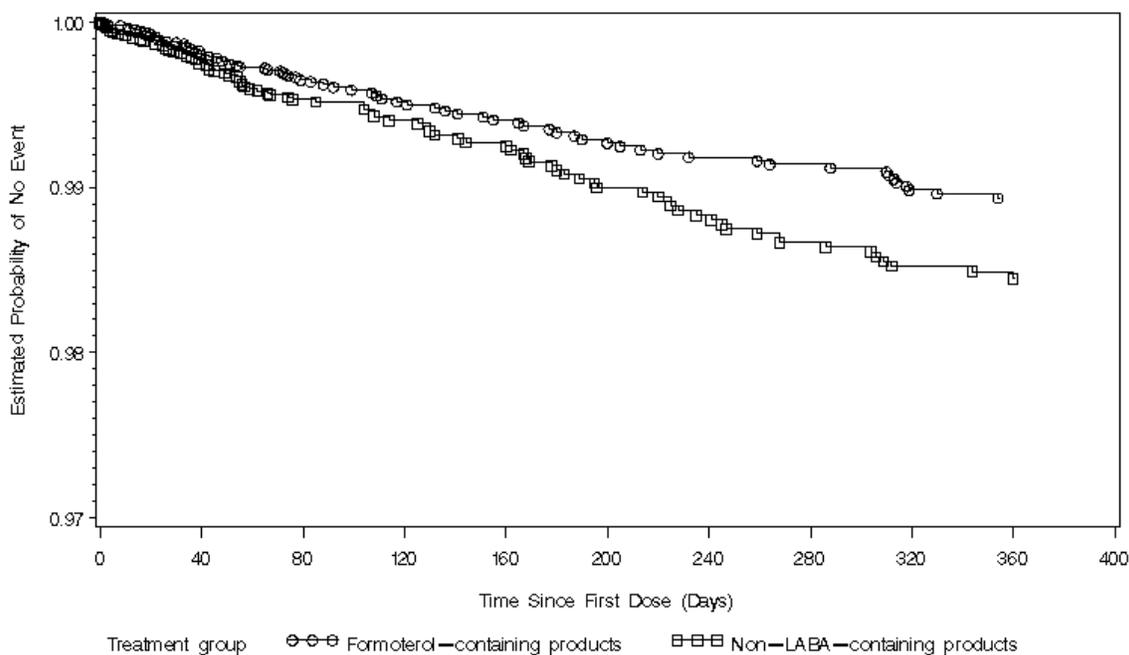
Treatment	No. of events ^a	Total exposure (years)	Crude event rate ^b	M-H analysis	
				Weighted event rate ^b (95% CI)	RR (95% CI)
Formoterol	78	6491.2	12.0	12.05 (9.59, 15.14)	0.73 (0.54, 1.01)
Non-LABA	83	4927.7	16.8	16.40 (13.17, 20.41)	

^a Note that a patient who was hospitalized on more than one occasion has only been counted once in this calculation.

^b Event rate per 1000 treatment years

[Figure 8](#) displays the Kaplan-Meier probability curve for time to first hospitalization.

Figure 8 Kaplan Meier probability curve for time to first asthma-related hospitalization during randomized treatment (adjudicated data, all ages)



The time to first asthma-related hospitalization was prolonged in the formoterol-containing group compared to the non-LABA group. The curves diverge over time, suggesting that the benefit of formoterol-containing products with regard to time to first asthma-related hospitalization is not only maintained but may increase over time. This is supported by a specific evaluation of long-term studies (see Section 2.2.6.3), which showed no increased risk of asthma-related hospitalization for formoterol-exposed patients compared with non-LABA-exposed patients during long-term treatment.

2.2.6.3 Asthma-related hospitalizations in long-term trials

The long-term effects of LABA treatment were studied in 11 trials of 6 to 12 months duration. Data from these studies were pooled. The results for asthma-related hospitalizations are summarized in Table 11 and Table 12.

Table 11 Patients with at least 1 asthma-related hospitalization in 6 to 12-month trials during randomized treatment (adjudicated population, all ages)

	Formoterol-exposed	Non-LABA-exposed	Total
Patients (N)	5991	4859	10 850
Total exposure (1000 treatment years)	5.03	3.98	9.01
Number (%) of patients with ≥ 1 asthma-related hospitalization	53 (0.88%)	64 (1.32%)	117 (1.08%)
Asthma-related hospitalizations/ 1000 treatment years ^a	10.54	16.08	12.99

^a Note that a patient who was hospitalized on more than 1 occasion has only been included once in this calculation.

Table 12 Odds ratio for asthma hospitalization in 6 to 12 months trials during randomized treatment (adjudicated population, all ages)

Formoterol-exposed		Non-LABA-exposed		Comparison formoterol-exposed vs non-LABA-exposed	
N	No. (%) with ≥ 1 hosp	N	No. (%) with ≥ 1 hosp	OR	95% CI
5991	53 (0.88%)	4859	64 (1.32%)	0.67	(0.45-0.98)

From [Table 11](#) and [Table 12](#)), there were numerically fewer formoterol-exposed patients hospitalized compared to non-LABA-exposed patients.

[Table 13](#) presents the odds ratio for asthma-related hospitalization from long-term trials classified on the basis of onset period: between day 1 and 31; between day 32 and 92; on day 93 or later. Five patients reported events in more than 1 of these time-periods.

Table 13 Odds ratio for asthma hospitalization estimated from the number of patients in 6 to 12 months trials by onset period (adjudicated population, all ages)

Onset	Formoterol-exposed		Non-LABA-exposed		Comparison formoterol-exposed vs non-LABA-exposed	
	N ^a	No. (%) with ≥ 1 hospitalization	N ^a	No. (%) with ≥ 1 hospitalization	OR	95% CI
Day 1 to 31	5991	5 (0.08%)	4859	8 (0.16%)	0.51	(0.13-1.76)
Day 32 to 92	5795	16 (0.28%)	4689	16 (0.34%)	0.81	(0.38-1.72)
Day 93 or later	5558	36 (0.65%)	4466	46 (1.03%)	0.63	(0.39-0.99)

^a Number of patients at risk on day 1, 32 or 93.
Note: multiple events in same patient allowed (not included in data submitted to FDA).

The results in [Table 13](#) are consistent with the results from the Kaplan Meier survival curve (see [Figure 8](#)), ie, there is no indication of an increased risk of asthma-related hospitalization

in patients receiving formoterol-containing treatment for more than 3 months, compared with patients receiving non-LABA treatment.

2.2.6.4 Asthma-related hospitalizations in trials comparing ICS + formoterol vs ICS alone

This section evaluates asthma-related hospitalizations in patients receiving ICS + formoterol compared with ICS alone. Only trials with treatment arms in which patients received ICS and either formoterol or non-LABA treatment as randomized treatment are included. Treatment arms that did not include an ICS are excluded from this analysis, eg, formoterol-only or placebo arms. The actual comparisons consist of budesonide + formoterol as monoproducts vs budesonide, or SYMBICORT (either formulation) vs budesonide. ICS doses were either equivalent or, in some cases, up to 4 times higher in the non-LABA treatment arms as in the ICS + formoterol treatment arms. A total of 28 trials were included in this analysis.

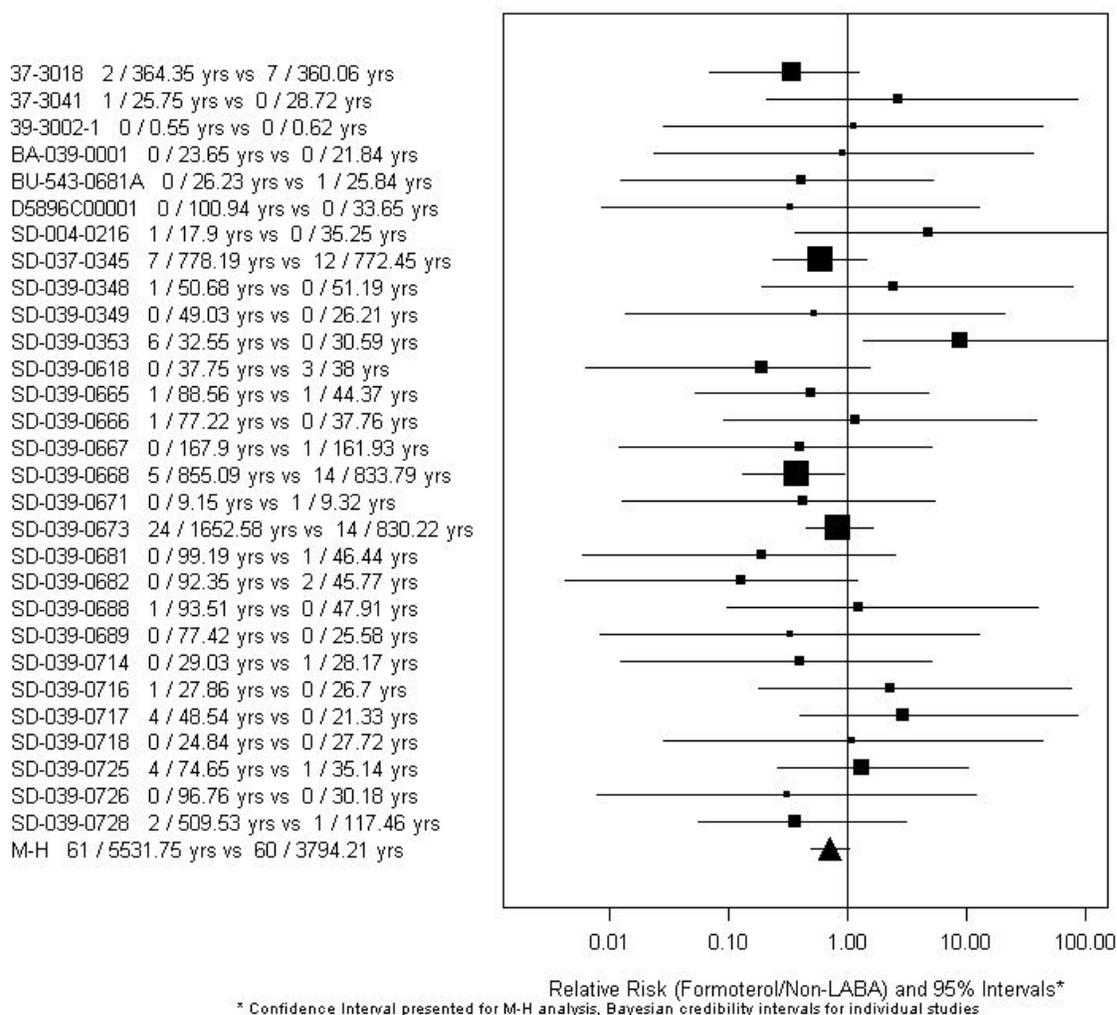
Table 14 presents the odds ratio for asthma hospitalization estimated from pooling the number of patients in trials comparing ICS + formoterol vs ICS alone. The odds ratio of 0.68 favored the ICS + formoterol treatment, and was in accordance with the results for the overall comparison between formoterol-containing treatment vs non-LABA treatment (see Table 9 and Table 10).

Table 14 Odds ratio for asthma hospitalization estimated from the number of patients in trials comparing ICS + formoterol vs ICS alone

ICS + formoterol		ICS alone		Comparison ICS + formoterol vs ICS alone	
N	No. (%) with ≥1 hospitalization	N	No. (%) with ≥1 hospitalization	OR	95% CI
10852	61 (0.56%)	7309	60 (0.82%)	0.68	(0.47-0.99)

Figure 9 displays the overall M-H relative risk estimate and 95% CI of asthma-related hospitalizations by trial comparing patients treated with ICS + formoterol versus ICS, stratified by study and adjusted for total exposure times between the treatment groups (see Section 2.2.1.4).

Figure 9 Relative risk estimates of asthma-related hospitalizations overall (M-H) and by individual trial, among patients in ICS + formoterol vs ICS trial designs



The overall pooled M-H estimate of relative risk (solid triangle at the bottom of [Figure 9](#) and presented in [Table 15](#)) stratified by study and adjusting for total exposure time, was 0.71 (95% CI: 0.49 to 1.02). Note that only the 22 studies with at least one event have contributed to this estimate. Potential differences in risk across individual studies were examined using a chi-square test for homogeneity ($p=0.044$), indicating some evidence of heterogeneity of relative risk across the studies. Thus, the overall pooled M-H estimate of relative risk should be interpreted with caution; nevertheless, the unstratified and stratified assessments of risk differences are similar.

Table 15 presents summary output for the M-H analysis of RR for asthma-related hospitalizations among patients in ICS + formoterol vs ICS trial designs. As before, both simple event rates and event rates using stratification corresponding to the M-H relative risk estimate are provided. Overall event rates are lower for ICS + formoterol versus ICS alone by either estimate.

Table 15 **Stratified M-H analysis for asthma-related hospitalizations, among patients receiving ICS + formoterol vs. ICS**

Treatment	No. of events ^a	Total exposure (years)	Crude event rate ^b	M-H analysis	
				Weighted event rate ^b (95% CI)	RR (95% CI)
ICS + formoterol	61	5531.8	11.0	11.14 (8.60, 14.42)	0.71 (0.49, 1.02)
ICS	60	3794.2	15.8	15.65 (12.12, 20.21)	

^a Note that a patient who was hospitalized on more than one occasion has only been counted once in this calculation.
^b Event rate per 1000 treatment years.

Figure 10 Kaplan Meier probability curve for time to first asthma-related hospitalization, among patients on ICS + formoterol vs ICS (28 trials)

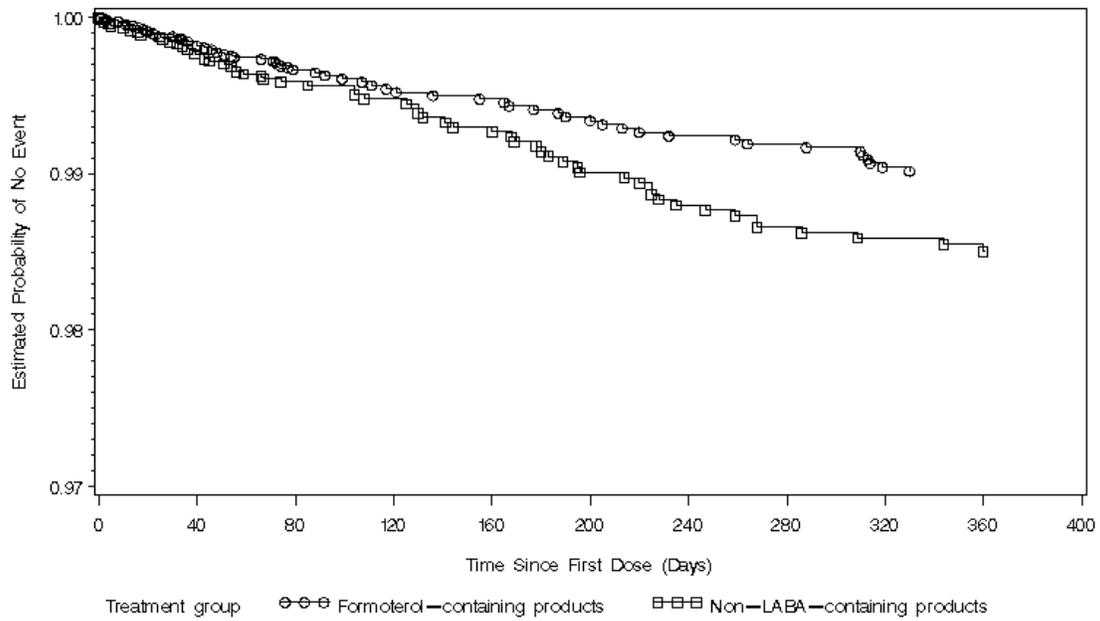


Figure 10 shows that time to first asthma-related hospitalization was prolonged in the ICS + formoterol group compared to the ICS group. The curves diverge over time, suggesting that the benefit of ICS + formoterol, relative to ICS alone, with regard to asthma-related hospitalization is not only maintained but may increase over time.

2.2.6.5 Asthma-related hospitalizations by baseline ICS use

For completeness, and in order to allow comparison with previous evaluation as part of the 2005 PADAC meeting, asthma-related hospitalizations were also evaluated in relation to baseline ICS use. In addition to the dataset (ICS + formoterol or ICS alone) described in Section 2.2.6.4, this analysis includes approximately 6000 patients not formally randomized to either ICS + formoterol or ICS monotherapy arms. The “ICS use at baseline” group includes patients who were expected to continue ICS treatment during the study, concomitant to their randomized treatment. In addition, this group includes the 384 patients in the US pMDI studies (SD-039-0716, SD-039-0717, and SD-039-0718) who were on ICS at baseline and were subsequently randomized to formoterol monotherapy. Note that the inclusion of patients in the “ICS at baseline” group that may or may not have received ICS provides a worst-case perspective on safety if concomitant ICS use is protective.

Table 16 presents the number of patients with at least 1 asthma-related hospitalization during randomized treatment, by baseline ICS use.

Table 16 Patients with at least 1 asthma-related hospitalization during randomized treatment, by baseline ICS use (adjudicated population, all ages)

	Formoterol-exposed		Non-LABA-exposed		Total	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp
ICS use at baseline	11767	72 (0.61%)	7988	74 (0.93%)	19755	146 (0.74%)
No ICS use at baseline	1775	6 (0.34%)	1980	9 (0.45%)	3755	15 (0.40%)

In patients using ICS at baseline, the proportion of patients with at least 1 asthma-related hospitalization was higher in the non-LABA group than in the formoterol-exposed group.

In both formoterol- and non-LABA exposed groups, the proportion of patients with at least 1 asthma-related hospitalization was slightly higher in patients receiving ICS at baseline, compared to no ICS at baseline, consistent with the greater asthma severity expected in patients previously treated with ICS.

Although there were no findings of concern identified, these data do not allow conclusions to be drawn regarding the potential protective effect of concomitant use of ICS with LABAs.

Because AstraZeneca has relatively little data on the use of formoterol as monotherapy, conclusions could not be drawn regarding safety of ICS/LABA versus LABA alone. In the

384 patients in the SYMBICORT pMDI development program who received OXIS TURBUHALER as comparator without concomitant ICS, no asthma-related deaths occurred during treatment, and there was only 1 asthma-related hospitalization. In addition, data from a clinical trial (SD-037-0716) in which OXIS TURBUHALER was used as needed in patients with intermittent asthma, without concomitant anti-inflammatory therapy, did not indicate any increased risk for serious asthma-related events (Chuchalin et al 2005, see also Table 46 in Appendix B). Although reassuring, these data are insufficient to conclude that addition of ICS to formoterol is protective based on comparisons to formoterol as monotherapy.

2.2.6.6 Asthma-related hospitalizations by daily dose of formoterol

Table 17 presents the number of patients with at least 1 asthma-related hospitalization in the formoterol-exposed patients by daily formoterol dose. There was no tendency towards an increase in asthma-related hospitalizations with increasing dose. The highest rate of asthma-related hospitalizations occurred in the patients randomized to non-LABA treatment, with the exception of the 4.5 µg daily dose. These patients derive from the pediatric arm of Study SD-039-0673, which received SYMBICORT 80/4.5 µg once daily, believed to be an inadequate dose of medication, based on the study outcomes; this is discussed in more detail in Section 3.2.7.3.

Table 17 Patients with at least 1 asthma-related hospitalization during randomized treatment, by daily dose of formoterol (adjudicated population, all ages)

Daily dose of formoterol	Patients (N)	Number (%) of patients reporting ≥1 asthma-related hospitalization
Patients not exposed to LABA	9968	83 (0.83%)
Patients exposed to formoterol		
4.5 µg	118	7 (5.93%) ^a
9 µg	4463	23 (0.52%)
18 µg	4565	24 (0.53%)
36 µg	1088	1 (0.09%)
As needed use or adjustable dosing	3308	23 (0.70%)
Total formoterol-exposed	13542	78 (0.58%)

^a Note that these 7 patients are from one arm in Study SD-039-0673 in which patients received exploratory treatment with SYMBICORT TURBUHALER 80/4.5 µg once daily. This dose of medication was subtherapeutic, based on the study results.

2.2.6.7 Asthma-related hospitalizations by age, sex and race

Table 18 presents the number of patients with at least 1 asthma-related hospitalization by age, sex and race. The proportion of patients with asthma-related hospitalization was numerically higher in the non-LABA group for all age groups with the exception of patients aged <12 years, where the proportion was slightly higher in the formoterol-exposed group (25 out

of 2155 [1.16%]) compared to the non-LABA-exposed patients (14 out of 1268 [1.10%]). As mentioned in the previous section, this group includes patients derived from the pediatric arm of Study SD-039-0673 that received exploratory treatment with SYMBICORT 80/4.5 µg once daily, believed to be a subtherapeutic dose of medication, based on the study outcomes; this is discussed in more detail in Section 3.2.7.3.

The proportion of patients with asthma-related hospitalizations was numerically higher in the non-LABA group than in the formoterol-exposed group for both male and female patients, and also among Caucasian patients. For Black patients and patients of Oriental ethnic origin, the number of patients was too low to allow any strong conclusions; however, there was no indication of an increased risk of asthma-related hospitalizations in the formoterol-exposed group compared with the non-LABA group for these patients.

Table 18 Patients with ≥1 asthma-related hospitalization during randomized treatment, by age, sex and race (adjudicated population, all ages)

	Formoterol-exposed		Non-LABA-exposed		Total	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp
By age group						
4 to 11	2155	25 (1.16%) ^a	1268	14 (1.10%)	3423	39 (1.14%)
12 to 17	1515	14 (0.92%)	1155	15 (1.30%)	2670	29 (1.09%)
18 to 64	9116	35 (0.38%)	6981	45 (0.64%)	16 097	80 (0.50%)
>65	756	4 (0.53%)	564	9 (1.60%)	1320	13 (0.98%)
By sex						
Male	6367	34 (0.53%)	4704	34 (0.72%)	11 071	68 (0.61%)
Female	7175	44 (0.61%)	5264	49 (0.93%)	12 439	93 (0.75%)
By race						
Caucasian	11 311	58 (0.51%)	8540	68 (0.80%)	19 851	126 (0.63%)
Black	436	2 (0.46%)	252	3 (1.19%)	688	5 (0.73%)
Oriental	1026	9 (0.88%)	678	7 (1.03%)	1704	16 (0.94%)
Other	711	9 (1.27%)	463	5 (1.08%)	1174	14 (1.19%)
Unknown	58	0	35	0	93	0

^a Note that this includes 7 patients from one arm in Study SD-039-0673 in which patients in an exploratory treatment arm with SYMBICORT TURBUHALER 80/4.5 µg once daily proved to have received a dose of medication that was subtherapeutic, based on the study results.

2.2.6.8 Asthma-related hospitalizations by asthma severity (baseline predicted FEV₁)

The number of patients with at least 1 asthma-related hospitalization by baseline FEV₁ (% predicted) was analyzed to evaluate the possible influence of disease severity (lower FEV₁

being an indicator of more severe disease). The percentage of patients with at least 1 asthma-related hospitalization was lower in the formoterol-exposed group than in the non-LABA-exposed group regardless of disease severity, as measured by baseline FEV₁ (see [Table 19](#)).

Table 19 Patients with ≥1 asthma-related hospitalizations during randomized treatment, by baseline percent predicted FEV₁ (adjudicated population, all ages)

Baseline % predicted FEV ₁	Formoterol-exposed		Non-LABA-exposed		Total	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp
≤29.9	14	0	8	0	22	0
30-49.9	417	3 (0.72%)	320	6 (1.88%)	737	9 (1.22%)
50-74.9	4209	30 (0.71%)	3126	35 (1.12%)	7335	65 (0.89%)
≥75	8371	45 (0.54%)	6083	40 (0.66%)	14454	85 (0.59%)
Unknown	531	0	431	2 (0.46%)	962	2 (0.21%)

2.2.7 Additional safety information

The following section summarizes additional safety variables that were considered relevant.

Total number of asthma-related hospitalizations during randomized treatment

A separate analysis was done for the total number of asthma-related hospitalizations, ie, accounting for multiple asthma-related hospitalizations experienced by a patient. Nine patients reported 2, one patient reported 3 and one patient reported 4 hospitalizations, for a total of 14 additional hospitalizations. Taking into account exposure, there were fewer asthma-related hospitalizations in the formoterol-exposed group than the non-LABA-exposed group (13 vs 18 per 1000 treatment years, see [Table 20](#)). Using the data in [Table 20](#) for Poisson regression (relating number of events to exposure time), the estimated common Poisson relative risk for asthma hospitalization over time for formoterol-exposed treatment vs non-LABA treatment is 0.73 (95% CI: 0.54-0.99). These results are very similar to the results based on data for patients with at least 1 asthma-related hospitalization (see Section [2.2.6.1](#)).

Table 20 Total number of asthma-related hospitalizations allowing for multiple events in the same patient (adjudicated population, all ages)

	Formoterol-exposed	Non-LABA-exposed	Total
Total exposure (1000 treatment years)	6.49	4.92	11.41
Number of hospitalized patients	78	83	161
Number of additional hospitalizations from patients with multiple events	8	6	14
Total number of hospitalizations	86	89	175
Hospitalizations / 1000 treatment years	13.3	18.1	15.3

Asthma-related serious adverse events in the non-adjudicated population

A brief analysis of asthma-related SAEs has been performed because this was one of the main outcome variables in the recent analysis of all AstraZeneca-sponsored randomized, controlled, parallel-group asthma trials of 3 to 12 months duration involving formoterol-containing treatment. SAEs that did not require hospitalizations were included in this analysis ([Sears et al 2008](#)). All events coded to the following preferred terms (MedDRA 10.0) were regarded as asthma-related: Asthma, Asthma exercise induced, Asthma late onset, Asthma prophylaxis, Asthmatic crisis, Bronchospasm, Bronchospasm paradoxical, Status asthmaticus. As mentioned previously (see Section 2.2.1.2), identification of asthma-related SAEs overall was not a part of the adjudication process, but the same dataset has been utilized for this evaluation of asthma-related SAEs as for asthma-related hospitalizations.

The results for asthma-related SAEs were very similar to those for asthma-related hospitalizations (see [Table 21](#) and [Table 22](#)), which is to be expected because, based on the criteria, most SAEs are classified as serious due to hospitalization. Due to the similarity of results for asthma-related hospitalizations and asthma-related SAEs, no further separate presentation of SAEs other than hospitalizations will be made.

Table 21 Patients with at least 1 asthma-related SAE (non-adjudicated, all ages)

	Formoterol-exposed	Non-LABA-exposed	Total
Patients (N)	13542	9968	23510
Total exposure (1000 treatment years)	6.49	4.92	11.41
Number (%) of patients with asthma-related SAE	72 (0.53%)	75 (0.75%)	147 (0.63%)
Asthma SAEs ^a / 1000 treatment years	11.09	15.24	12.88

^a Note that a patient who had more than one asthma-SAE has only been presented once in this calculation.

Table 22 Odds ratio for asthma SAEs (non-adjudicated, all ages)

Formoterol-exposed		Non-LABA-exposed		Comparison formoterol-exposed vs non-LABA-exposed	
N	No. with ≥ 1 asthma-related SAE	N	No. with ≥ 1 asthma-related SAE	OR	95% CI
13542	72 (0.53%)	9968	75 (0.75%)	0.71	(0.50-0.99)

The number of patients who reported at least 1 asthma-related SAE is lower than the number of patients with adjudicated asthma-related hospitalizations. In all, there were 19 hospitalizations that were not identified as asthma-related SAEs. In most cases this was because the event was reported with a preferred term other than asthma, status asthmaticus or bronchospasm; the reported terms include bronchitis (n=6), pneumonia (n=5) and upper respiratory tract infection (n=2) as the most common. Five asthma-related SAEs were not identified as asthma-related hospitalizations, in most cases because the event was reported as serious based on the criterion “medically important event”.

Discontinuations due to any cause

In order to assess if any imbalance in the results may be caused by different discontinuation rates in the formoterol- and non-LABA treatment groups, clinical study reports were reviewed for patients who prematurely discontinued from the trials due to any cause. Reasons for discontinuation were classified as lack of effect, adverse event, lost to follow-up and other causes. The percentage of discontinuations was lower in the formoterol-exposed group than in the non-LABA group (12.7% vs 15.4%; see [Table 23](#)).

Table 23 Discontinuations due to any cause (adjudicated population, all ages)

Treatment	Patients (N)	Number of discontinuations (%)
Formoterol-exposed patients	13542	1720 (12.7%)
Non-LABA-exposed patients	9968	1536 (15.4%)
Total	23510	3256 (13.8%)

[Table 24](#) presents the crude RR as approximated by the odds ratio obtained from StatXact using the pooled number of patients and the number of withdrawals. A higher proportion of patients on non-LABA treatments discontinued the trials prematurely. This lower withdrawal rate in the formoterol group suggests that the favorable results already presented for formoterol-containing products compared with non-LABA treatment with regard to asthma-related hospitalizations may represent a conservative view.

Table 24 Odds ratio for discontinuation due to any cause (adjudicated population, all ages)

Formoterol-exposed		Non-LABA-exposed		Comparison formoterol-exposed vs non-LABA-exposed	
N	No. (%) discontinued	N	No. (%) discontinued	OR	95% CI
13 542	1720 (12.7%)	9968	1536 (15.4%)	0.80	(0.74-0.86)

Other variables of interest

Although not presented in this document, the possible influence of smoking status and body mass index (BMI) at baseline were evaluated. No influence on the risk of asthma-related exacerbations was discerned.

2.2.8 Overall discussion of asthma-related risks

The adjudicated data included a total of 23,510 patients, 13,542 exposed to formoterol (approximately 20% received SYMBICORT pMDI), and 9,968 exposed to non-LABA treatment. The vast majority of patients in this dataset were treated with ICS at baseline, and most were expected to have continued concomitant ICS during randomized treatment based on study protocol designs. In this large number of patients, the number of deaths from any cause during randomized treatment was low (7 of 23,510); none of these occurred in the clinical studies contained in the US NDA for SYMBICORT pMDI. There were 3 deaths in patients on formoterol-containing treatment and 4 deaths in patients on non-LABA treatment. No deaths were asthma-related and there was only 1 asthma-related intubation (in a formoterol-exposed patient). While the overall event rate is low, in this large population of over 23,000 patients, there is no evidence of any imbalance in deaths favoring non-LABA treatments.

Among the overall population, there was no indication of an increased risk of asthma-related hospitalizations during randomized treatment with formoterol-containing treatment compared with non-LABA treatment; rather, there was evidence of a lower rate of asthma-related hospitalizations in the formoterol-exposed group. This was also observed for patients receiving treatment over longer periods of time (3 months to 1 year). Similarly, the time to first asthma-related hospitalization was prolonged in the formoterol-containing group compared to the non-LABA group. When analyzed by sex, race, severity (based on FEV₁), and dose there were no findings that suggested an increased risk in the formoterol-exposed group compared to non-LABA treatment.

In order to address the question of whether ICS modifies a presumed risk of LABA therapy, analysis of all cause mortality and asthma-related hospitalizations in patients randomized to receiving ICS + formoterol (N=10,852) compared with ICS alone (N=7,309) was performed. Although there were few deaths, results suggested no increase in risk for ICS + formoterol versus ICS monotherapy with regard to all cause mortality. As there were no asthma-related deaths and only one intubation, no conclusions could be drawn. With regard to asthma-related

hospitalizations, results favored ICS + formoterol treatment, and were in accordance with the results for the overall comparison between formoterol-containing treatment vs non-LABA treatment. This was also observed for patients receiving treatment over longer periods of time (3 months to 1 year). Similarly, time to first asthma-related hospitalization was prolonged in the ICS + formoterol group compared to the ICS group. Results suggested that for asthma-related hospitalization, the benefit of ICS + formoterol, relative to ICS alone, is not only maintained but may increase over time.

Overall, there is no indication of increased risk of asthma-related deaths or hospitalizations in patients using formoterol-containing treatment compared with non-LABA treatment. Because AstraZeneca has relatively little data on the use of formoterol as monotherapy, the impact of adding ICS to formoterol alone on the risk of asthma-related deaths, intubations, or hospitalizations could not be adequately assessed.

Importantly, as per guidelines and recommended clinical practice, the clinically relevant question is whether there is increased risk of adding formoterol to maintenance ICS therapy. Analysis of AstraZeneca's data showed that the addition of formoterol to ICS compared with ICS treatment alone presented no additional risk of asthma-related deaths, intubations or hospitalizations. These data provide strong evidence that there is no additional risk of adding formoterol to maintenance therapy with ICS.

Appropriateness of current SYMBICORT pMDI label

As a result of these overall findings AstraZeneca believes that the currently approved SYMBICORT prescribing information and Medication Guide ([Appendix F](#)) appropriately convey any potential risk regarding the use of the combination formoterol and budesonide. Specifically the Boxed Warning states:

WARNING

Long-acting beta2-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (eg, low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta2-adrenergic agonist), one of the active ingredients in SYMBICORT (see WARNINGS).

The Warning section states:

Long-acting beta2-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (eg, low- to

medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

- A 28-week placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta2-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.
- Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

Similar safety information can also be found in the Information for Patients, Adverse Reactions and Dosage and Administration sections of the SYMBICORT prescribing information as well as the FDA-approved Medication Guide that accompanies each SYMBICORT inhaler (see [Appendix F](#)).

AstraZeneca believes the new information presented in this briefing document, specifically the safety findings as a result of the large number of studies conducted by AstraZeneca with formoterol (SYMBICORT [budesonide/formoterol] and OXIS), should be appropriately considered and incorporated into future labeling (both in the PI and accompanying Medication Guide) to reflect the safety profile of this product when used as indicated.

3. BENEFIT/RISK OF FORMOTEROL IN PEDIATRIC ASTHMA PATIENTS

3.1 Benefits of formoterol in pediatric patients

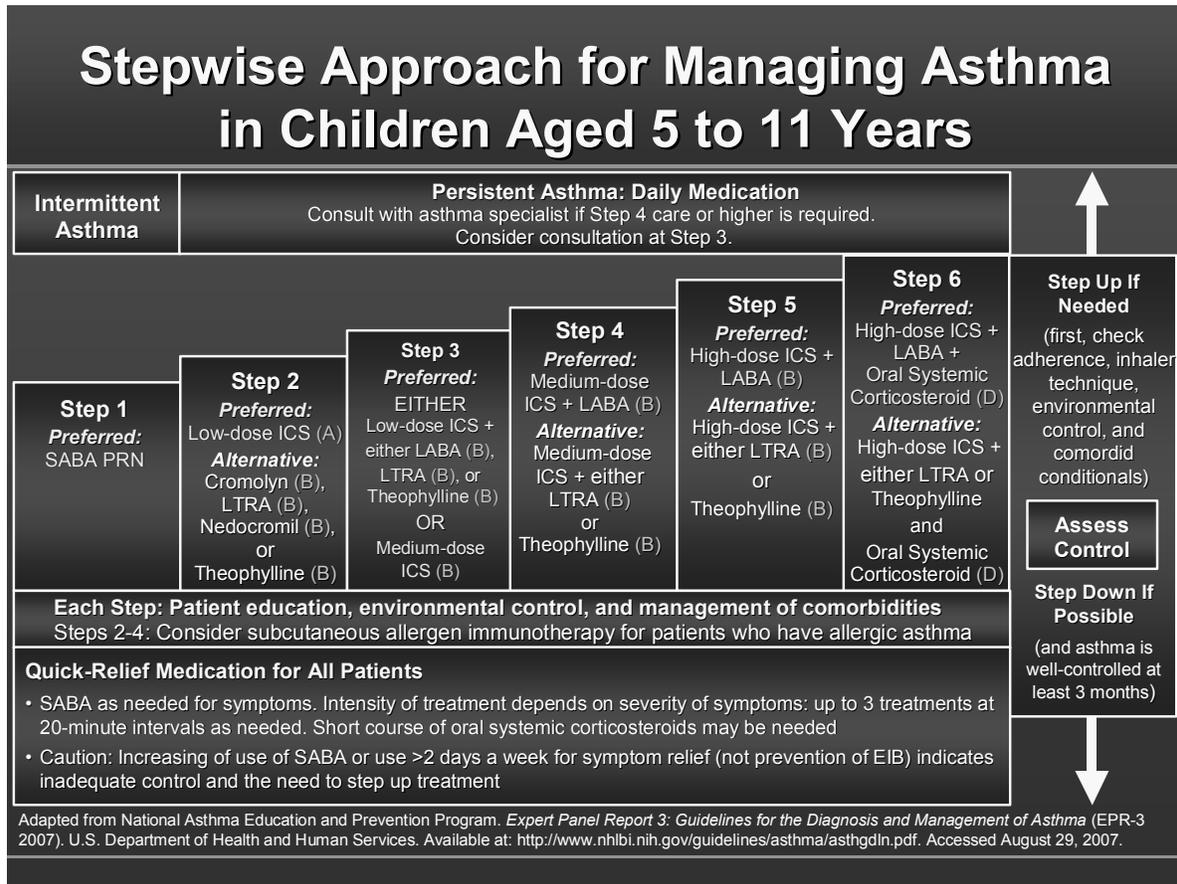
3.1.1 LABAs as a therapeutic option

Because the November 2007 PAC expressed specific concerns regarding the understanding of potential risks of LABA treatment in children with asthma, this document separately considers the benefit/risk of formoterol in children (6 to <18). Salmeterol (as the monotherapy Serevent and the ICS/LABA combination Advair) is approved for use in children 4 years of age or older, and formoterol (as the monotherapy Foradil) is approved for use in children 5 years of age and older. SYMBICORT pMDI is currently approved for the treatment of asthma in patients ≥ 12 years of age; an sNDA for an indication in children 6 through 11 years is currently under review at the FDA. LABAs are not approved for use in children with asthma less than 4 years of age.

Although the prevalence and pattern of asthma varies across age groups, the underlying pathophysiology and characterizing clinical features of asthma are similar in adults and children. Relative to adolescents and adults, school-aged children are likely to have more episodic disease, with relatively normal lung function between episodes. Therapeutic options for children are similar to those for adults.

Similar to adults, asthma treatment in children is approached in a stepwise fashion based on level of symptomatology and response to intervention. The NAEPP guidelines for treatment of asthma in children 5 through 11 years are shown in [Figure 11](#) below. As was previously noted, LABAs are a treatment option starting at Step 3, as an alternative to increasing ICS dose in patients uncontrolled on low- to medium-dose ICS. Similar to the guidelines for patients >12 years, at Step 3 in children 5 to 11 years, the option of adding LABA to low-dose ICS or increasing to a medium-dose of ICS are both preferred options, equally weighted. Unlike the guidelines for patients >12 years, where these 2 options are preferred over adding other adjunctive therapies such as theophylline or LTRAs to low-dose ICS, in children 5 to 11 these are equally recommended options at Step 3. At Steps 4 and 5 for children 5 to 11 years, ICS plus LABA are the preferred option. Therefore, it is expected that LABAs may be used less frequently in school-aged children with moderate asthma than they are in adolescents and adults ([EPR III 2007](#), [GINA 2007](#)). For children <5 years, increasing from low-dose ICS to medium-dose ICS is preferred at Step 3, and LABAs are not recommended before Step 4. AstraZeneca is not seeking an indication for use in pediatric patients in that age group.

Figure 11 Stepwise approach to managing asthma in children 5 to 11 years according to EPR III guidelines



3.1.2 AstraZeneca data demonstrating the clinical benefit of formoterol in pediatric patients

3.1.2.1 Clinical benefits of SYMBICORT pMDI in pediatric patients

The intended starting dose for pediatric patients 6 years of age and older is 80/9 µg bid and all available data from subjects age 6 to <12 were included in the original NDA. Doses of 80/9 µg bid, 160/9 µg bid, and 320/9 µg bid were evaluated in this program and showed efficacy in children 6 to <12 years of age in short- and long-term (up to 6 months) safety and efficacy studies. As described in the SYMBICORT pMDI PI, 1447 patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT pMDI studies, of whom 539 received SYMBICORT twice daily. Please note that a sNDA to support approval of SYMBICORT in pediatric patients 6 to <12 years is currently under FDA review.

Figure 12 and Figure 13 show the mean (solid boxes) change in predose morning PEF and morning FEV₁, respectively, for all AstraZeneca trials included in the NDA, by age group (6-<12, 12-<16, 16-<65, >65 years) and by individual study, for SYMBICORT versus

budesonide. The SYMBICORT dose and the number of patients treated with budesonide versus SYMBICORT, respectively, are shown next to each study number. Confidence intervals are shown and are broad for those subgroups that are small and where the study was not powered to show effect in the individual subgroup.

In general, favorable point estimates for mean morning predose PEF and morning FEV₁, respectively, were seen in all age groups for SYMBICORT pMDI versus budesonide. The increasing magnitude of effect with increasing age is expected, because lung size increases with increasing age.

Figure 12 Morning predose PEF: SYMBICORT pMDI versus budesonide for each study within each age group

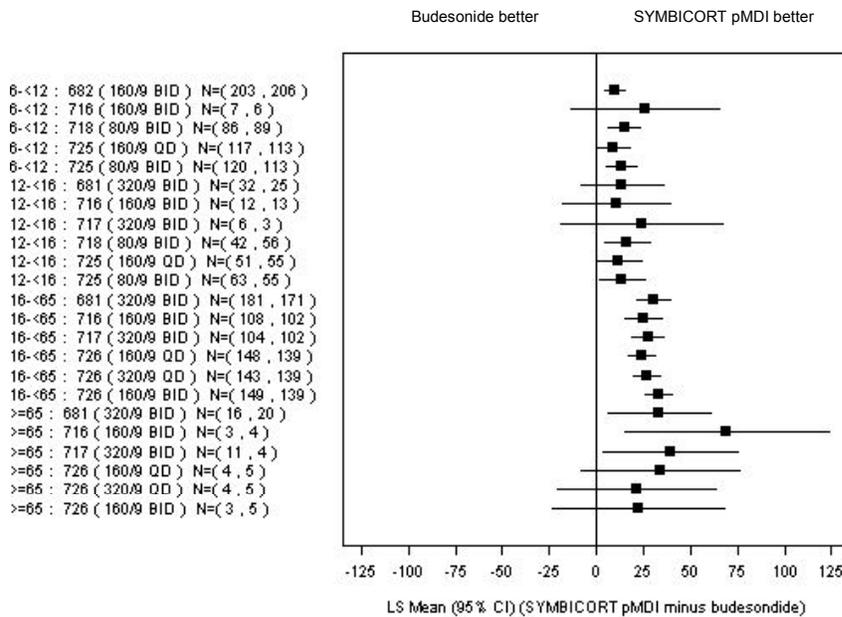
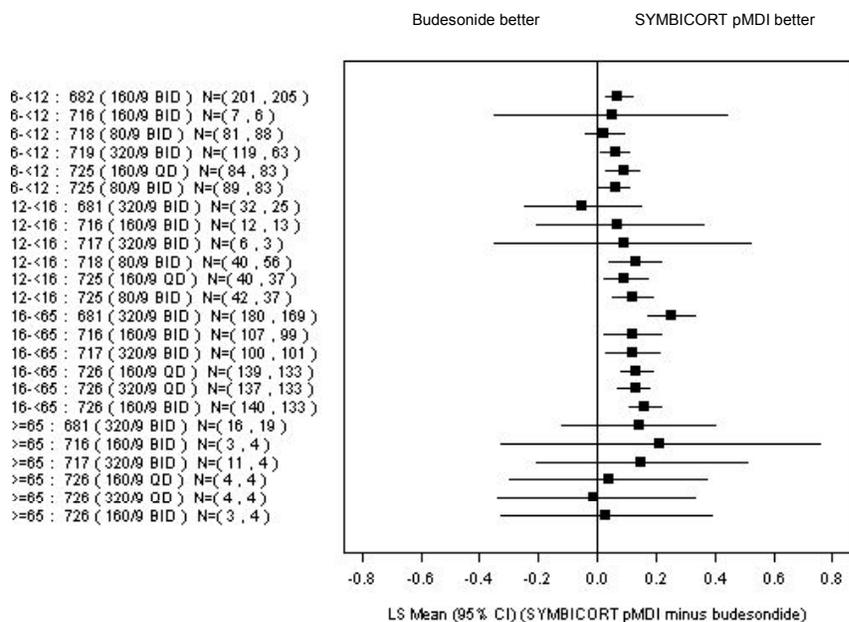


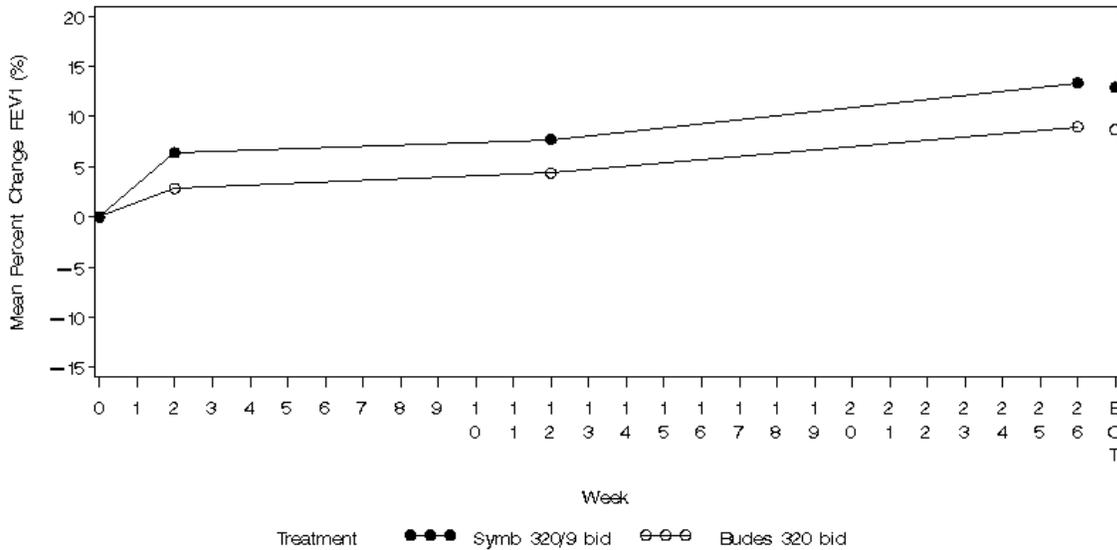
Figure 13 Morning FEV₁: SYMBICORT pMDI versus budesonide for each study within each age group



Note: FEV₁ was collected pre-dose in all studies except studies 681 and 682.

As shown in [Figure 14](#) these improvements in lung function were maintained over 26 weeks of treatment in an open-label safety study of pediatric patients (6 to <12 years of age) that included measures of predose FEV₁ (SD-039-0719). This study was not included in the adjudicated data due to open-label design. In this same open-label study, a high SYMBICORT pMDI dose, 640/18 µg daily (n=123), was superior to a corresponding dose of budesonide alone (n=63) in improving FEV₁ in patients previously treated with ICS. Thus, the added benefit of formoterol can be expected both at low and high doses of ICS, in accordance with results for adults and adolescents (see [Section 3.2.7.2](#) for details).

Figure 14 Mean percent change from baseline in morning predose FEV₁ by visit in Study SD-039-0719 (Subjects 6 to <12 years of age)



The effect of SYMBICORT pMDI on asthma control parameters other than lung function in subjects 6 to <12 years of age was evaluated in clinical studies with measures including assessment of asthma worsening criteria, withdrawal due to asthma worsening criteria, symptom scores/symptom free days and the use of rescue medication/rescue-free days. While improvements in measures of asthma control were observed as early as one day in patients treated with SYMBICORT, in general, no statistical differences were observed for SYMBICORT pMDI versus budesonide during the overall treatment periods.

In addition to traditional measures of asthma efficacy, some clinical trials in children 6 to <12 years also assessed measures of Quality of Life and Patient Reported Outcomes. Against the proven active comparator budesonide, statistically significant differences were observed; however, the Minimally Important Difference (MID) on measures such as Pediatric Asthma Quality of Life Questionnaire (standardized version) (PAQLQ[S]) was inconsistently achieved across studies. It is worth noting that in the long-term safety Study SD-039-0719, the change from baseline for the SYMBICORT pMDI 320/9 µg bid group exceeded the MID for the PAQLQ(S) on the overall score, as well as the symptom and emotional function domains, and approached the MID on the activity limitation domain. In addition, statistically significant improvements in the overall score as well as each of the domain scores were seen for SYMBICORT pMDI 320/9 µg bid vs budesonide 320 µg bid. These findings are further supported by analyses of the Pediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ) in Study SD-039-0719 and the PAQLQ(S) in Study SD-039-0682, which showed that the MID was met or exceeded in some of the individual domain scores and approached the MID on the overall scores.

3.1.2.2 Clinical benefits of SYMBICORT TURBUHALER in pediatric patients

The efficacy of fixed-dose treatment with SYMBICORT TURBUHALER has also been demonstrated for pediatric patients previously using ICS, in randomized, controlled, double-blinded, 12-week studies. In Study SD-039-0353 (Tal et al 2002), SYMBICORT TURBUHALER was compared with a corresponding dose of ICS alone over 12 weeks in patients with asthma aged 4 to 17 years (N=286; 171 <12 years). Study SD-039-0688 (Pohunek et al 2006) was similar in design, but limited to patients between 4 to 11 years (N=630), and also included the free combination of budesonide and formoterol at corresponding doses. In both studies, SYMBICORT TURBUHALER was superior to budesonide with regard to lung function; no benefit could be demonstrated for secondary symptom-related variables or health-related quality of life.

3.1.3 Summary of clinical benefit in pediatric patients

In summary, the benefits of an ICS such as budesonide in children younger than 12 years of age have been well demonstrated by improvements across a range of measures of asthma control in numerous clinical trials. In studies presented in this document, evaluating children between the age of 6 to <12, the additional benefits of adding formoterol to budesonide compared to budesonide alone have been unequivocally demonstrated on measures of control such as FEV₁ and PEF as well as in some measures of HRQL across a range of ICS doses, while parity on other measures of control was observed in patients with asthma previously treated with ICS. In light of potential systemic effects of high-dose ICS (eg. adrenal axis suppression and effects on growth) an additional benefit of ICS/LABA in this population may be the ability to gain asthma control with a lower dose of ICS. In this regard, the addition of formoterol to budesonide presents a definitive benefit to patients not adequately controlled on ICS monotherapy.

3.2 Assessment of risk profile of formoterol during randomized treatment in pediatric clinical trials

3.2.1 Scope of presentation

The presentation of data for pediatric patients <18 years is a sub-set of the data presented previously, and is thus also based on the adjudicated data requested by the FDA. In accordance with the previous presentation, only studies including a non-LABA comparator are included in the summary presentations; however, Appendix B includes a by-study presentation of results for studies in which all treatment arms included a LABA. For a summary of the design of included studies, see Appendix A. For a presentation of asthma-related adverse events as presented in the SYMBICORT pMDI 4-month safety update and pediatric sNDA, see Appendix D.

3.2.2 Overview of the dataset in patients <18 years of age

There were a total of 6093 patients <18 years of age in the adjudicated population. Of these 3670 were exposed to formoterol and 2423 were non-LABA exposed during randomized treatment. Note that in the formoterol-exposed group, approximately 95% of patients below 12 years and 85% of patients 12 to <18 years received ICS at baseline.

3.2.3 Baseline characteristics of patients <18 years

Baseline demographics are presented for the patients aged <18 year, by age group (<12 or 12 to <18) in [Table 25](#).

Table 25 Baseline characteristics (adjudicated population, patients <18 years, by age group)

Parameter	Class	Treatment group (patients <12 years)			Treatment group (patients 12 to <18 years)		
		Formoterol-exposed (N=2155)	Non-LABA-exposed (N=1268)	Total (N=3423)	Formoterol-exposed (N=1515)	Non-LABA-exposed (N=1155)	Total (N=2670)
Age (years)	N	2155	1268	3423	1515	1155	2670
	Mean	8.5	8.6	8.5	13.9	14.1	14.0
	Range	4.0-11.0	4.0-11.0	4.0-11.0	12.0-17.0	12.0-17.0	12.0-17.0
Sex	Female	731 (33.9%)	417 (32.9%)	1148 (33.5%)	617 (40.7%)	430 (37.2%)	1047 (39.2%)
	Male	1424 (66.1%)	851 (67.1%)	2275 (66.5%)	898 (59.3%)	725 (62.8%)	1623 (60.8%)
Race	Asian	64 (3.0%)	49 (3.9%)	113 (3.3%)	80 (5.3%)	60 (5.2%)	140 (5.2%)
	Black or African-American	104 (4.8%)	45 (3.5%)	149 (4.4%)	81 (5.3%)	53 (4.6%)	134 (5.0%)
	White	1785 (81.6%)	1054 (83.1%)	2812 (82.2%)	1259 (83.1%)	975 (84.4%)	2234 (83.7%)
	Other	229 (10.6%)	120 (9.5%)	349 (10.2%)	95 (6.3%)	67 (5.8%)	162 (6.1%)
BMI at entry (kg/m ²)	N	2153	1267	3420	1508	1150	2658
	Mean	18.0	17.9	18.0	21.3	21.0	21.2
	Range	11.1-36.1	11.7-37.3	11.1-37.3	11.7-48.2	11.7-39.8	11.7-48.2
FEV ₁ at baseline (%pred)	N	2148	1265	3413	1472	1116	2588
	Mean	88.9	88.3	88.7	84.6	85.0	84.8
	Range	20.0-172.0	39.5-175.0	20.0-175.0	28.0-141.0	37.0-150.0	28.0-150.0
ICS use at baseline	No	102 (4.7%)	99 (7.8%)	201 (5.9%)	226 (14.9%)	262 (22.7%)	488 (18.3%)
	Yes	2053 (95.3%)	1169 (92.2%)	3222 (94.1%)	1289 (85.1%)	893 (77.3%)	2182 (81.7%)
Region	United States	420 (19.5%)	218 (17.2%)	638 (18.6%)	437 (28.8%)	221 (19.1%)	658 (24.6%)
	Non-United States	1735 (80.5%)	1050 (82.8%)	2785 (81.4%)	1078 (71.2%)	934 (80.9%)	2012 (75.4%)

3.2.4 All-cause mortality in patients <18 years in the adjudicated population

There were no deaths due to any cause (all cause and/or asthma related) in the pediatric/adolescent <18 years subset of the adjudicated data set.

3.2.5 Asthma-related intubations in patients <18 years in the adjudicated population

There were no asthma-related intubations in patients <18 years in the adjudicated data set.

3.2.6 Asthma-related hospitalizations in patients <18 years in the adjudicated population

3.2.6.1 Number of patients with at least 1 asthma-related hospitalization in the adjudicated population

Asthma-related hospitalizations for patients <18 years of age are presented in [Table 26](#). Note that “Asthma hospitalizations per 1000 treatment years” does not account for multiple occurrences for the same individual. The presentation gives an estimate of the rate in relation to the duration of the exposure.

Table 26 Patients with at least 1 asthma-related hospitalization (adjudicated data, patients <18 years, by age group)

	Formoterol-exposed	Non-LABA-exposed	Total
Patients <12 years			
Patients (N)	2155	1268	3423
Total exposure (1000 treatment years)	0.77	0.48	1.25
Number (%) of patients with ≥1 asthma-related hospitalization	25 (1.16%) ^a	14 (1.10%)	39 (1.14%)
Asthma-related hospitalizations/ 1000 treatment years ^b	32.4	29.4	31.3
Patients 12 to <18 years			
Patients (N)	1515	1155	2670
Total exposure (1000 treatment years)	0.76	0.59	1.34
Number (%) of patients with ≥1 asthma-related hospitalization	14 (0.92%)	15 (1.30%)	29 (1.09%)
Asthma-related hospitalizations/ 1000 treatment years ^b	18.5	25.5	21.6

^a Note that this includes 7 patients from one arm in Study SD-039-0673 in which patients in an exploratory treatment arm with SYMBICORT TURBUHALER 80/4.5 µg once daily proved to have received a dose of medication that was too low, based on the study results.

^b Note that a patient who was hospitalized on more than one occasion has only been included once in this calculation.

For patients 12 to <18 years of age, the proportion of patients with an asthma-related hospitalization was numerically lower in the group exposed to formoterol-containing products than the group exposed to non-LABA treatment (0.92% vs 1.30%), whereas among patients below 12 years of age, the proportion was numerically higher in the formoterol-exposed patients (1.16% vs 1.10%). The slight imbalance against formoterol-treatment in the younger

age group results from a high number of asthma-related hospitalizations in one arm of study SD-039-0673; in this arm, patients were treated with an exploratory low dose of SYMBICORT TURBUHALER (80/4.5 µg once daily) that proved to be subtherapeutic. When data from this arm of Study SD-039-0673 are excluded from the overall analysis, results were consistent with those for patients 12 years and older, ie, they slightly favor formoterol treatment (discussed in more detail in Section 3.2.7.3).

3.2.6.2 Asthma-related hospitalizations in patients <12 and 12 to <18 years

Table 27 presents the crude relative risk of asthma-related hospitalization for patients <18 years, by age group, as approximated by the odds ratio using the pooled total number of patients (6,093) and the number of patients experiencing at least one asthma hospitalization among patients randomized to formoterol-containing treatment vs patients randomized to non-LABA treatment. There was no evidence of a difference between the formoterol-containing and non-LABA treatment groups.

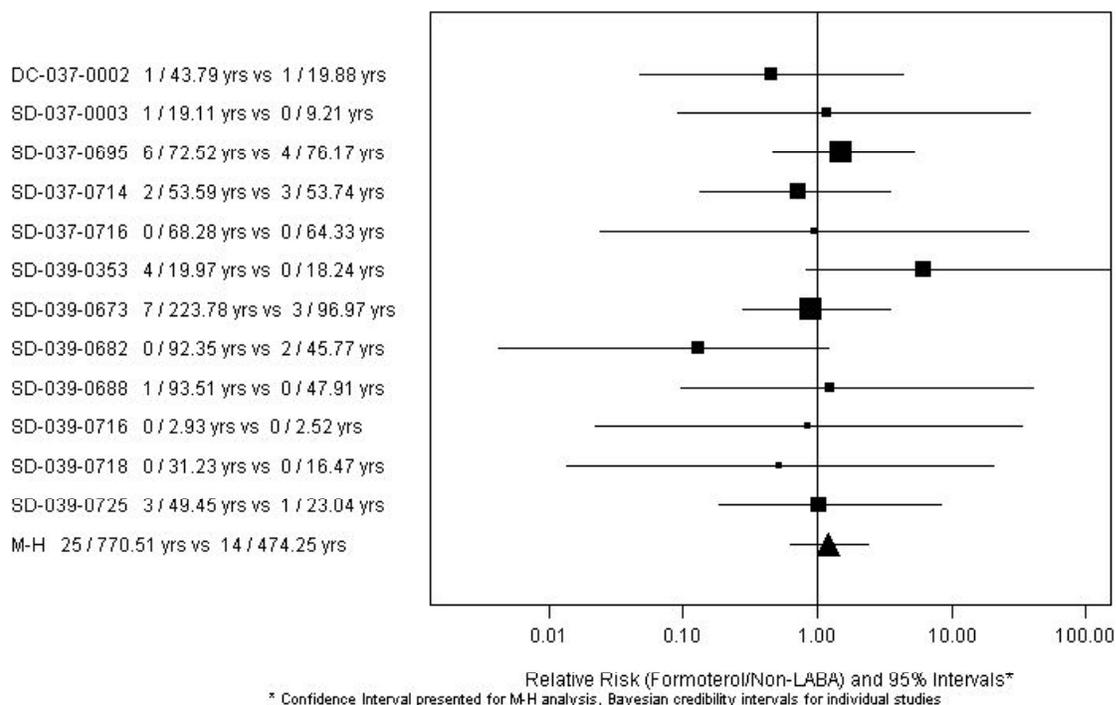
Table 27 Odds ratio (formoterol-exposed vs non-LABA-exposed) for asthma-related hospitalization during randomized treatment (adjudicated data, patients <18 years, by age group)

Age group	Formoterol-exposed		Non-LABA-exposed		Comparison formoterol-exposed vs non-LABA-exposed	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	OR	95% CI
<12 years	2155	25 (1.16%)	1268	14 (1.10%)	1.05 ^a	(0.52-2.20)
12 to <18 years	1515	14 (0.92%)	1155	15 (1.30%)	0.71	(0.32-1.58)

^a Note that if the 7 patients below 12 years that received SYMBICORT 80/4.5 µg once daily in Study SD-039-0673 are excluded, the OR is 0.80 (95% CI 0.37-1.74).

Figure 15 displays the overall Mantel-Haenszel (M-H) relative risk estimate and 95% CI of asthma-related hospitalizations in the <12 years group, stratified by study and adjusted for total exposure times between the treatment groups (see Section 2.2.1.4).

Figure 15 Relative risk estimates of asthma-related hospitalizations overall (Mantel-Haenszel) and by individual trial among patients <12 years



In general, RR estimates among individual studies are generally centered around the line of unity, representing no increased risk for formoterol-exposed versus non-LABA exposed patients in the <12 years group.

The overall pooled M-H estimate of RR (shown as the solid triangle at the bottom of [Figure 15](#) and presented in [Table 28](#)) stratified by study and adjusting for total exposure time, was 1.22 (95% CI: 0.62 to 2.37). As previously noted, the slight imbalance against formoterol-treatment in this age group results from a high number of asthma-related hospitalizations in an arm of study SD-039-0673 that received a sub therapeutic dose of SYMBICORT. When data from this arm of Study SD-039-0673 are excluded from the overall analysis, results are consistent with those for adults and patients 12 years and older, ie they slightly favor formoterol treatment (discussed in more detail in [Section 3.2.7.3](#)).

Note that only 9 studies with at least 1 event contributed to this estimate. Potential differences in risk across individual studies were examined using a chi-square test for homogeneity (p=0.360), indicating no clear evidence of heterogeneity of relative risk across the studies.

[Table 28](#) presents summary output for the overall M-H analysis of RR for asthma-related hospitalizations among patients <12 years. As before, both simple event rates and event rates using stratification corresponding to the M-H relative risk estimate are provided. Event rates

are numerically higher for formoterol-exposed versus non-LABA-exposed patients by either estimate, although the CI for the overall RR includes unity. When data from the subtherapeutic arm of Study SD-039-0673 are excluded, the event rates favor formoterol treatment (see Section 3.2.7.3).

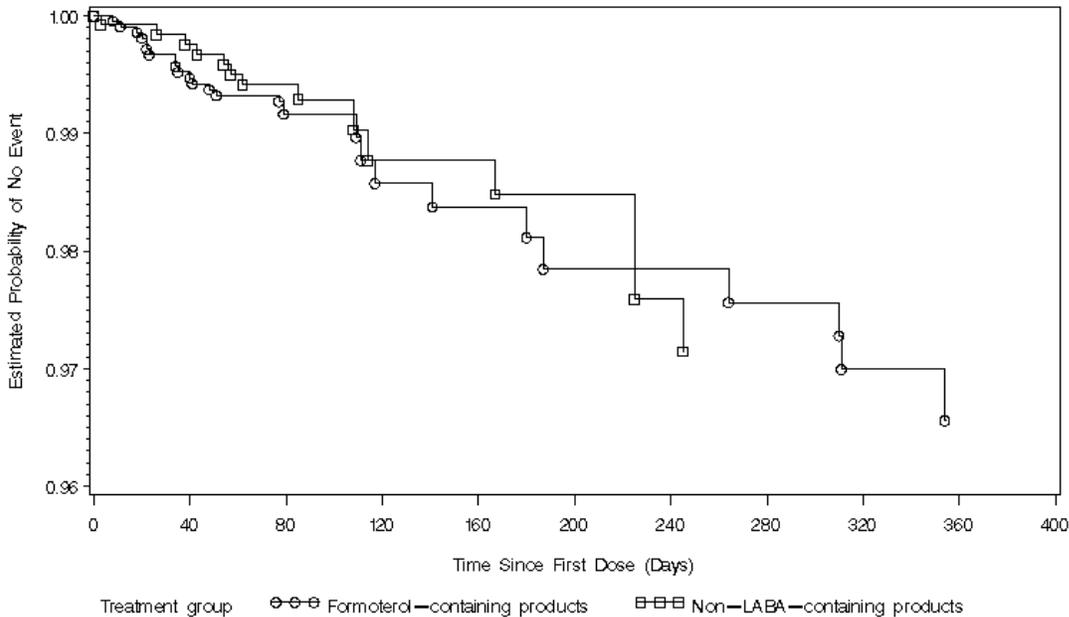
Table 28 Stratified M-H analysis for asthma-related hospitalizations, among patients <12 years

Treatment	No. of events ^a	Total exposure (years)	Crude event rate ^b	M-H analysis	
				Weighted event rate ^b (95% CI)	RR (95% CI)
Formoterol	25 ^c	770.5	32.4	35.28 (23.58, 52.78)	1.22 (0.62, 2.37)
Non-LABA	14	474.3	29.5	29.01 (17.06, 49.33)	

^a Note that a patient who was hospitalized on more than one occasion has only been counted once in this calculation.
^b Event rate per 1000 treatment years.
^c Note that this includes 7 patients from one arm in Study SD-039-0673 in which patients in an exploratory treatment arm with SYMBICORT TURBUHALER 80/4.5 µg once daily proved to have received a dose of medication that was too low, based on the study results.

Figure 16 displays the Kaplan-Meier curve for time to first hospitalization in the <12 years group. The time to hospitalization was similar between treatment groups.

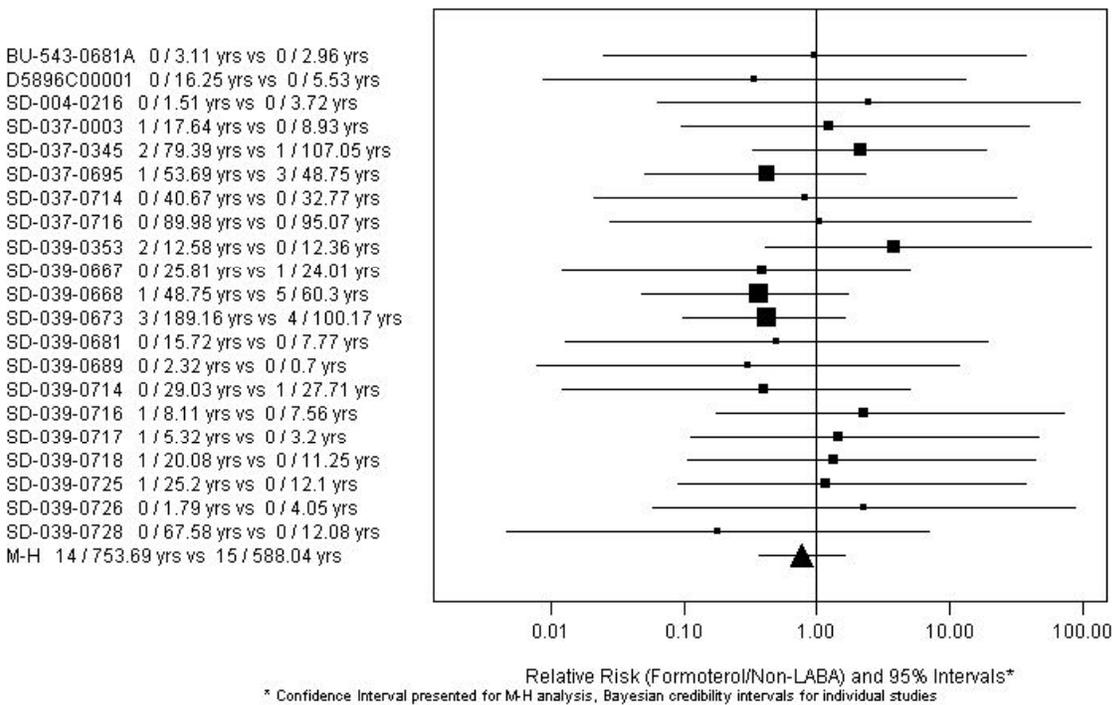
Figure 16 Kaplan Meier survival curve for time to asthma-related hospitalization (adjudicated data, patients <12 years)



Relative risk in patients 12 to <18 years

Figure 17 displays the overall Mantel-Haenszel (M-H) relative risk estimate and 95% CI of asthma-related hospitalizations, stratified by study and adjusted for total exposure times between the treatment groups (see Section 2.2.1.4).

Figure 17 Relative risk estimates of asthma-related hospitalizations overall (Mantel-Haenszel) and by individual trial among patients 12 to <18 years



In general, RR estimates among individual studies are generally centered around the line of unity, representing no increased risk for formoterol versus non-LABA exposed patients.

The overall pooled M-H estimate of RR (shown as the solid triangle at the bottom of Figure 17 and presented in Table 29) stratified by study and adjusting for total exposure time, was 0.77 (95% CI: 0.37 to 1.62), again indicating no increase in risk for formoterol versus non-LABA exposed patients. Note that only 12 studies with at least 1 event contributed to this estimate. Potential differences in risk across individual studies were examined using a chi-square test for homogeneity ($p=0.360$), indicating no clear evidence of heterogeneity of relative risk across the studies.

Table 29 presents summary output for the overall M-H analysis of RR for asthma-related hospitalizations. As before, both simple event rates and event rates using stratification

corresponding to the M-H relative risk estimate are provided. Event rates are lower for formoterol versus non-LABA exposed patients by either estimate.

Table 29 Stratified M-H analysis for asthma-related hospitalizations, among patients 12 to <18 years

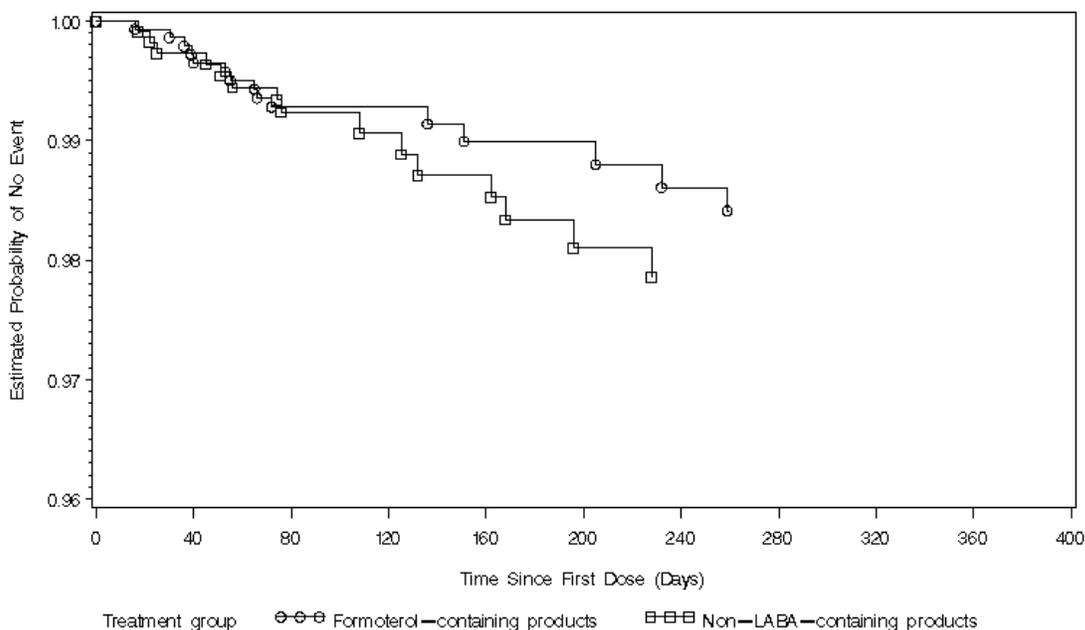
Treatment	No. of events ^a	Total exposure (years)	Crude event rate ^b	M-H analysis	
				Weighted event rate ^b (95% CI)	RR (95% CI)
Formoterol	14	753.7	18.6	19.50 (11.42, 33.32)	0.77 (0.37, 1.62)
Non-LABA	15	588.0	25.5	25.25 (15.13, 42.16)	

^a Note that a patient who was hospitalized on more than one occasion has only been counted once in this calculation.

^b Event rate per 1000 treatment years.

Figure 18 displays the Kaplan-Meier curve for time to first hospitalization. The time to hospitalization was similar between treatment groups.

Figure 18 Kaplan Meier survival curve for time to asthma-related hospitalization (adjudicated data, patients 12 to <18 years)



3.2.6.3 Asthma-related hospitalizations in long-term studies

In order to focus on possible long-term effect of LABA treatment in patients <18 years, data from 8 trials of 6 to 12 months duration were pooled. The results for asthma-related

hospitalizations are summarized in [Table 30](#). There was no evidence of a difference between formoterol- and non-LABA-exposed groups for patients <12 years (RR: 1.15; 95% CI: 0.49-2.90). For patients aged 12 to <18 years, there was a numerical difference in favor of the formoterol-exposed group (OR: 0.40; 95% CI: 0.13-1.08).

Table 30 Odds ratio of asthma-related hospitalization during randomized treatment estimated in 6 to 12-month trials (adjudicated data, patients <18 years)

Age group	Formoterol-exposed		Non-LABA-exposed		Comparison formoterol-exposed vs non-LABA-exposed	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	OR	95% CI
<12 years	528	15 (2.84%)	404	10 (2.48%)	1.15	(0.49-2.90)
12 to <18 years	752	7 (0.93%)	615	14 (2.28%)	0.40	(0.13-1.08)

Hosp Hospitalization; OR Odds ratio.

The dataset was then updated with information on multiple events, and the asthma-related hospitalizations were classified as follows: onset between day 1 and 31, between day 32 and 92, on day 93 or later. One patient reported events in more than one of these time-periods. The patients were then grouped according to their exposure time in studies: treatment duration at least 1 day, at least 31 days, or at least 92 days.

The number of patients who reported at least one asthma-related hospitalization during each of these time periods was then related to the number of patients at risk. The results are presented in [Table 31](#). The results are in accordance with the Kaplan Meier survival curves for time to asthma-related hospitalization among pediatric patients (see [Figure 16](#) and [Figure 18](#)), and suggest that there is no increased risk for asthma-related hospitalizations in formoterol-exposed patients compared with non-LABA-exposed patients even during long-term treatment.

Table 31 Patients with asthma-related hospitalizations during randomized treatment in 6 to 12-month trials by onset period (adjudicated data, patients <18 years)

Onset/Treatment	Patients <12 years		Patients 12 to <18 years	
	Patients (N) ^a	Number (%) of hospitalized patients	Patients (N) ^a	Number (%) of hospitalized patients
Onset between day 1 and 31				
Formoterol-exposed patients	528	0	752	1 (0.13%)
Non-LABA-exposed patients	404	1 (0.25%)	615	2 (0.33%)
Onset between day 32 and 92				
Formoterol-exposed patients	519	5 (0.96%)	734	1 (0.14%)

Table 31 Patients with asthma-related hospitalizations during randomized treatment in 6 to 12-month trials by onset period (adjudicated data, patients <18 years)

Onset/Treatment	Patients <12 years		Patients 12 to <18 years	
	Patients (N) ^a	Number (%) of hospitalized patients	Patients (N) ^a	Number (%) of hospitalized patients
Non-LABA-exposed patients	400	3 (0.75%)	598	5 (0.84%)
Onset on day 93 or later				
Formoterol-exposed patients	508	10 (1.97%)	704	5 (0.71%)
Non-LABA-exposed patients	387	7 (1.81%)	573	7 (1.22%)

^a Number of patients at risk on day 1, 32 or 93.

3.2.6.4 Asthma-related hospitalizations in trials comparing ICS + LABA vs ICS alone

Asthma-related hospitalizations were also evaluated in patients <18 years receiving ICS + LABA compared with ICS alone. Similar to Section 2.2.6.4, only trials with treatment arms in which patients received ICS and either formoterol or non-LABA treatment as randomized treatment are included. Twenty-two trials were included in this analysis; of these, 20 included patients aged 12 to < 18 and 12 included patients aged 4 to <12 (2 trials included only patients aged 4 to <12). ICS doses were generally either equivalent or, in some cases, up to 4 times higher in the non-LABA treatment arms as in the ICS + formoterol treatment arms. It should be noted, however, that 2 pediatric studies evaluated exploratory doses of ICS+formoterol that incorporated formoterol doses substantially below 18 µg daily (SD-039-0673 and SD-039-0725), ie, below the intended registered dose of formoterol in children. In both studies, there were more asthma-related hospitalizations in the low-dose formoterol treatment arms than in higher-dose groups, particularly in children <12. This effect was most notable in Study SD-039-0673 where 7 events occurred in the low-dose formoterol treatment arm (see Section 3.2.7.3 for further details). These events have been incorporated in the following analyses for completeness, but should be carefully considered when drawing conclusions based on comparisons of ICS + formoterol vs. ICS.

Table 32 presents the odds ratio for asthma hospitalization estimated from the number of patients in trials comparing ICS + formoterol vs ICS alone. The results are generally in accordance with the overall comparison between formoterol-containing treatment and non-LABA treatment (see Table 27), with a numerical difference in favor of non-LABA treatment in the children under 12 years and a numerical difference in favor of formoterol-containing treatment in the patients aged 12 to <18 years. While the odds ratio of 1.38 for patients <12 appears to favor budesonide alone, the slight imbalance against ICS + formoterol treatment in the younger age group results from the 7 events in low-dose SYMBICORT patients from study SD-039-0673 who received a SYMBICORT dose of only 80/4.5 µg once daily. When the 7 patients in this treatment arm are excluded, the difference in patients below 12 years also is numerically in favor of formoterol-containing treatment (OR 0.79 [95% CI 0.24-2.79]).

Table 32 Odds ratio of asthma hospitalization estimated from the number of patients in trials comparing ICS + formoterol vs ICS alone (patients <18 years)

Age group	Randomized to ICS + formoterol		Randomized to ICS alone		Comparison formoterol + ICS vs ICS alone	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	OR	95% CI
<12 years	1489	15 (1.01%) ^a	820	6 (0.73%)	1.38	(0.50-4.36)
12 to <18 years	1006	11 (1.09%)	783	12 (1.53%)	0.71	(0.28-1.77)

^a Note that this includes 7 patients from one arm in Study SD-039-0673 in which patients in an exploratory treatment arm with SYMBICORT TURBUHALER 80/4.5 µg once daily proved to have received a dose of medication that was too low, based on the study results.

Note that a patient who was hospitalized on more than one occasion has only been included once in this calculation.

3.2.6.5 Asthma-related hospitalizations by baseline ICS use

For completeness, and in order to allow comparison with previous analyses performed as part of the 2005 PADAC meeting evaluation, asthma-related hospitalizations were evaluated in relation to baseline ICS use. In addition to the dataset (ICS + formoterol or ICS alone) described in Section 3.2.6.4, this analysis includes approximately 990 patients not formally randomized to either ICS + formoterol or ICS monotherapy arms. Note that in the formoterol-exposed group, approximately 95% of patients below 12 years and 85% of patients 12 to <18 years received ICS at baseline. However, this “ICS use at baseline” group includes over 800 patients who were either expected to continue ICS treatment during the study but were not monitored for compliance with that therapy (approximately 15%), or were participants in US pMDI studies (SD-039-0716, SD-039-0717, and SD-039-0718) who were on ICS at baseline, but were subsequently randomized to formoterol monotherapy (approximately 6%) (see Section 2.2.6.5). Note that the inclusion of patients in the “ICS at baseline” group that may or may not have received ICS provides a worst-case perspective on safety if concomitant ICS use is protective.

The number of patients <18 years with asthma-related hospitalizations by baseline ICS use is presented by age group in Table 33.

Table 33 Patients with asthma-related hospitalizations during randomized treatment by ICS use at baseline (adjudicated data, patients <18 years, by age group)

	Formoterol-exposed		Non-LABA-exposed	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp
<12 years				
ICS use at baseline	2053	25 (1.22%)	1169	14 (1.20%)
No ICS-use at baseline	102	0	99	0

Table 33 Patients with asthma-related hospitalizations during randomized treatment by ICS use at baseline (adjudicated data, patients <18 years, by age group)

	Formoterol-exposed		Non-LABA-exposed	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp
12 to <18 years				
ICS use at baseline	1289	12 (0.93%)	893	15 (1.68%)
No ICS-use at baseline	226	2 (0.88%)	262	0

Similar to results described in Section 2.2.6.5, in patients using ICS at baseline, the proportion of patients 12 to <18 years with asthma-related hospitalizations was higher in the non-LABA group than in the formoterol-exposed group. In patients <12 years, the proportion with asthma-related hospitalizations was similar in the non-LABA and formoterol-exposed groups; however, when patients from Study SD-039-0673 who received a SYMBICORT dose of only 80/4.5 µg daily are removed from this analysis, the proportion favors formoterol-exposed patients. In both formoterol- and non-LABA-exposed groups, the proportion of patients with at least 1 asthma-related hospitalization was slightly higher in patients receiving ICS at baseline, compared to no ICS at baseline, consistent with the greater asthma severity expected in patients previously treated with ICS. Although there were no findings of concern identified, these data do not allow conclusions to be drawn regarding the potential protective effect of concomitant use of ICS with LABAs.

3.2.6.6 Asthma-related hospitalizations by daily dose of formoterol

Table 34 presents the number of patients with asthma-related hospitalizations in formoterol-exposed patients <18 years of age, by age group and daily formoterol dose. There was no tendency in either age group (<12 or 12 to <18) towards an increase in asthma-related hospitalizations with increasing dose of formoterol. The highest rate of asthma-related hospitalizations occurred in the patients < 12 randomized to the 80/4.5 µg daily dose SYMBICORT in Study SD-039-0673; this was believed to be a subtherapeutic dose of medication based on the study results (see Section 3.2.7.3).

Table 34 Patients with asthma-related hospitalizations during randomized treatment by daily dose of formoterol (adjudicated data, patients <18 years, by age group)

Daily dose of formoterol	<12 years		12 to <18 years	
	N	Number (%) with ≥1 hospitalization	N	Number (%) with ≥1 hospitalization
Non-LABA	1268	14 (1.10%)	1155	15 (1.30%)
4.5 µg	115	7 (6.09%)	1	0
9 µg	264	2 (0.76%)	475	5 (1.05%)

Table 34 Patients with asthma-related hospitalizations during randomized treatment by daily dose of formoterol (adjudicated data, patients <18 years, by age group)

Daily dose of formoterol	<12 years		12 to <18 years	
	N	Number (%) with ≥1 hospitalization	N	Number (%) with ≥1 hospitalization
18 µg	1366	8 (0.59%)	494	6 (1.21%)
36 µg	0	NA	67	0
As needed use or adjustable dosing	410	8 (1.95%)	478	3 (0.63%)
Total formoterol	2155	25 (1.16%)	1515	14 (0.92%)

3.2.6.7 Asthma-related hospitalizations by sex and race

Table 35 presents patients <18 years of age with an asthma-related hospitalization by age group (<12 or 12 to <18), sex, and race. In general, analysis by sex and by race revealed only small differences between the formoterol- and non-LABA-exposed treatment groups. In patients <12, there was a slightly higher frequency of asthma-related hospitalizations in the formoterol-exposed group compared to the non-LABA-exposed group among Caucasian patients; an opposite trend was noted for subjects age 12 to <18. For Black patients and patients of Oriental ethnic origin, the number of patients was too low to allow any definitive conclusions; however, there was no indication of an increased risk of asthma-related hospitalizations in the formoterol-exposed patients compared with the non-LABA-exposed patients. These results are consistent with those described in Section 2.2.6.7.

Table 35 Patients with asthma-related hospitalizations during randomized treatment by sex and race (adjudicated data, patients <18 years, by age group)

	<12 years				12 to <18 years			
	Formoterol-exposed		Non-LABA-exposed		Formoterol-exposed		Non-LABA-exposed	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp
Patients with asthma-related hospitalizations by sex								
Male	1424	15 (1.05%)	851	9 (1.06%)	898	5 (0.56%)	725	8 (1.10%)
Female	731	10 (1.37%)	417	5 (1.20%)	617	9 (1.46%)	430	7 (1.63%)
Patients with asthma-related hospitalizations by race								
Caucasian	1758	19 (1.08%)	1054	7 (0.66%)	1259	11 (0.87%)	975	10 (1.03%)
Black	104	1 (0.96%)	45	3 (6.67%)	81	1 (1.23%)	53	0
Oriental	64	2 (3.13%)	49	1 (2.04%)	80	1 (1.25%)	60	5 (8.33%)
Other	229	3 (1.31%)	120	3 (2.50%)	95	1 (1.05%)	67	0

3.2.6.8 Asthma-related hospitalizations by asthma severity (baseline FEV₁)

The number of patients with asthma-related hospitalizations was also analyzed by baseline FEV₁ to evaluate the possible influence of disease severity (lower FEV₁ being an indicator of more severe disease). Table 36 presents asthma-related hospitalizations by FEV₁ (as % of predicted normal) at baseline for patients <18 years. There were very few patients (n=49) with FEV₁ <50% of predicted normal at baseline in either treatment category, and among these asthma-related hospitalizations were reported in 2 of 15 patients from the non-LABA exposed group. Overall, differences between the formoterol- and non-LABA-exposed groups were small. It should be noted that because the vast majority of patients <18 received ICS at baseline, baseline FEV₁ may underestimate the asthma severity of the population, limiting the conclusions that can be drawn from this analysis.

Table 36 Patients with asthma-related hospitalizations during randomized treatment by baseline percent predicted FEV₁ (adjudicated data, patients <18 years, by age group)

FEV ₁ (%PN)	<12 years				12 to <18 years			
	Formoterol-exposed		Non-LABA-exposed		Formoterol-exposed		Non-LABA-exposed	
	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp	N	No. (%) with ≥1 hosp
≤29.9	1	0	0	NA	1	0	0	0
30-49.9	20	0	6	1 (16.67%)	14	0	9	1 (11.11%)
50-74.9	330	5 (1.52%)	202	6 (2.97%)	335	4 (1.19%)	248	5 (2.02%)
≥75	1797	20 (1.11%)	1057	7 (0.66%)	1122	10 (0.89%)	859	9 (1.05%)
Unknown	7	0	3	0	43	0	39	0
Total	2155	25 (1.16%)	1268	14 (1.10%)	1515	14 (0.92%)	1155	15 (1.30%)

3.2.6.9 Additional safety information

The following subsections summarizes results in patients <18 for additional safety variables evaluated in the adjudicated dataset, as was presented for patients >18 years in Section 2.2.7.

Total number of asthma-related hospitalizations during randomized treatment

For patients <18, a separate analysis was done for the total number of asthma-related hospitalizations, ie, allowing for the same patient to experience multiple hospitalizations. Three pediatric patients (<18 years) reported 2 and one patient reported 3 hospitalizations, which gives an additional 5 hospitalizations. The results are summarized in Table 37.

Taking into account exposure, there was a similar number of asthma-related hospitalizations in the formoterol-exposed group and the non-LABA-exposed group in patients <12 (32.4 vs 31.5 per 1000 treatment years). In patients age 12 to <18 there were fewer asthma-related

hospitalizations in the formoterol-exposed group than the non-LABA-exposed group (21.2 vs 28.9 per 1000 treatment years).

These results are very similar to the results based on data for patients with at least 1 asthma-related hospitalization (see Section 3.2.6.1). When compared to results presented in Section 2.2.7, results are comparable to those for the overall population, particularly when events from Study SD-039-0673 are taken into consideration for the subgroup of patients <12 years.

Table 37 Total number of asthma-related hospitalizations during randomized treatment, allowing for multiple events in the same patient (adjudicated population, patients <18 years)

	Patients <12 years		Patients 12 to <18 years	
	Formoterol-exposed	Non-LABA-exposed	Formoterol-exposed	Non-LABA-exposed
N	2155	1268	1515	1155
Total exposure (1000 treatment years)	0.77	0.48	0.76	0.59
Number of hospitalized patients	25	14	14	15
Number of additional hospitalizations from patients with multiple events	0	1	2	2
Total number of hospitalizations	25	15	16	17
Asthma hospitalizations / 1000 treatment years	32.4	31.5	21.2	28.9

3.2.7 Comment on individual pediatric clinical studies

As described previously (see Table 27, Table 28, and Table 29), the proportion of patients with at least 1 asthma-related hospitalization overall was not higher in patients randomized to formoterol-containing treatment than patients randomized to non-LABA treatment. However, there were some studies with diverging results, ie, where the proportion of asthma-related hospitalizations was higher in the formoterol-containing treatment group, and the purpose of this section is to comment on these studies. For a summary of asthma-related events by study, please see Appendix B.

3.2.7.1 Study SD-039-0725

With regard to SYMBICORT pMDI, there were 5 asthma-related hospitalizations during formoterol-containing treatment (n=354) as compared with 1 during non-LABA treatment (n=169) in Study SD-039-0725. There were 2 formoterol-containing treatment arms in this study, which evaluated both an exploratory once daily (160/9 µg od) and twice daily (80/9 µg bid) SYMBICORT pMDI treatment in comparison with budesonide at a corresponding dose. Three of the asthma-related hospitalizations occurred in the once-daily arm, and it is possible that this is due to inferior efficacy with the once-daily dosing. It should also be noted that the total daily dose of formoterol was only half as high in the once-daily group, and based on the

study results it is conceivable that this dose was too low to provide asthma control for this group of patients. For the group of patients randomized to twice-daily SYMBICORT pMDI (n=184), the proportion of patients with asthma-related hospitalizations was similar to that in the budesonide arm (n=169) (2 vs 1 event).

3.2.7.2 Study SD-039-0719

Although not included in the current data set (because it was an open-label trial), a 26-week trial for patients 6 to 11 years of age (SD-039-0719) was an important component of the SYMBICORT pMDI pediatric clinical program. In this trial of 186 subjects (2:1 randomization), 1 SAE of asthma and 1 SAE of pneumonia were identified in the 123 patients treated with SYMBICORT vs 0 in the 63 patients treated with budesonide. Neither SAE led to discontinuation from the study.

3.2.7.3 Study SD-039-0673

With regard to SYMBICORT TURBUHALER, a finding of interest was the distribution of asthma-related hospitalizations in Study SD-039-0673, which was a non-US study evaluating use of SYMBICORT TURBUHALER as maintenance and reliever therapy, compared with SYMBICORT TURBUHALER fixed dose treatment and compared with a 4-times higher fixed dose of budesonide. This study had 6 parallel arms, as shown in [Table 38](#), which also presents the asthma-related hospitalizations by treatment arm. The children in the fixed-dose SYMBICORT arm received only 80/4.5 µg/day, an explorative dose not approved for treatment. The number of patients reporting asthma-related hospitalizations was 7 (5.9%) in this treatment group compared to zero in the SYMBICORT as maintenance and reliever therapy group (80/4.5 µg once daily and as needed), and 3 (2.8%) in the group receiving a 4-times higher dose of budesonide without formoterol.

We conclude that the fixed low dose of SYMBICORT was too low to provide asthma control for this population, because the patients who received higher daily doses of formoterol and hence of inhaled corticosteroid (in the SYMBICORT maintenance plus reliever therapy arm) had no asthma-related hospitalizations. This is supported by lack of any corresponding difference for adults and adolescents, who received a higher maintenance dose of SYMBICORT. It is not possible to differentiate between the benefit of the formoterol and the corticosteroid dose, since both differed between the treatment arms.

Table 38 Summary of asthma-related hospitalizations during randomized treatment in Study SD-039-0673 (adjudicated data)

Treatment and total daily dose (µg)	Number of patients	Number (%) of patients reporting at least one asthma-related hospitalization
Children 4 to ≤11 years		
Budesonide 320 + terbutaline prn	107	3 (2.8%)
SYMBICORT 80/4.5 + terbutaline prn	118 ^a	7 (5.9%)
SYMBICORT 80/4.5 + SYMBICORT 80/4.5 prn	118	0

Table 38 Summary of asthma-related hospitalizations during randomized treatment in Study SD-039-0673 (adjudicated data)

Treatment and total daily dose (µg)	Number of patients	Number (%) of patients reporting at least one asthma-related hospitalization
Adults and adolescents 12 to <18 years		
Pulmicort 640 + terbutaline prn	818	11 (1.3%)
SYMBICORT 160/9 + terbutaline prn	788	10 (1.3%)
SYMBICORT 160/9 + SYMBICORT 80/4.5 prn	804	7 (0.9%)

^a Three of these 118 patients were >11 years old and thus were erroneously randomized to this treatment.

3.2.7.4 Study SD-039-0353

A further finding of interest is the occurrence of 6 asthma-related hospitalizations (4 of which in patients below 12 years) during fixed-dose treatment with SYMBICORT TURBUHALER, compared with zero during budesonide treatment in Study SD-039-0353 (Tal et al 2002). This was a randomized, double-blind, 12-week study comparing SYMBICORT TURBUHALER to a corresponding dose of budesonide among 286 children <18 years, whereof 171 were below 12 years of age (90 on SYMBICORT). However, no such finding was seen in Study SD-039-0688 (Pohunek et al 2006), which was a larger follow-up study that recruited only children below 12 years (N=630, whereof 417 receiving SYMBICORT or formoterol + budesonide). This study had a design similar to that of Study SD-039-0353, but included comparison with the budesonide + formoterol as monoproductions at corresponding doses, and patients were required to have a minimum level of symptoms despite previous use of ICS. There was only 1 asthma-related hospitalization seen in this study (in the formoterol + budesonide group).

Importantly, as indicated by the compiled adjudicated data (see Table 26), there is only a small numerical difference between the proportion of patients with asthma-related hospitalizations in the formoterol- and non-LABA-exposed treatment groups among patients <12 years of age (1.16% vs 1.10%), even taking into account the studies mentioned above. For patients 12 to 17 years of age, the numerical difference (0.92% vs 1.30%) was in favor of the formoterol-containing treatment group, in accordance with the results for the population as a whole.

3.2.8 Overall discussion of asthma-related risks of formoterol in pediatric patients

The results for patients <18 years in the adjudicated data were in line with results for the population as a whole, in that there was no indication of an increased risk of asthma-related deaths or hospitalizations in this sub-population. There were no asthma-related deaths or intubations during randomized treatment in patients <18 years. Neither was there any tendency towards an increased risk of asthma-related hospitalizations in this age group. As indicated by the compiled adjudicated data (see Table 26), there is only a small numerical difference between the proportion of patients with asthma-related hospitalizations in the

formoterol-containing and non-LABA treatment groups among patients <12 years of age (1.16% vs 1.10%). This small difference is unlikely to represent a true imbalance, and includes data from studies, described in Section 3.2.7, where exploratory doses of SYMBICORT were included. For patients 12 to <18 years of age, the numerical difference in the proportion of patients with asthma-related hospitalizations (0.92% vs 1.30%) was in favor of the formoterol-exposed group.

For the comparison of ICS + formoterol vs ICS alone, the results are generally in accordance with the overall comparison between formoterol-containing treatment and non-LABA treatment (see Table 27). When the 7 patients from study SD-039-0673 were excluded, results in patients below 12 years also numerically favored the formoterol-containing treatment.

Results for asthma-related SAEs as presented in the SYMBICORT pMDI pediatric sNDA are consistent with these findings, see Appendix D.

4. POST-TREATMENT EVENTS IN CLINICAL TRIALS

All deaths (any cause), asthma-related deaths, asthma-related intubations, and asthma-related hospitalizations with an onset date after the date of last dose were also reviewed, adjudicated, and are reported in this section and in Appendix C for completeness.

4.1 All-cause and asthma-related mortality in the adjudicated population

An additional 5 deaths were identified in the 13,542 formoterol-exposed patients occurring within 1 to 23 days after the end of randomized treatment and 1 additional death in the 9,968 non-LABA-exposed group 13 days after the last dose of treatment, with no consistent pattern in cause of death observed. Among these 6 patients, only one death was determined to be asthma-related in the adjudication process (SD-039-0673/448/1488). This event occurred 1 day after the last dose of randomized treatment in a patient in the formoterol-exposed group. There were no post-treatment asthma-related deaths in patients <18 years in the adjudicated dataset.

Table 39 provides a brief description of all post-treatment deaths. See Appendix C for subject narratives of these cases.

4.2 Asthma-related intubations in the adjudicated population

There were no post-treatment asthma-related intubations in the adjudicated population.

4.3 Asthma-related hospitalizations in the adjudicated population

There were 10 asthma-related hospitalizations that occurred after the end of randomized treatment; these were evenly divided across formoterol vs non-LABA treatment groups (5 in each group).

Table 39 Brief description of all post-treatment deaths (all cause)

Study code/ Center/ Patient No	Age/ Sex/ Race	Randomized treatment (daily dose)	ENDT RTDY	EVEN TDAY	ENDTRTDY -EVENTDAY	Onset in relation to last dose	Days since randomization when death occurred	Cause of death
Formoterol-exposed patients								
37-3018/47/64719	32/M/C	PULMICORT_OXIS_TBH (640/18)	334	336	-2	2 days later	336	Completed suicide
SD-037- 0003/34/3403	12/M/C	OXIS_TBH (18)	26	27	-1	Next day	26	Respiratory failure
SD-039- 0666/105/532	74/M/C	SYMBICORT_TBH (320/9)	56	79	-23	23 days later	79	Cardiac arrest
SD-039- 0673/448/1488	64/F/O	SYMBICORT_TBH_BRICAN YL_TBH_prn (160/9/400 prn)	299	300	-1	Next day	300	Asthma
SD-039- 0673/75/1527	53/F/C	SYMBICORT_TBH_BRICAN YL_TBH_prn (160/9/400 prn)	325	326	-1	Next day	326	Sudden death ^a
Non-LABA -exposed patients								
SD-039- 0668/327/1774	23/M/C	PULMICORT_TBH_BRICANY L_TBH_prn (640/400 prn)	276	289	-13	13 days later	289	Cardiac failure ^b

^a Cause of death unknown. Medical history included hypertension

^b Cause of death unknown. Patient experienced loss of consciousness, cyanosis, and died 4 days later.
ENDTRTDY Days on randomized treatment; EVENTDAY Day of onset of event leading to death.

4.4 Overall conclusions

In the post-treatment period, there were 1 asthma-related death and 5 asthma-related hospitalizations in 13,542 formoterol-exposed patients, and there were 5 asthma-related hospitalizations in 9,968 non-LABA-exposed patients. Hence, there were too few events reported following the randomized treatment period from which to draw definitive conclusions regarding asthma-related death. With regard to asthma-related hospitalizations, no apparent increased risk was observed for patients previously treated with formoterol vs non-LABA therapy.

As some regulatory agencies have requested incorporation of this data into analyses (ie, during treatment+post treatment), it is important to note that no meaningful changes in overall results or conclusions followed when these events were included in analyses presented within this briefing document.

5. OVERALL BENEFIT/RISK OF FORMOTEROL IN CLINICAL TRIALS

AstraZeneca's clinical trial data is supportive of LABA usage as described in current evidence-based national and international asthma treatment guidelines, which recommend that patients with persistent asthma should always receive concomitant anti inflammatory medication (eg, inhaled corticosteroid) before considering starting maintenance treatment with a long-acting β_2 -agonist.

In patients age 12 and above, the benefit of formoterol in combination with budesonide, has been unequivocally demonstrated in numerous AstraZeneca clinical trials. These benefits include improvements across a range of measures of asthma control such as lung function; asthma worsening and exacerbations; asthma symptoms, use of rescue medication, and asthma-related quality of life measures in patients with moderate and severe asthma. Many of these benefits are apparent even when compared to high doses of ICS monotherapy.

The benefits of an effective ICS such as budesonide in children younger than 12 years of age have been well demonstrated by improvements across a range of measures of asthma control in numerous clinical trials. In studies presented in this document, evaluating children between the ages of 6 to <12, the additional benefits of adding formoterol to budesonide compared to budesonide alone have been unequivocally demonstrated on measures of control such as FEV₁ and PEF as well as in some measures of HRQL across a range of ICS doses, while parity on other measures of control was observed in patients with asthma previously treated with ICS. In light of potential systemic effects of high-dose ICS (eg, adrenal axis suppression and effects on growth) an additional benefit of ICS/LABA in this population may be the ability to gain asthma control with a lower dose of ICS. In this regard, the addition of formoterol to budesonide presents a definitive benefit to patients not adequately controlled on ICS monotherapy.

This document has reviewed asthma-related serious adverse events of possible concern using data specified by and provided to the FDA earlier this year. The adjudicated data included a total of 23,510 patients, 13,542 exposed to formoterol and 9,968 exposed to non-LABA treatment. There was no indication of any increased risk of asthma-related deaths, intubations or hospitalizations with formoterol compared with non-LABA treatment in this large number of patients. In addition, the rate of asthma-related hospitalizations was numerically lower for formoterol- vs non-LABA-exposed patients. In a subset analysis, the addition of formoterol to ICS presented no additional risk of asthma-related deaths, intubations or hospitalizations compared with ICS treatment alone. The results for patients <18 years in the adjudicated data were in line with results for the population as a whole, in that there was no indication of an increased risk of asthma-related deaths or hospitalizations in this sub-population.

Based on a comprehensive review of the safety and efficacy of formoterol-containing products, AstraZeneca believes that SYMBICORT pMDI exhibits a favorable benefit-risk profile in patients 6 years of age and older. The currently approved SYMBICORT pMDI prescribing information and Medication Guide ([Appendix F](#)) for patients greater than 12 years of age appropriately convey any potential risks regarding the use of SYMBICORT. SYMBICORT pMDI offers an important therapeutic option for asthma patients who cannot be adequately controlled on other asthma-controller medications (eg, low- to medium-dose ICS) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

6. PHARMACOGENETICS

Polymorphisms in the β_2 adrenergic receptor gene (*ADRB2*) have been genotyped in human populations within the last decade to evaluate pharmacogenetic responses on the safety and efficacy of β_2 -agonist therapy in asthma. Particular attention has been focused on the Arg/Gly polymorphism at amino acid 16, especially in the African American population where a higher frequency of patients genotyped as Arg/Arg has been observed compared to the Caucasian population.

Results from several small studies have suggested that patients genotyped Arg/Arg at amino acid 16 manifest an impaired lung function response to regularly administered albuterol (qid), a practice no longer considered appropriate ([Israel et al 2000](#), [Israel et al 2004](#)). However, with 1 exception ([Wechsler et al 2006](#)), a number of analyses have found no relationship of *ADRB2* polymorphisms to variations in response to LABA therapy ([Hancox et al 1998](#), [Taylor et al 2000](#), [Bleecker et al 2006](#)). In general, for many studies, small sample size (Arg/Arg subjects ranging in number from 8 to 37) and methodologic considerations have made it difficult to draw definitive conclusions.

In order to further evaluate this issue, AstraZeneca collected samples for genetic testing from more than 4000 patients in SYMBICORT studies. The duration of treatment ranged from 3 months to 1 year, included placebo and active-treatment controls, and evaluated measures of lung function and asthma control. This data set, which included over 700 patients identified

as Arg/Arg, those believed to be at highest risk, was of sufficient size and scope to define the relationship of polymorphisms and haplotype effects across the entirety of the *ADRB2* gene to asthma outcomes. AstraZeneca made a voluntary submission of this pharmacogenetic data to the FDA in October of 2006 under the auspices of the Critical Path Initiative. Importantly, this dataset included 2 long-term studies in patients treated with ICS+LABA (Bleecker et al 2007a). The first study included 363 Arg/Arg patients and demonstrated no influence of specific 11 SNPs or haplotypes across the *ADRB2* gene on lung function response or on exacerbations. A second study, conducted in the US, confirmed these findings. These data show that neither polymorphisms at amino acid 16 nor other evaluated *ADRB2* SNPs or haplotypes affect the safety or efficacy of SYMBICORT therapy in this subpopulation of asthma patients.

The pharmacogenetic analyses of AstraZeneca data as well as similar analyses on patients treated with FP/SM (Bleecker et al 2006) represent new information since the July 2005 PADAC meeting and have called into question the relevance of initial findings to patients treated with ICS/LABA combination therapy. These new analyses strongly suggest that the findings in the GSK SMART study and Mann pooled analysis are not related to known *ADRB2* polymorphisms. Importantly, it should be recognized that therapeutic recommendations based on known *ADRB2* polymorphisms are unfounded and, in fact, may place patients at substantial risk should prescribers respond by either restricting therapeutic choices for poorly controlled patients or by discontinuing effective regimens in well-controlled patients.

7. ONGOING ASTHMA STUDIES

The data in this document are from completed asthma studies conducted by AstraZeneca. However, for transparency, there are currently 6 ongoing asthma clinical studies being conducted by AstraZeneca (details in Table 40, below). Four of these are controlled clinical trials similar in design and duration to the large number of completed studies presented in this document. The safety data from these trials are not likely to alter the conclusions in this document. In addition, there is 1 pharmacoepidemiology study and 1 patient registry study being conducted outside the US for the Symbicort Maintenance and Reliever indication.

Table 40 Ongoing asthma studies

Study identifier	Location (US/non-US)	Treatment approach evaluated	Comparator	Design / Duration	Target population / age	Total Planned Enrollment	Anticipated LABA Safety population			Reference
							≥12 years old	≥18 years old	Total	
D5896C00022	US	Symbicort Fixed Main	Budesonide pMDI	d-b / 52 wk	African American/ ≥12 years	720	360		360	Recruiting
D5896C00021	US	Symbicort Fixed Main	Budesonide pMDI	d-b / 12 wk	Hispanic asthmatics/ ≥12 years	240	120		120	Treatment phase
D589BL00003	US	Symbicort Fixed Main	Budesonide DPI	d-b / 12 week	African Americans/ ≥12 years	300	150		150	Recruiting
D5890C00003	Non-US	Symbicort Maintenance and Reliever	Symbicort TBH bid + Terbutaline prn	d-b / 52 wk	Asthmatics/ ≥18 years	100		100	100	Treatment phase
D5890C00017	Non-US	Symbicort Maintenance and Reliever	N/A	N/A	Pharmaco epi study Asthma / All Ages	1000			1000	Recruiting, data base study
D5890C00018	Non-US	Symbicort Maintenance and Reliever	N/A	52 wk	Patient Registry Asthma / All Ages	8000			8000	Recruiting

8. THEORETICAL CONCERNS REGARDING USE OF LABAS

There have long been concerns that treatment with β_2 -agonists, whether short-acting or long-acting, by effective relief of symptoms could mask an increase in airway inflammation and delay awareness of worsening asthma. Formoterol in the form of OXIS TURBUHALER has not been found to cause or mask any underlying airway inflammation over 12 months if used together with a low dose of budesonide in patients with moderate asthma (Kips et al 2000). In this study, after a 4-week run-in on budesonide 800 μg bid, no significant changes in the proportion of inflammatory cells or ECP levels in sputum were observed during the ensuing 1-year treatment with budesonide 100 μg bid plus formoterol or budesonide 400 μg bid. Clinical asthma control was not significantly different between both groups. Furthermore, as previously described, adding formoterol to either 100 or 400 μg bid of budesonide reduced the number of severe asthma exacerbations over the 12-month study period of the FACET study (Pauwels et al 1997). In summary, masking of airway inflammation does not appear to be a clinical problem when LABAs are used together with ICSs.

Another possible mechanism behind an increased risk of serious asthma exacerbations is that regular use of β_2 -agonists leads to development of desensitization of the β_2 -receptor and tolerance to the effect of β_2 -agonists. This has been shown in experimental situations using methacholine or adenosine phosphate challenge and exercise challenge with both formoterol and salmeterol, although the relevance of this phenomenon in terms of long-term asthma control remains unclear (Hancox and Taylor 2001, Lipworth 1997). Long-term asthma clinical trials with formoterol have shown that there is no reduction in bronchodilator effect, and thus, benefit is maintained over time when formoterol is used together with ICS (FitzGerald et al 1999, Rabe 2001, Kips et al 2000, Pauwels et al 1997). This has been confirmed in recent studies with SYMBICORT pMDI maintenance treatment (Corren et al 2007, Noonan et al 2006) and with SYMBICORT TURBUHALER as maintenance and reliever therapy (Kuna et al 2007, O'Byrne et al 2005, Rabe et al 2006a, Rabe et al 2006b, Scicchitano et al 2004), where results for lung function, symptom control, reliever use and severe exacerbations all confirmed maintained benefit over 6 to 12 month treatment periods in clinical studies allowing occasional use of up to 54 μg of formoterol per day, in combination with budesonide.

It has been shown that ICSs can modulate β_2 -receptors and their function by protection against desensitization and inflammation-induced receptor down-regulation and uncoupling (Aziz and Lipworth 1999, Johnson 2002, Tan et al 1997). Such effects of ICS may be beneficial also from a safety perspective, as they allow patients who are experiencing a worsening of their asthma to receive adequate effect of their rescue medication. This is supported by data from Study SD-039-0728 (Peters et al 2008), a randomized, double-blind, parallel-group study in which the long-term (1-year) safety of SYMBICORT pMDI at twice the highest approved dose in the US (ie, 1280/36 $\mu\text{g}/\text{day}$) was evaluated in comparison with a corresponding dose of budesonide and in comparison with half the dose of SYMBICORT pMDI (640/18 $\mu\text{g}/\text{day}$) among patients ≥ 12 years. In a subset of patients, albuterol response was evaluated in the

setting of maintenance therapy with either SYMBICORT pMDI or budesonide alone. Subjects in the SYMBICORT pMDI groups experienced similar small decreases from baseline in post-albuterol maximum FEV₁ at Week 6, end of Month 6, and for treatment average, compared with subjects in the budesonide group, but the post-albuterol maximum FEV₁ values achieved were generally higher for each SYMBICORT pMDI group than for the budesonide group. Importantly, in all groups, substantial bronchodilation with albuterol was seen following the initial dose of 4 inhalations, indicating that adequate bronchodilation can be achieved with rescue medication during long-term treatment with SYMBICORT pMDI.

9. FORMOTEROL POST-MARKETING EXPERIENCE

9.1 General considerations regarding post-marketing reporting

As part of the formal safety evaluation of AstraZeneca's formoterol-containing products, spontaneous adverse event reports are collected in an ongoing fashion and evaluated on a periodic basis. Data from spontaneous reporting are especially important for generating hypotheses concerning potential safety signals, but have multiple limitations with regard to validation and quantitation of signals. The section below outlines the spontaneously-reported adverse events of particular focus in this review, ie asthma-related serious adverse events including deaths and hospitalizations. However, these spontaneously-reported events should not be viewed in isolation and should be interpreted in the context of the more comprehensive and better-validated data from randomized control trials, as presented in previous sections of this document.

9.2 Background

As of 30 September 2008, the estimated postmarketing exposure to AstraZeneca formoterol-containing products approached 6 billion treatment days (SYMBICORT pMDI >48 million, SYMBICORT TURBUHALER >4.4 billion, OXIS TURBUHALER >1.4 billion). This section provides an overview of asthma-related deaths and other asthma-related serious adverse events (including deaths and hospitalizations) spontaneously reported to AstraZeneca through 30 September 2008. The search was conducted for all post-marketing serious adverse events using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) version 11.0 included in the narrow Standardised MedDRA Query 20000025 Asthma/ Bronchospasm (Asthma, Asthma exercise induced, Asthma late onset, Bronchospasm, Status asthmaticus, Infantile asthma, Analgesic asthma syndrome, Asthmatic crisis and Bronchial hyperreactivity).

9.3 Respiratory-related deaths

There were 5 spontaneous reports of asthma-related deaths for SYMBICORT (3 with the pMDI formulation and 2 with the TURBUHALER formulation) and 2 spontaneous reports of asthma-related death for OXIS TURBUHALER.

Four of the 5 SYMBICORT reports (2008UW15559, 2007UW25601, 2006AP03797, 2008AP05209) involved patients 7 through 15 years of age with a history of severe asthma

who died from acute asthma exacerbations. None of these reports contained sufficient information to suggest a causal relationship to SYMBICORT.

Details relevant to potential SYMBICORT relatedness for the 5 deaths are provided below:

In report 2007UW25601, the patient, age 11 years, had been prescribed SYMBICORT pMDI; however, it was uncertain whether SYMBICORT pMDI was ever administered.

In report 2008UW15559, the patient, age 7 years, was reported as having severe asthma since the age of 2 years (including multiple episodes of hospitalizations and steroid dosing), and the treating physician reported a clear improvement after switching from Advair to SYMBICORT pMDI. The patient complained of increasing asthma symptoms for several days prior to his death. He was prescribed ipratropium/albuterol nebulizer treatments; however, he collapsed at home before the treatments were initiated; unsuccessful resuscitation attempts were made.

Report 2008UW13220 described an 18-year-old pregnant (16 weeks' gestation) patient who experienced asthma-related respiratory problems a few days prior to collapsing from acute bronchospasm and/or asthma at home. She had a history of moderate asthma which reportedly was controlled with montelukast and SYMBICORT pMDI. In this report the specific details leading up to the event were unavailable because the event occurred at home. No further evaluation took place in the ER, because upon arrival in the ER, CPR was being conducted. It is not known if an autopsy was done. Due to the limited information available in this report, a proper assessment is not feasible.

In addition to the asthma-related death reports mentioned above, 2 reports in adults described non-asthma-related fatal respiratory events (ie, angioedema leading to respiratory failure, and cardio-respiratory arrest) after treatment with SYMBICORT pMDI. Both patients had severe underlying cardiac disease, along with other confounding factors, which may have contributed to the eventual outcome of death. The indication for SYMBICORT use in both reports was non-asthmatic.

The following asthma-related deaths have been reported for SYMBICORT TURBUHALER and OXIS TURBUHALER.

Report 2006AP03797 described a 15-year-old male being treated with SYMBICORT TURBUHALER (unknown dose and duration) for asthma. At an unknown time after starting treatment the patient died from an acute asthma exacerbation; an autopsy was not performed. Other concomitant medications were not reported. The reporting physician indicated that the patient had a known history of being non-compliant with his medication.

Report 2008AP05209 described a 13-year old male patient who experienced an asthma flare-up 6 months after the start of treatment with SYMBICORT TURBUHALER. The patient was treated with oral prednisolone. A few days later, the patient experienced a respiratory arrest and died. It is unclear whether the respiratory arrest was directly related to the asthma exacerbation and limited information on this precludes a proper case assessment.

The first OXIS TURBUHALER report (2000AD00129) described a 77-year old female patient on treatment with OXIS TURBUHALER who was found dead after 17 days of treatment. Apart from asthma bronchiale she had no relevant medical history. The reported cause of death after an autopsy was asthma bronchiale, hypertension, and cardiosclerosis.

The second OXIS TURBUHALER report (2000AD00141) described a 16-year-old boy with a history of asthma for several years who developed a severe asthmatic attack with bronchospasms followed by respiratory arrest and cardiac arrest leading to death. A day prior to the event, he experienced increased shortness of breath and worsening of asthma symptoms and initiated treatment with OXIS TURBUHALER several times. The next morning, he experienced another onset of respiratory distress and collapsed 3 hours later. Resuscitation was successful and patient was intubated but died four days later. No autopsy was performed; however, probable cause of death was reported as brain stem death due to hypoxic cardiac arrest following a severe asthma attack. The patient had been receiving salbutamol and beclomethasone for many years but reportedly had not taken any salbutamol on the morning of the arrest.

In both OXIS TURBUHALER reports, causal relationship to OXIS TURBUHALER was difficult to assess due to lack of information on the time preceding the events and the patients' medical histories.

9.4 Asthma-related serious adverse events (SAE) and hospitalizations

Overall, AstraZeneca's global safety database includes 623 SAE reports for SYMBICORT (507 for TURBUHALER and 116 for pMDI); 182 of the 623 SAE reports were serious due to hospitalization. As shown in Table 41, 64 (10%) of the 623 SAE reports included asthma-related events. The 5 asthma-related deaths previously described are included in these SAE counts; 16 of the 64 asthma-related SAEs were serious due to hospitalization.

Table 41 Serious asthma-related events with the use of SYMBICORT from post-marketing surveillance

Event Preferred Term	Number of SAE reports	Number of hospitalizations	Number of SAE reports per SYMBICORT Formulation Turbuhaler/pMDI
Asthma	50	14	44/6
Asthmatic crisis	2	1	2/0
Bronchospasm	12	1	6/6
Total	64	16	52/12

Based on the estimated total patient exposures for the SYMBICORT TURBUHALER (>4 billion patient treatment days) and pMDI (>48 million patient treatment days) respectively, Table 41 suggests that the number of spontaneously reported asthma-related SAEs for the pMDI is relatively higher than that for the TURBUHALER. Several factors are

likely to account for this difference. First, SYMBICORT pMDI is a newly-launched product and had a boxed warning regarding potential for asthma-related deaths and/or hospitalizations in its prescribing information at the time of launch; in contrast, SYMBICORT TURBUHALER was launched in 2000, before safety concerns regarding LABAs had been raised. It is well recognized that spontaneous reporting is greatest in the immediate post-launch period (known as the “Weber effect”), and that awareness of safety concerns also increases the number of spontaneously reported events. In addition, it is well known that there are reporting differences between the US and other countries and that in the US, the sensitivity to drug-related safety concerns is currently very high. Furthermore, based on overall availability and prescribing of AstraZeneca formoterol-containing products across the world, US physicians have less familiarity with the combination of budesonide and formoterol, the two components in SYMBICORT, than prescribers outside of the US.

AstraZeneca’s global safety database includes 89 SAE reports for OXIS TURBUHALER. Of these, 29 reports were serious due to hospitalization. As shown in [Table 42](#), ten (11%) of the 89 SAE reports include asthma-related events. The 2 asthma-related deaths previously described are included in the total number of asthma-related SAEs.); 1 of the 10 asthma-related SAEs was serious due to hospitalization.

Table 42 Serious asthma-related events with the use of OXIS TURBUHALER

Event Preferred Term	Number of SAE reports	Number of hospitalisations
Asthma	7	1
Bronchospasm	3	0
Total	10	1

9.5 Summary and conclusions

In summary, the post-marketing experience with SYMBICORT and OXIS includes isolated reports of possible asthma-related death and/or other SAEs due to asthma-related symptoms (including hospitalizations). These events cannot be assessed quantitatively because there is uncertainty on both the denominator (actual number of patients on the drug) and the numerator (the actual number of events). For many reports a clear cause for the observed event was lacking, and/or the medical circumstances around the time of the event were absent and/or incompletely documented.

It is expected that asthma patients would experience asthma-related events even when appropriately treated, and the recommended clinical use of LABAs, ie at Steps 3-6 of the treatment guidelines, suggests that these products are most likely to be used in moderate to severe asthma patients who are at greater risk of hospitalization and death than asthma patients with milder disease. These inherent limitations make it impossible to draw firm conclusions from this spontaneously-reported data. However, it can be generally concluded that no new safety signals around asthma have emerged from the post-marketing data analysis,

and that the current risk communication in the US Prescribing Information appropriately conveys any potential risks regarding the use of SYMBICORT.

10. ASTRAZENECA'S CURRENT PHARMACOVIGILANCE PROCESS FOR SYMBICORT pMDI

As a result of the FDA approval, AstraZeneca implemented a post-approval US Patient Risk Management Plan for SYMBICORT pMDI. In addition to the routine post-marketing surveillance activities (such as adverse event collection and assessment, reporting and analysis processes), this plan includes enhanced pharmacovigilance practices for specific adverse events of interest, including asthma and asthma-related deaths and other serious adverse events.

The enhanced pharmacovigilance consists of enhanced follow-up activities, which include direct telephone contact with the initial AE reporter and site visits (if necessary) in order to obtain high-quality post-marketing reports. For asthma specifically, AstraZeneca is conducting these enhanced follow-up activities for all fatal or other serious asthma and asthma-related events, which include bronchospasm, wheezing, dyspnea and chest tightness. Practically, for individual post-marketing cases, AstraZeneca makes at least 3 attempts to obtain additional medical information if incomplete information is received in the initial report. The first step is typically a direct telephone contact with the initial reporter. However, written requests through regular mail, e-mail or fax are used if the initial telephone contact is unsuccessful. In order to facilitate data collection AstraZeneca created a questionnaire to gather additional medical information on asthma events. Also, in the case of an initial consumer report, efforts are made to obtain additional medical details from the Health Care Provider (HCP) upon receipt of consent from the consumer.

AstraZeneca also conducts pro-active ongoing monitoring of all post-approval SYMBICORT pMDI AE data to ensure an ongoing assessment of the products' risk profile. Besides the individual case review, a drug safety surveillance team conducts aggregate AE data review and safety data mining on a regular basis. Whenever safety signals are identified they are further discussed and evaluated during AstraZeneca's Safety Evaluation and Review Meeting (SERM) process, which leads to appropriate safety conclusions and actions (eg, label changes) on the reviewed safety data.

Also in other countries worldwide, other procedures for enhanced pharmacovigilance are in place.

11. OVERALL CONCLUSIONS ON BENEFIT/RISK

A comprehensive review of the available safety and efficacy data for formoterol-containing products marketed by AstraZeneca (SYMBICORT pMDI, SYMBICORT TURBUHALER, OXIS TURBUHALER) has been conducted. AstraZeneca believes that SYMBICORT pMDI,

which is currently approved for the long-term maintenance treatment of asthma in the US for patients 12 years of age and older, has a favorable benefit-risk profile when used as indicated.

Numerous AstraZeneca clinical trials have unequivocally demonstrated the benefit of formoterol in combination with budesonide over ICS alone or LABA monotherapy. In patients age 12 years and above, these benefits include improvements across a range of measures of asthma control such as lung function, asthma worsening and exacerbations, asthma symptoms, use of rescue medication, and asthma-related quality of life in patients with moderate to severe asthma. Many of these benefits are apparent even when compared to high-dose ICS monotherapy. In children 6 to 11 years of age, the additional benefits of adding formoterol to budesonide compared to budesonide alone have been clearly demonstrated on measures of control such as FEV₁ and PEF, as well as in some measures of HRQL across a range of ICS doses. In these clinical trials, as demonstrated by an extensive review including blinded adjudication of serious asthma-related events during randomized treatment, there was no evidence of increased risk in any age group for asthma-related deaths, intubations, or hospitalizations in formoterol vs non-LABA exposed patients.

The FDA requested data on all-cause deaths, asthma-related deaths, asthma-related intubations, and asthma-related hospitalizations during randomized treatment. AstraZeneca's adjudicated data included a total of 23,510 patients, 13,542 exposed to formoterol, and 9,968 exposed to non-LABA treatment. For all-cause mortality, there were 3 deaths in patients on formoterol-containing treatment and 4 deaths in patients on non-LABA treatment; none of these occurred in the clinical studies contained in the US NDA for SYMBICORT pMDI. No deaths were asthma-related and there was only 1 asthma-related intubation (in a formoterol-exposed patient). While the overall event rate is low, in this large population of over 23,000 patients, there is no evidence of any imbalance in deaths favoring non-LABA treatments. There was also no indication of an increased risk of asthma-related hospitalizations during randomized formoterol-containing treatment compared with non-LABA treatment for patients receiving treatment for up to 1 year. AstraZeneca also reviewed events that occurred after the end of the randomized treatment; no consistent patterns were observed.

The post-marketing experience with SYMBICORT and OXIS TURBUHALER includes isolated reports of possible asthma-related death and/or other SAEs due to asthma-related symptoms (including hospitalizations). Although the inherent limitations of this data make it impossible to draw firm conclusions, no new safety signals around asthma emerged from the post-marketing data analysis.

Epidemiological data also support a favorable benefit-risk profile. There is no evidence from epidemiological data that the introduction of LABAs has been associated with an increase in mortality or hospitalizations due to asthma; rather, there is some evidence that the introduction of LABAs and ICS/LABA combinations has been associated with a reduction in asthma-related mortality.

AstraZeneca therefore believes that the currently approved SYMBICORT pMDI prescribing information and Medication Guide ([Appendix F](#)) for patients greater than 12 years of age appropriately convey any potential risks regarding the use of SYMBICORT. SYMBICORT

pMDI offers an important therapeutic option for asthma patients who cannot be adequately controlled on other asthma-controller medications (eg, low- to medium-dose ICS) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

AstraZeneca believes the new information presented in this briefing document, specifically the safety findings as a result of the large number of studies conducted by AstraZeneca with formoterol (SYMBICORT [budesonide/formoterol] and OXIS), should be appropriately considered and incorporated into future labeling (both in the PI and accompanying Medication Guide) to reflect the safety profile of this product when used as indicated.

AstraZeneca remains committed to close surveillance of adverse events (as described in Section 10) and will continue to gather and assess information as new studies are completed and additional information is reported. Any findings that change the current safety profile will be promptly reviewed and appropriate actions (ie, label changes) will be implemented.

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Appendix A: Overview of included trials

SUMMARY OF TRIALS THAT INCLUDED BOTH LABA AND NON-LABA TREATMENTS

Table 43 Summary of trials including both LABA and non-LABA treatments

Study identifier	Location (US/non-US)	Treatment approach evaluated	Comparator	Design Duration	Target pop	Safety population					Reference
						4-11	12-17	18-64	≥65	Total	
SYMBICORT pMDI studies											
SD-039-0716	US	Fixed maintenance	Budesonide Formoterol Placebo	d-b, p-g 12 wk	≥6	31	75	390	15	511	Corren et al 2007
SD-039-0717	US	Fixed maintenance	Budesonide Formoterol Budesonide + formoterol Placebo	d-b, p-g 12 wk	≥12	-	43	516	37	596	Noonan et al 2006
SD-039-0718	US	Fixed maintenance	Budesonide Formoterol	d-b, p-g 12 wk	6-15	256	155	-	-	411	Pearlman et al 2008
SD-039-0725	US	Fixed maintenance	Budesonide	d-b, p-g 12 wk	6-15	351	170	-	-	521	Noonan et al 2008
SD-039-0726	US	Fixed maintenance	Budesonide Placebo	d-b, p-g 12 wk	≥16	-	28	704	19	751	Bleecker et al 2007b
SD-039-0728	US	Fixed maintenance	Budesonide	d-b, p-g 52 wk	≥12	-	90	564	54	708	Peters et al 2008
D5896C00001	US	Fixed maintenance	Budesonide	d-b, p-g 12 wk	≥12	-	97	502	19	618	LaForce et al 2008
SD-039-0681	Non-US	Fixed maintenance	Budesonide Symbicort TBH	d-b, p-g 12 wk	≥12	1	107	520	51	679	Morice et al 2007
SD-039-0682	Non-US	Fixed maintenance	Budesonide Symbicort TBH	d-b, p-g 12 wk	6-11	622	-	-	-	622	Morice et al 2008b

Table 43 Summary of trials including both LABA and non-LABA treatments

Study identifier	Location (US/non-US)	Treatment approach evaluated	Comparator	Design Duration	Target pop	Safety population					Reference
						4-11	12-17	18-64	≥65	Total	
SYMBICORT TURBUHALER studies											
BA-039-0001	Non-US	Adjustable maintenance	Budesonide	d-b, p-g 4 mo	≥19	-	-	117	16	133	Pohl et al 2006
SD-039-0348	Non-US	Fixed maintenance	Budesonide	d-b, p-g 12 wk	≥18	-	-	440	27	467	Lalloo et al 2003
SD-039-0349	Non-US	Fixed maintenance	Budesonide Budesonide + formoterol	d-b, p-g 12 wk	≥18	-	-	305	57	362	Zetterström et al 2001
SD-039-0353	Non-US	Fixed maintenance	Budesonide	d-b, p-g 12 wk	4-17	171	115	-	-	286	Tal et al 2002
SD-039-0618	Non-US	Fixed maintenance	Fluticasone	d-b, p-g 12 wk	≥18	-	1	319	24	344	Bateman et al 2003
SD-039-0665	Non-US	Fixed maintenance	Budesonide	d-b, p-g 12 wk	≥18	-	-	543	73	616	Kuna et al 2006
SD-039-0666	Non-US	Fixed maintenance	Budesonide	d-b, p-g 12 wk	≥18	-	-	478	45	523	Buhl et al 2003
SD-039-0667	Non-US	Maintenance and reliever	Budesonide + terbutaline prn	d-b, p-g 6 mo	12-80	1	108	551	36	696	Rabe et al 2006a
SD-039-0668	Non-US	Maintenance and reliever	Budesonide + terbutaline prn	d-b, p-g 12 mo	12-80	1	120	1620	149	1890	Scicchitano et al 2004
SD-039-0671	Non-US	Fixed maintenance	Fluticasone	d-b, p-g 2 wk	≥18	-	1	431	6	438	Eliraz et al 2002
SD-039-0673	Non-US	Maintenance and reliever	Symbicort + terbutaline prn Budesonide + terbutaline prn	d-b, p-g 12 mo	4-80	341	316	1922	174	2753	O'Byrne et al 2005 (total pop) Bisgaard et al 2006 (pediatric pop)

Table 43 Summary of trials including both LABA and non-LABA treatments

Study identifier	Location (US/non-US)	Treatment approach evaluated	Comparator	Design Duration	Target pop	Safety population					Reference
						4-11	12-17	18-64	≥65	Total	
SD-039-0688	Non-US	Fixed maintenance	Budesonide Budesonide + formoterol	d-b, p-g 12 wk	4-11	630	-	-	-	630	Pohunek et al 2006
SD-039-0689	Non-US	Fixed maintenance	Budesonide (3 mo) Budesonide + formoterol (6 mo)	d-b, p-g 3/6 mo	≥12	-	13	392	51	456	Jenkins et al 2006
SD-039-0714	Non-US	Fixed maintenance	Budesonide	d-b, p-g 12 wk	12-17	2	268	-	-	270	Data on file
OXIS TURBUHALER studies											
37-3002	Non-US	Maintenance	Placebo	d-b, p-g 4 wk	≥18	-	-	192	29	221	Schreurs et al 1996
37-3006	Non-US	Maintenance	Placebo Terbutaline	d-b, p-g 12 wk	≥18	-	-	294	49	343	Ekström et al 1998a
37-3008	Non-US	Maintenance	Placebo	d-b, p-g 6 mo	≥18	-	-	225	14	239	van der Molen et al 1997
37-3018	Non-US	Maintenance	Budesonide	d-b, p-g 12 mo	18-70	-	2	799	52	853	Pauwels et al 1997
37-3026	Non-US	Maintenance	Placebo Terbutaline	d-b, p-g 12 wk	≥18	-	-	333	63	396	Ekström et al 1998b
37-3027	Non-US	Maintenance	Placebo	d-b, p-g 7 d	≥18	-	-	165	-	165	Data on file
37-3041	Non-US	Maintenance	Budesonide	d-b, p-g 12 mo	18-70	-	-	58	2	60	Kips et al 2000
39-3002-1	Non-US	Maintenance	Budesonide	d-b, c-o, 4 wk	18-60	-	-	21	-	21	Data on file
BU-543-0681A	Non-US	Maintenance	Budesonide	d-b, p-g 4 wk	≥12	-	73	541	49	663	Price et al 2002

Table 43 Summary of trials including both LABA and non-LABA treatments

Study identifier	Location (US/non-US)	Treatment approach evaluated	Comparator	Design Duration	Target pop	Safety population					Reference
						4-11	12-17	18-64	≥65	Total	
DC-037-0002	Non-US	Maintenance	Placebo	d-b, p-g 3 mo	6-11	301	-	-	-	301	Zimmerman et al 2004
SD-004-0216	Non-US	Maintenance	Placebo Zafirlukast	d-b, p-g 8 wk	12-70	-	35	309	8	352	Data on file
SD-037-0003	Non-US	Maintenance	Placebo	d-b, p-g 3 mo	6-17	126	122	-	-	248	Von Berg et al 2003
SD-037-0011	Non-US	Maintenance	Placebo Terbutaline	d-b, p-g 2 wk	≥18	-	-	70	2	72	Lipworth et al 1998
SD-037-0345	Non-US	Maintenance	Placebo Budesonide	d-b, p-g 12 mo	≥12	1	217	1685	67	1970	O'Byrne et al 2001
SD-037-0745	Non-US	Maintenance	Placebo	d-b, p-g 1 mo	≥20	-	-	203	79	282	Data on file
SD-037-0123	Non-US	As-needed	Terbutaline	d-b, p-g 12 wk	≥18	-	-	323	39	362	Tattersfield et al 2001
SD-037-0695	Non-US	As-needed	Terbutaline	d-b, p-g 6 mo	6-17	324	228	-	-	552	Villa et al 2002
SD-037-0714	Non-US	As-needed	Terbutaline	d-b, p-g 12 mo	≥6	118	83	251	3	455	Chuchalin et al 2005
SD-037-0716	Non-US	As-needed	Terbutaline	d-b, p-g 12 mo	≥6	146	203	314	11	674	Chuchalin et al 2005

SUMMARY OF TRIALS IN WHICH ALL TREATMENT ARMS CONTAINED LABA TREATMENT

Table 44 Summary of trials in which all arms contained LABA treatment

Study identifier	Location (US/non-US)	Treatment approach evaluated	Comparator	Design Duration	Target pop	Safety population					Reference
						4-11	12-17	≥18	≥65	Total	
SYMBICORT TURBUHALER studies											
AF-039-0001	Non-US	As needed	Formoterol prn	d-b, p-g 6 mo	6-65	-	2	90	-	92	Hahtela et al 2006
D5890C00002	Non-US	Maintenance and reliever	Salmeterol/ fluticasone	d-b, p-g 6 mo	≥12	-	324	1817	163	2304	Bousquet et al 2007
DC-039-0002	Non-US	Fixed maintenance	Budesonide + formoterol	d-b, p-g 1 mo	18-75	-	-	224	13	237	Data on file
SD-039-0686	Non-US	Adjustable maintenance	Fixed maintenance with: Symbicort or Salmeterol/ fluticasone	d-b/open, p-g, 6 mo	≥12	-	15	572	71	658	Aalbers et al 2004
SD-039-0734	Non-US	Maintenance and reliever	Symbicort + formoterol prn Symbicort + terbutaline prn	d-b, p-g 12 mo	≥12	-	354	2742	286	3382	Rabe et al 2006b
SD-039-0735	Non-US	Maintenance and reliever	Symbicort + terbutaline prn Salmeterol/ fluticasone + terbutaline prn	d-b, p-g 6 mo	≥12	2	619	2505	195	3321	Kuna et al 2007

Table 44 Summary of trials in which all arms contained LABA treatment

Study identifier	Location (US/non-US)	Treatment approach evaluated	Comparator	Design Duration	Target pop	Safety population					Reference
						4-11	12-17	≥18	≥65	Total	
OXIS TURBUHALER studies											
37-3007-1	Non-US	Maintenance	Formoterol	d-b, c-o, 2 wk	≥18	-	-	54	12	66	Data on file
SD-037-0175	Non-US	Maintenance and as needed	Terbutaline	d-b, p-g, 3 mo	≥18	-	-	327	30	357	Ind et al 2002
37-3011-1	Non-US	Maintenance	Formoterol	d-b, c-o, 2 wk	≥18	-	1	53	12	66	Data on file
37-3040-1	Non-US	Maintenance	Salmeterol	d-b, c-o, 3 wk	≥18	-	-	38	1	39	Data on file

Appendix B: Summary of safety results by study

SUMMARY OF SAFETY RESULTS, BY STUDY, FOR TRIALS THAT INCLUDED BOTH LABA AND NON-LABA TREATMENT ARMS

Table 45 Asthma-related hospitalizations by trial for trials including both LABA and non-LABA treatment (adjudicated data, all ages)

Study code	Number of patients			Number of asthma-related hospitalizations			Percent of patients reporting asthma-related hospitalizations		
	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total
SYMBICORT pMDI trials									
SD-039-0716	253	258	511	1	0	1	0.40%	0%	0.20%
SD-039-0717	362	234	596	4	0	4	1.10%	0%	0.67%
SD-039-0718	266	145	411	1	0	1	0.38%	0%	0.24%
SD-039-0725	352	169	521	4	1	5	1.14%	0.59%	0.96%
SD-039-0726	453	298	751	0	0	0	0%	0%	0%
SD-039-0728	575	133	708	2	1	3	0.35%	0.75%	0.42%
D5896C00001	465	153	618	0	0	0	0%	0%	0%
SD-039-0681	462	217	679	0	1	1	0%	0.46%	0.15%
SD-039-0682	415	207	622	0	2	2	0%	0.97%	0.32%
SYMBICORT TURBUHALER trials									
BA-039-0001	65	68	133	0	0	0	0%	0%	0%
SD-039-0348	230	237	467	1	0	1	0.43%	0%	0.21%
SD-039-0349	238	124	362	0	0	0	0%	0%	0%
SD-039-0353	148	138	286	6	0	6	4.05%	0%	2.10%
SD-039-0618	168	176	344	0	3	3	0%	1.70%	0.87%

Table 45 Asthma-related hospitalizations by trial for trials including both LABA and non-LABA treatment (adjudicated data, all ages)

Study code	Number of patients			Number of asthma-related hospitalizations			Percent of patients reporting asthma-related hospitalizations		
	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total
SD-039-0665	409	207	616	1	1	2	0.24%	0.48%	0.32%
SD-039-0666	352	171	523	1	0	1	0.28%	0%	0.19%
SD-039-0667	354	342	696	0	1	1	0%	0.29%	0.14%
SD-039-0668	947	943	1890	5	14	19	0.53%	1.48%	1.01%
SD-039-0671	218	220	438	0	1	1	0%	0.45%	0.23%
SD-039-0673	1828	925	2753	24	14	38	1.31%	1.51%	1.38%
SD-039-0688	417	213	630	1	0	1	0.24%	0%	0.16%
SD-039-0689	341	115	456	0	0	0	0%	0%	0%
SD-039-0714	136	134	270	0	1	1	0%	0.75%	0.37%
OXIS TURBUHALER trials									
37-3002	165	56	221	1	0	1	0.61%	0%	0.45%
37-3006	114	229	343	0	3	3	0.00%	1.31%	0.87%
37-3008	125	114	239	1	1	2	0.80%	0.88%	0.84%
37-3018	426	427	853	2	7	9	0.47%	1.64%	1.06%
37-3026	135	261	396	0	4	4	0%	1.53%	1.01%
37-3027	123	42	165	0	0	0	0%	0%	0%
37-3041	29	31	60	1	0	1	3.45%	0%	1.67%
39-3002-1	14	7	21	0	0	0	0%	0%	0%
BU-543-0681A	333	330	663	0	1	1	0%	0.30%	0.15%
DC-037-0002	200	101	301	1	1	2	0.50%	0.99%	0.66%
SD-004-0216	118	234	352	1	0	1	0.85%	0%	0.28%

Table 45 Asthma-related hospitalizations by trial for trials including both LABA and non-LABA treatment (adjudicated data, all ages)

Study code	Number of patients			Number of asthma-related hospitalizations			Percent of patients reporting asthma-related hospitalizations		
	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total
SD-037-0003	164	84	248	2	0	2	1.22%	0.00%	0.81%
SD-037-0011	44	28	72	0	0	0	0%	0%	0%
SD-037-0123	182	180	362	0	0	0	0%	0%	0%
SD-037-0345	869	1101	1970	7	12	19	0.81%	1.09%	0.96%
SD-037-0695	277	275	552	7	7	14	2.53%	2.55%	2.54%
SD-037-0714	228	227	455	3	5	8	1.32%	2.20%	1.76%
SD-037-0716	333	341	674	1	2	3	0.30%	0.59%	0.45%
SD-037-0745	209	73	282	0	0	0	0%	0%	0%
Total	13542	9968	23510	78	83	161	0.58%	0.83%	0.68%

Table 46 Asthma-related hospitalizations by trial for trials including both LABA and non-LABA treatment (adjudicated data, patients <18 years)

Study code	Number of patients			Number of asthma-related hospitalizations			Percent of patients reporting asthma-related hospitalizations		
	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total
SYMBICORT pMDI trials									
SD-039-0716	55	51	106	1	0	1	1.82%	0%	0.94%
SD-039-0717	26	17	43	1	0	1	3.85%	0%	2.33%
SD-039-0718	266	145	411	1	0	1	0.38%	0%	0.24%
SD-039-0725	352	169	521	4	1	5	1.14%	0.59%	0.96%
SD-039-0726	8	20	28	0	0	0	0%	0%	0%
SD-039-0728	77	13	90	0	0	0	0%	0%	0%
D5896C00001	73	24	97	0	0	0	0%	0%	0%
SD-039-0681	73	35	108	0	0	0	0%	0%	0%
SD-039-0682	415	207	622	0	2	2	0%	0.97%	0.32%
SYMBICORT TURBUHALER trials									
SD-039-0353	148	138	286	6	0	6	4.05%	0%	2.10%
SD-039-0618	0	1	1	-	0	0	-	0%	0%
SD-039-0667	56	53	109	0	1	1	0%	1.89%	0.92%
SD-039-0668	56	65	121	1	5	6	1.79%	7.69%	4.96%
SD-039-0671	0	1	1	-	0	0	-	0%	0%
SD-039-0673	444	213	657	10	7	17	2.25%	3.29%	2.59%
SD-039-0688	417	213	630	1	0	1	0.24%	0%	0.16%
SD-039-0689	10	3	13	0	0	0	0%	0%	0%
SD-039-0714	136	134	270	0	1	1	0%	0.75%	0.37%

Table 46 Asthma-related hospitalizations by trial for trials including both LABA and non-LABA treatment (adjudicated data, patients <18 years)

Study code	Number of patients			Number of asthma-related hospitalizations			Percent of patients reporting asthma-related hospitalizations		
	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total	Formoterol	Non-LABA	Total
OXIS TURBUHALER trials									
37-3018	2	0	2	0	-	0	0%	-	0%
BU-543-0681A	36	37	73	0	0	0	0%	0%	0%
DC-037-0002	200	101	301	1	1	2	0.50%	0.99%	0.66%
SD-004-0216	11	24	35	0	0	0	0%	0%	0%
SD-037-0003	164	84	248	2	0	2	1.22%	0.00%	0.81%
SD-037-0345	93	125	218	2	1	3	2.15%	0.80%	1.38%
SD-037-0695	277	275	552	7	7	14	2.53%	2.55%	2.54%
SD-037-0714	102	99	201	2	3	5	1.96%	3.03%	2.49%
SD-037-0716	173	176	349	0	0	0	0%	0%	0%
Total	3670	2423	6093	39	29	68	1.06%	1.20%	1.12%

**Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment:
number of patients reporting ≥ 1 event**

Trial/ treatment (μg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
SYMBICORT pMDI trials						
SD-039-0681						
PULM_CFC 400 bid	217	16 952				1
SYMB_HFA 320/9 bid	233	18 118				
SYMB_TBH 320/9 bid	229	18 087				
SD-039-0682						
PULM_CFC 200 bid	207	16 707				2
SYMB_HFA 160/9 bid	203	16 280				
SYMB_TBH 160/9 bid	212	17 428				
SD-039-0716						
OXIS_TBH 9 bid	123	8217				
PLACEBO	131	7227				
PULM_HFA 160 bid	127	9745				
SYMB_HFA 160/9 bid	130	10 169				1
SD-039-0717						
OXIS_TBH 9 bid	123	7121				
PLACEBO	125	6169				
PULM_HFA 320 bid	109	7786				
PULM_HFA_OXIS_TBH 320/9 bid	115	8571				1
SYMB_HFA 320/9 bid	124	9147				3

**Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment:
number of patients reporting ≥ 1 event**

Trial/ treatment (μg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
SD-039-0718						
OXIS_TBH 9 bid	138	9662				1
PULM_HFA 80 bid	145	10 119				
SYMB_HFA 80/9 bid	128	9066				
SD-039-0725						
PULM_HFA 160 qd	169	14 382				1
SYMB_HFA 80/9 bid	184	16 263				2
SYMB_HFA 160/9 qd	168	14 093				2
SD-039-0726						
PLACEBO	153	10 982				
PULM_HFA 320 qd	145	12 338				
SYMB_HFA 160/9 qd	152	13 361				
SYMB_HFA 160/9 bid	154	13 386				
SYMB_HFA 320/9 qd	147	12 804				
SD-039-0728						
PULM_HFA 640 bid	133	42 913				1
SYMB_HFA 640/18 bid	443	142 902				
SYMB_HFA 320/9 bid	132	43 044				2

**Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment:
number of patients reporting ≥ 1 event**

Trial/ treatment (μg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
D5896C00001						
PULM_HFA 320 qd	153	12 283				
SYMB_HFA 160/9 qd	157	12 205				
SYMB_HFA 160/9 bid	155	12 340				
SYMB_HFA 320/9 qd	153	12 297				
Total: SYMBICORT pMDI trials	5417	592 164	0	0	0	17
SYMBICORT TURBUHALER trials						
BA-039-0001						
PULM_TBH AD	68	7973				
SYMB_TBH AD	65	8634				
SD-039-0348						
PULM_TBH 200 bid	237	18 684				
SYMB_TBH 80/4.5 bid	230	18 497				1
SD-039-0349						
PULM_OXIS_TBH 9 plus 400 bid	115	8607				
PULM_TBH 400 bid	124	9566				
SYMB_TBH 320/9 bid	123	9289	1			
SD-039-0353						
PULM_TBH 200 bid	138	11 167				
SYMB_TBH 160/9 bid	148	11 882				6

**Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment:
number of patients reporting ≥ 1 event**

Trial/ treatment (μg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
SD-039-0618						
FLUT 250 bid	176	13 869				3
SYMB_TBH 160/4.5 bid	168	13 777				
SD-039-0665						
PULM_TBH 160 qd	207	16 194				1
SYMB_TBH 160/9 qd	202	15 775				
SYMB_TBH 80/4.5 bid	207	16 584				1
SD-039-0666						
PULM_TBH 320 qd	171	13 782				
SYMB_TBH 160/4.5 bid	176	14 063				1
SYMB_TBH 320/9 qd	176	14 124				
SD-039-0667						
PULM_TBH_ 320 evening plus TERB_TBH_prn	342	59 105				1
SYMB_TBH_160/9 evening plus SYMB_TBH_prn	354	61 283				
SD-039-0668						
PULM_TBH 320 bid plus _TERB_TBH_prn	943	304 334	2			14
SYMB_TBH 320/9 evening plus _SYMB_TBH_prn	947	312 109	1			5
SD-039-0671						
FLUT 250 bid	220	3403				1
SYMB_TBH 80/4.5 bid	218	3338				

Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment: number of patients reporting ≥1 event

Trial/ treatment (µg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
SD-039-0673						
PULM_TBH 320 od plus _TERB_TBH_prn	107	35 435				3
PULM_TBH 320 bid plus _TERB_TBH_prn	818	267 597	1			11
SYMB_TBH 80/4.5 bid plus _TERB_TBH_prn	788	256 429				10
SYMB_TBH 80/4.5 od plus _TERB_TBH_prn	118	41 082				7
SYMB_TBH 80/4.5 bid plus _SYMB_TBH_prn	804	265 097				7
SYMB_TBH 80/4.5 od plus _SYMB_TBH_prn	118	40 582				
SD-039-0688						
PULM_OXIS_TBH 9 plus 200 bid	201	16 525				1
PULM_TBH 200 bid	213	17 486				
SYMB_TBH 160/9 bid	216	17 607				
SD-039-0689						
PULM_OXIS_TBH 18 plus 800 bid	115	9582				
PULM_TBH 800 bid	115	9338				
SYMB_TBH 640/18 bid	226	18 675				
SD-039-0714						
PULM_TBH 200 bid	134	10 283				1
SYMB_TBH 160/4.5 bid	136	10 597				
Total: SYMBICORT TURBUHALER trials	9864	1 982 354	4	0	0	74

**Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment:
number of patients reporting ≥ 1 event**

Trial/ treatment (μg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
OXIS TURBUHALER TRIALS						
37-3002						
OXIS_TBH 9 μg bid	55	1537				1
OXIS_TBH 18 μg bid	55	1548				
OXIS_TBH 4.5 μg bid	55	1550				
PLACEBO	56	1526				
37-3006						
TERB_TBH 500 μg qid	116	9190				3
OXIS_TBH 9 μg bid	114	9460				
PLACEBO	113	8862				
37-3008						
OXIS_TBH 18 μg bid	125	20 069				1
PLACEBO	114	18 344				1
37-3018						
PULM_OXIS_TBH 80/9 μg bid	211	65 012				1
PULM_OXIS_TBH 320/9 μg bid	215	67 976				1
PULM_TBH 80 μg bid	213	64 488				3
PULM_TBH 320 μg bid	214	66 933				4

**Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment:
number of patients reporting ≥1 event**

Trial/ treatment (µg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
37-3026						
TERB_TBH 500 µg qid	132	10 378				2
OXIS_TBH 4.5 µg bid	135	11 235				
PLACEBO	129	10 216				2
37-3027						
OXIS_TBH 9 µg bid	42	334				
OXIS_TBH 18 µg bid	40	316				
OXIS_TBH 4.5 µg bid	41	320				
PLACEBO	42	327				
37-3041						
PULM_OXIS_TBH 80/9 µg bid	29	9400				1
PULM_TBH 320 µg bid	31	10 481				
39-3002-1						
OXIS_TBH 9 µg bid	7	179				
PULM_OXIS_TBH 160/9 µg bid	7	201				
PULM_TBH 160 µg bid	7	226				
BU-543-0681A						
PULM_OXIS_TBH 320/9 µg bid	333	9575				
PULM_TBH 320 µg bid	330	9431	1			1

**Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment:
number of patients reporting ≥ 1 event**

Trial/ treatment (μg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
DC-037-0002						
OXIS_TBH 9 μg bid	95	7311				1
OXIS_TBH 4.5 μg bid	105	8672				
PLACEBO	101	7257				1
SD-004-0216						
PULM_OXIS_TBH 9 plus 200 μg bid	118	6533				1
PULM_TBH 200 μg bid	116	6548				
PULM_TBH // ACCOLATE 200 μg plus 20 mg bid	118	6317				
SD-037-0003						
OXIS_TBH 9 μg bid	83	6888				1
OXIS_TBH 4.5 μg bid	81	6526				1
PLACEBO	84	6624				
SD-037-0011						
TERB_TBH 2 mg qid	14	251				
OXIS_TBH 18 μg bid	15	281				
OXIS_TBH 4.5 μg bid	14	256				
OXIS_TBH 9 μg morning	15	264				
PLACEBO qid	14	271				

Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment: number of patients reporting ≥ 1 event

Trial/ treatment (μg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
SD-037-0123						
TERB_TBH_prn Bricanyl 500 prn	180	13 655				
OXIS_TBH_prn Oxis 4,5 prn	182	14 404				
SD-037-0345						
PLACEBO	239	75 921				
PULM_OXIS_TBH 4,5 plus 80 ug bid	554	178 912	1		1	3
PULM_OXIS_TBH 4,5 plus 160 ug bid	315	105 128				4
PULM_TBH 80 ug bid	550	177 404				4
PULM_TBH 160 ug bid	312	104 540				8
SD-037-0695						
TERB_TBH_prn Bricanyl 250 prn	275	45 596				7
OXIS_TBH_prn Oxis 4,5 prn	277	46 064				7
SD-037-0714						
TERB_TBH_prn Bricanyl 500 prn	227	72 640				5
OXIS_TBH_prn prn	228	75 501				3
SD-037-0716						
TERB_TBH_prn Bricanyl 500 prn	341	107 771				2
OXIS_TBH_prn Oxis 4,5 prn	333	106 530				1

Table 47 Safety data by trial and treatment arm for trials including both LABA and non-LABA treatment: number of patients reporting ≥1 event

Trial/ treatment (µg unless otherwise specified)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
SD-037-0745						
OXIS_TBH 9 µg bid	70	1994				
OXIS_TBH 18 µg bid	69	1962				
OXIS_TBH 4.5 µg bid	70	1997				
PLACEBO	73	2056				
Total: OXIS TURBUHALER trials	8229	1 605 188	2	0	1	70

FLUT fluticasone; PULM Pulmicort; SYMB Symbicort; TBH Turbuhaler; TERB terbutaline; CFC “Old pMDI”; HFA “New pMDI”;

SUMMARY OF SAFETY RESULTS BY STUDY FOR TRIALS IN WHICH ALL TREATMENT ARMS CONTAINED LABA TREATMENT

Table 48 Asthma-related hospitalizations by trial for trials in which all arms contained LABA treatment (adjudicated data, all ages)

Study code	Number of patients			Number of asthma-related hospitalizations			Percent of patients reporting asthma-related hospitalizations		
	Formoterol	Salmeterol	Total	Formoterol	Salmeterol	Total	Formoterol	Salmeterol	Total
SYMBICORT TURBUHALER TRIALS									
AF-039-0001	92		92	0		0	0%	-	0%
D5890C00002	1151	1153	2304	4	4	8	0.35%	0.35%	0.35%
DC-039-0002	237		237	0		0	0%	-	0%

Table 48 Asthma-related hospitalizations by trial for trials in which all arms contained LABA treatment (adjudicated data, all ages)

Study code	Number of patients			Number of asthma-related hospitalizations			Percent of patients reporting asthma-related hospitalizations		
	Formoterol	Salmeterol	Total	Formoterol	Salmeterol	Total	Formoterol	Salmeterol	Total
SD-039-0686	434	224	658	0	0	0	0%	0%	0%
SD-039-0734	3382		3382	63		63	1.86%	-	1.86%
SD-039-0735	2202	1119	3321	21	14	35	0.95%	1.25%	1.05%
OXIS TURBUHALER trials									
37-3007-1	66		66	0		0	0%	-	0%
37-3011-1	66		66	0		0	0%	-	0%
37-3040-1	19	20	39	0	0	0	0%	0%	0%
SD-037-0175	357		357	4		4	1.12%	-	1.12%

Table 49 Asthma-related hospitalizations by trial for trials in which all arms contained LABA treatment (adjudicated data, patients <18 years)

Study code	Number of patients			Number of asthma-related hospitalizations			Percent of patients reporting asthma-related hospitalizations		
	Formoterol	Salmeterol	Total	Formoterol	Salmeterol	Total	Formoterol	Salmeterol	Total
SYMBICORT TURBUHALER trials									
AF-039-0001	2	0	2	0	-	0	0%	-	0%
D5890C00002	163	161	324	0	1	1	0%	0.62%	0.31%
SD-039-0686	11	4	15	0	0	0	0%	0%	0%
SD-039-0734	354	0	354	4	-	4	1.13%	-	1.13%
SD-039-0735	410	211	621	0	0	0	0%	0%	0%
OXIS TURBUHALER trial									
37-3011-1	1	0	1	0	-	0	0%	-	0%

Table 50 Safety data by trial and treatment arm for trials in which all arms contained LABA treatment. Number of patients reporting ≥ 1 event

Trial/ treatment (μg)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
SYMBICORT TURBUHALER trials						
AF-039-0001						
OXIS_TBH_prn	47	6992				
SYMB_TBH_prn	45	7082				
D5890C00002						
SERETIDE_50/500 bid plus TERB_TBH_prn	1153	198 631				4
SYMB_TBH_320/9 bid plus SYMB_TBH_prn	1151	200 192	1			4
DC-039-0002						
PULM_OXIS_TBH 320/9 bid	120	3380				
SYMB_TBH 320/9 bid	117	3299				
SD-039-0686						
SERETIDE 50/250 μg bid	224	6754				
SYMB_TBH 320/9 μg bid	215	6502				
SYMB_TBH ind	219	6578				
SD-039-0734						
SYMB_TBH_160/4.5 bid plus TERB_TBH_prn	1138	381 451	1			25
SYMB_TBH_160/4.5 bid plus OXIS_TBH_prn	1137	386 820	1			23
SYMB_TBH_160/4.5 bid plus SYMB_TBH_prn	1107	377 137				15
SD-039-0735						
SERETIDE_50/250 bid plus TERB_TBH_prn	1119	184 943	1			14
SYMB_TBH_320/9 bid plus TERB_TBH_prn	1099	180 254				12

Table 50 Safety data by trial and treatment arm for trials in which all arms contained LABA treatment. Number of patients reporting ≥ 1 event

Trial/ treatment (μg)	N	Exposure (days)	Data from adjudication procedure			
			Any death	Asthma-related death	Asthma-related intubation	Asthma-related hospitalization
SYMB_TBH_160/4.5 bid plus SYMB_TBH_prn	1103	180 870	1	1	1	9
Total: SYMBICORT TURBUHALER trials	9994	2 130 885	5	1	1	106
OXIS TURBUHALER trials						
37-3007-1						
FORMOTEROL_FORADIL 24 μg bid	33	503				
OXIS_TBH 18 μg bid	33	518				
37-3011-1						
FORMOTEROL_FORADIL 12 μg bid	35	530				
OXIS_TBH 9 μg bid	31	479				
37-3040-1						
OXIS_TBH 9 μg bid	19	646				
SALM 50 μg bid	20	694				
SD-037-0175						
OXIS_TBH_9 bid plus TERB_TBH_prn	181	13 984				
OXIS_TBH_9 bid plus OXIS_TBH_prn	176	13 885				4
Total: OXIS TURBUHALER trials	528	31 239	0	0	0	4

PULM Pulmicort; SALM Salmeterol; SYMB Symbicort; TERB Terbutaline; TBH Turbuhaler.

Appendix C: Narratives of patients who died (all cause)

Table 51 Unblinded death narratives

CASE_ ID	TRIAL	CENTER	PID	NARRATIVE
1999AD 01020	BU-543- 0681	5604	1304	<p>The patient was diagnosed with an intracerebral haemorrhage on day three of treatment with investigational product. She had developed a severe headache the same day, and lost consciousness an hour later. The patient was admitted to hospital and MRI revealed a cerebral bleed. The day after the patient was transferred to another hospital where she was pronounced brain dead. Ventilation was discontinued and the patient's liver and kidneys were removed for transplantation.</p> <p>Additional information from formoterol safety database: The patient was randomized to Pulmicort Turbuhaler</p>
1998AD 01220	SD-037- 0345	181	30801	<p>The patient was hospitalized due to an asthma attack of severe intensity on day 238 of treatment with the investigational product. An orotracheal intubation was performed and the patient was helped with mechanical ventilation. During the hospitalization she received treatment with Rohypnol (flunitrazepam), cimetidine, methylprednisolone, Enoxaparin (heparin-fraction), aminophylline, Nubain (nalbuphine), ceftriaxone, metoclopramide, insuline, dopamine and noradrenaline. The investigational product was discontinued. The condition deteriorated due to a nosocomial infection, resistant to the administered antibiotic treatment. The patient developed pneumonia and a septic chock. She died at the Respiratory Intensive Care Unit after eight days. Probable cause of death was septic chock. Afterwards a multiresistant <i>Moraxella catarrhalis</i> was observed in culture.</p> <p>Additional information from formoterol safety database: The patient was randomized to Pulmicort Turbuhaler plus Oxis Turbuhaler</p>
1999AD 01130	SD-039- 0349	401	578070	<p>The patient committed suicide on day one of treatment with the investigational product. He came to the clinic in the morning and received the first dose of the investigational product, but it is not known if he received any more.</p> <p>Additional information from formoterol safety database: The patient was randomized to Symbicort Turbuhaler</p>

Table 51 Unblinded death narratives

CASE_ ID	TRIAL	CENTER	PID	NARRATIVE
2002U W02181	SD-039- 0668	153	945	{MYOCARDIAL INFARCTION} A report has been received from a study investigator from Canada concerning a 55 year old Caucasian male patient who enrolled in an efficacy and safety study of Symbicort (budesonide/formoterol) Turbuhaler (STEP study) as single therapy in patients with moderate-severe asthma. Comparison with conventional asthma therapy, Pulmicort (budesonide) Turbuhaler as maintenance therapy, complemented with Bricanyl (terbutaline). The study is double-blind, randomized, active-controlled and parallel group designed. Medical history and concurrent condition included asthma which was first diagnosed in 1998, allergies, and nasal polyps. The patient had no previous cardiac or hypertension history. Concomitant medications included budesonide nasal spray and vitamin B complex. The patient was placed on therapy with the study medication on 15-Nov-2001 for the treatment of asthma. On 08-Feb-2002, the patient began experiencing an increase in epigastric pain. On the evening of 13-Feb-2002, the patient experienced a collapse and died around 7:00 PM. The last dose of the investigational product was taken on 13-Feb-2002. The cause of death was myocardial infarction. The investigator considered the event to be severe in intensity and not related to study medication or other medication that the patient was taking. Summary of follow up information received by AstraZeneca on 15-Feb-2002: The intensity and the event stop date were provided. Summary of follow up information received by AstraZeneca on 13-Sep-2002: The causality for other medication (not related) was provided. No further information is available. The treatment code for this patient was unblinded on 03-May-2003; the patient was receiving PULMICORT as maintenance, complemented with BRICANYL as needed.

Table 51 Unblinded death narratives

CASE_ ID	TRIAL	CENTER	PID	NARRATIVE
2002U W15510	SD-039- 0668	153	946	{HYPERTROPHIC CARDIOMYOPATHY} A report was received from an investigator regarding a 47 year-old female who was a participant in the trial entitled, Efficacy and Safety of Symbicort (budesonide/formoterol) Turbuhaler as Single Therapy in patients with moderate-severe asthma. Comparison with conventional therapy, complemented with Bricanyl (terbutaline Turbuhaler) (STEP). Medical history included hypertension, nasal polyps, allergies, insomnia, depression, hip pain, occasional lightheadedness, and migraines with visual disturbances. The patient has been smoking cigarettes for approximately 26 years. Surgical history included a hysterectomy. Concomitant medications included Nasacort (triamcinolone acetonide), Apo-Methopromazine (methopromazine), conjugated estrogens, venlafaxine, and losartan. It was reported the patient had a routine electrocardiogram (EKG) done as follow-up for this study and paroxysmal atrial fibrillation was noted. She was asymptomatic. She was seen by a cardiologist on 16-JUL-2002. Her EKG that day showed a complete left bundle branch block and a sinus rhythm of 79 per minute. She had a submaximal stress test done where she achieved only 74% of her predicted heart rate with no significant EKG changes. An echocardiogram done on 26-AUG-2002 showed that the left ventricle appeared to be dilated, a dyskinetic septum, and an ejection fraction of 37%. Results from a heart catheterization on 27-SEP-2002 showed a dilated left ventricle, moderate global hypokinesis - more pronounced on the anterior wall, calcification in the proximal left coronary artery (LAD), minimal lesion coronary artery disease and dilated cardiomyopathy. Treatment included the continuation of Hyzaar. The patient expired on 28-OCT-2002. An autopsy report indicated that the lungs were clear and the cause of death was attributed to a likely arrhythmia due to hypertrophic cardiomyopathy. Study drug dosing started on 16-NOV-2001 and stopped on 15-AUG-2002 (estimated date). The investigator assessed the event as not related to study drug and severe in intensity. Summary of follow-up information received by AstraZeneca on 28-JAN-2003 provided information regarding start and stop dates for study drug dosing, event intensity, and action taken with study drug. Summary of follow-up received on 04-MAR-2003 provided the autopsy reports findings' cause of death as likely arrhythmia due to hypertrophic cardiomyopathy. Summary of follow-up information received by AstraZeneca on 18-Mar-2003: The investigator's causality has been changed from related to not related. Company Clinical Comment: the subject had significant underlying cardiac abnormalities. The treatment code for this patient was unblinded on 13-Nov-2002; the patient was receiving Pulmicort Turbuhaler and Bricanyl.

Table 51 Unblinded death narratives

CASE_ ID	TRIAL	CENTER	PID	NARRATIVE
2002PK 00648	SD-039- 0668	286	248	{PERITONEAL METASTASES} A preliminary report has been received concerning a 74-year-old female who is enrolled in a double-blind, randomized, active-controlled, parallel group designed study: Efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler as Single Therapy in patients with moderate-severe asthma. Comparison with conventional asthma therapy, Pulmicort (budesonide) Turbuhaler as maintenance therapy, complemented with Bricanyl (terbutaline) Turbuhaler. The patient started therapy with the investigational product on 31-Aug-2001. Concomitant medication was not reported. In Apr-02, eight months after commencing study treatment, abdominal CT showed peritoneal metastases. Histology revealed an adenocarcinoma of unknown primary site at time of this report. Study medication was withdrawn on 15-Apr-2002. Three months later the patient died due to progression of peritoneal metastases. The reporter considered there was no reasonable possibility that the event may have been caused by investigational product. Follow up received on 10-Sep-2002 included outcome death. Follow-up information after SAE reconciliation on 10-Feb-2003: study medication was stopped and the patient was withdrawn from the study on 15-Apr-2003. Narrative updated. The treatment code for this patient was unblinded on 03-May-2003; the patient was receiving SYMBICORT as maintenance, complemented with SYMBICORT as needed.
2002AP 02464	SD-039- 0673	572	1742	{DEATH CAUSE UNKNOWN, LOSS OF CONSCIOUSNESS, CYANOSIS} A report has been received from a study investigator concerning a 67 year-old male patient who is enrolled in a double-blind, randomized study to assess the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler as single therapy in patients with mild-moderate asthma, in comparison with Symbicort Turbuhaler or Pulmicort Turbuhaler as maintenance therapy, both complemented with Bricanyl Turbuhaler (STAY). The patient was diagnosed with asthma in 1990, and was concurrently suffering from dyspepsia, stomach function disorders and chronic sinusitis. He concomitantly received Topaal (multiple ingredients including alginic acid). The patient had been enrolled in the study since 21st August 2001. Forty-three weeks and three days later the patient experienced loss of consciousness and cyanosis. He was admitted and withdrawn from trial therapy. He received cardiopulmonary resuscitation but died on 24 June 2002, four days after being admitted. The cause of death was given as unknown and an autopsy was not performed. The reporter did not consider there to be a causal relationship between trial therapy and the events. The treatment code for this patient was unblinded on 26-Apr-2003; the patient was receiving PULMICORT as maintenance, complemented with BRICANYL as needed.

Table 51 Unblinded death narratives

CASE_ ID	TRIAL	CENTER	PID	NARRATIVE
POST TREATMENT				
1995AD 00851	37-3018	47	64719	<p>The patient died due to suicide, hanging (suicide attempt) two days after stopping the study medication which he had for 334 days. The investigator reported that there was no depression before the suicide but that the patient had talked about suicide to colleagues many years prior to the event.</p> <p>Additional information from formoterol safety database: The patient was randomized to Pulmicort Turbuhaler plus Oxis Turbuhaler</p>
1996AD 00902	SD-037- 0003	34	3403	<p>{RESPIRATORY FAILURE}The patient woke up at night, after 26 days of treatment with investigational product, with fatigue and moderate dyspnoea. He took four inhalations of Bricanyl (terbutaline) Turbuhaler and felt better. He went to the toilet and after defecation, the patient fell, had a convulsion and a respiratory arrest. The patient arrived at hospital after about an hour. After resuscitation at the emergency room, a recovery of cardiac pulse was obtained but the patient's EEG was plain. A CT-scan of the patient's brain showed a cerebral haemorrhage with blood clots. The patient was maintained with cardio- pulmonary support and two days after the event he was declared dead. The patient had a family history of diagnosed aneurysm. At visit 1 in the study (one month and 13 days prior to the event) the patient's blood pressure was 105/55 and his pulse rate 92. At visit two (13 days later) his blood pressure was 110/65 and pulse rate 76. Summary of follow up information received by AstraZeneca 16-Sep-2002 included information originating from a legal procedure. According to four external experts, there is no relationship between Oxis Turbuhaler and the death. The autopsy report states the cause of death as respiratory failure. The clinical event has been recoded to respiratory failure.</p> <p>Additional information from formoterol safety database: The patient was randomized to Oxis Turbuhaler</p>
2000AD 01025	SD-039- 0666	105	532	<p>The patient had a fatal cardiac arrest on day 79 of treatment with the investigational product. At the time of his death he was in Brazil, and died at hospital there. There are no laboratory or ECG measurements available. He had a medical history of adult diabetes mellitus, stable ischaemic heart disease, myocardial infarction and was on anticoagulant treatment. No autopsy was performed. No further information is available.</p> <p>Additional information from formoterol safety database: The patient was randomized to Symbicort Turbuhaler</p>

Table 51 Unblinded death narratives

CASE_ ID	TRIAL	CENTER	PID	NARRATIVE
2002SE 05537	SD-039- 0668	327	1774	{CARDIAC FAILURE, CELEBRAL OEDEMA} A report has been received from a study investigator concerning a 23-year-old male who is enrolled in a double-blind, randomized, active-controlled, parallel group design study. Efficacy and safety of Symbicort Turbuhaler as Single Therapy in patients with moderate-severe asthma. Comparison with conventional asthma therapy, Pulmicort Turbuhaler as maintenance therapy, complemented with Bricanyl Turbuhaler. The patient had previously this year, on 12-Jul-2002, been hospitalized due to an asthmatic attack and he had also experienced severe asthma exacerbation on 1-Jul-2002 and 4-Sep-2002. He had a concurrent disease of allergic rhinitis that had aggravated and he was a habitual smoker. At visit number one the physical examination showed no abnormalities in general appearance, mouth, teeth, throat, cardiovascular, lungs and abdomen. His pulse was 65 beats/min and his blood pressure was 121/72 mmHg. On 1-Oct-2002 the patient discontinued the study because of the three severe asthma exacerbations within three months. Two weeks after the study terminated the patient died at home because of acute cardiac failure followed by cerebral oedema. No autopsy was performed. The investigator considered that there was no reasonable possibility that the study medication may have caused the event. Follow-up information received on 28-Oct-2002 included: concomitant medication, medical history, patient details. The treatment code for this patient was unblinded on 03-May-2003; the patient was receiving PULMICORT as maintenance, complemented with BRICANYL as needed.
2002SE 01735	SD-039- 0673	75	1527	{SUDDEN DEATH} A report has been received concerning a 54 year-old female who is enrolled in the SD-039-0673 Symbicort study, a double-blind, randomized, active-controlled, parallel group design study. Efficacy and safety of budesonide/formoterol (Symbicort) Turbuhaler as Single Therapy in patients with mild-moderate asthma. Comparison with Symbicort Turbuhaler and Pulmicort Turbuhaler as maintenance therapy, both complemented with Bricanyl Turbuhaler (STAY). The subject had been receiving double-blind treatment for 46 weeks and four days when she was found dead in her bed on 03-Mar-2002. Cause of death is unknown. The date of last contact with the patient (being alive) was on 10-Jan-2002. No autopsy was performed. The subject had a medical history of hypertension and rhinitis allergic. Concomitant medication was Verapamil. Serious criteria were sudden death. Summary of follow-up information received by AstraZeneca 25-JAN-2003: Changed event from death to sudden death and the cause of death from pulmonary embolism to unknown. Summary of follow-up information received by AstraZeneca 10-MAR-2003: Enrolment ID and changed action taken from NA to none. The treatment code for this patient was unblinded on 26-Apr-2003; the patient was receiving SYMBICORT as maintenance, complemented with BRICANYL as needed.

Table 51 Unblinded death narratives

CASE_ ID	TRIAL	CENTER	PID	NARRATIVE
2002AP 01643	SD-039- 0673	448	1488	{SEVERE ASTHMA EXACERBATION}A report containing minimal information has been received concerning a 65 year old female patient enrolled in study SD-039-673 (STAY) looking at the efficacy and safety of budesonide/formoterol (Symbicort) Turbuhaler as Single Therapy in patients with mild-moderate asthma. Comparison with Symbicort Turbuhaler and Pulmicort Turbuhaler as maintenance therapy, both complemented with Bricanyl Turbuhaler. The patient had a history of severe asthma exacerbations. The patient received her first dose of study medication on 16 August 2001. On 11 June 2002, she was apparently well during the morning but developed dyspnoea, chest pain and tremors later in the day. She was nebulized at home with ventolin, which provided no relief. She was rushed to a nearby hospital where she died, despite attempts at cardiopulmonary resuscitation. The reporting investigator considered that there was no relationship between the event and trial therapy. The treatment code for this patient was unblinded on 26-Apr-2003; the patient was receiving SYMBICORT as maintenance, complemented with BRICANYL as needed.

Appendix D: Asthma-related adverse events as presented in SYMBICORT pMDI applications to FDA

The following data supported the NDA for SYMBICORT pMDI 4-month safety update and pediatric sNDA. The data presented here include long-term safety studies (715 and 719) that were not relevant for the adjudicated data presented in the main part of the document, due to the open-label design.

Table 52 Overview of asthma-related AEs during randomized treatment for SYMBICORT pMDI and budesonide (from 4-month safety update)

Class effect category/ Type of event	SYMBICORT pMDI			Budesonide		
	NDA N=2193	4MSU N=1856	NDA+4MSU N=4049	NDA N=1182	4MSU N=286	NDA+4MSU N=1468
Total asthma-related events (AZ), n (%) of subjects	148 (6.7)	151 (8.1)	299 (7.4)	90 (7.6)	19 (6.6)	109 (7.4)
Asthma-related events (AZ) that were serious and/or led to discontinuation	30 (1.4)	13 (0.7)	43 (1.1)	28 (2.4)	1 (0.3)	29 (2.0)
Serious asthma-related events (AZ)	14 (0.6)	3 (0.2)	17 (0.4)	4 (0.3)	0	4 (0.3)
Asthma-related events (AZ) leading to discontinuation	22 (1.0)	11 (0.6)	33 (0.8)	27 (2.3)	1 (0.3)	28 (1.9)
Total asthma-related events (Novartis), n (%) of subjects	145 (6.6)	139 (7.5)	284 (7.0)	89 (7.5)	17 (5.9)	106 (7.2)
Asthma-related events (Novartis) that were serious and/or led to discontinuation	30 (1.4)	13 (0.7)	43 (1.1)	28 (2.4)	1 (0.3)	29 (2.0)
Serious asthma-related events (Novartis)	14 (0.6)	3 (0.2)	17 (0.4)	4 (0.3)	0	4 (0.3)
Asthma-related events (Novartis) leading to discontinuation	22 (1.0)	11 (0.6)	33 (0.8)	27 (2.3)	1 (0.3)	28 (1.9)

Note: Application of the Novartis definition of asthma-related events was not included in the initial NDA, but was provided for NDA data for comparison purposes.

**Table 53 Overview of asthma-related AEs during randomized treatment:
(SYMBICORT pMDI pediatric studies)**

Event of interest	Treatment ^a , number (%) of subjects with an adverse event			
	SYMBICORT pMDI bid N=539	Budesonide ^a N=479	Formoterol bid N=90	SYMBICORT TURBUHALER bid N=212
Subjects with ≥1 AE representing asthma or potentially asthma-related AEs	61 (11.3)	52 (10.9)	9 (10.0)	9 (4.2)
Asthma-related events that were serious and/or led to discontinuation	7 (1.3)	14 (2.9)	1 (1.1)	0
Serious asthma-related events	2 (0.4)	3 (0.6)	0	0
Asthma-related events leading to discontinuation	6 (1.1)	13 (2.7)	1 (1.1)	0

^a Budesonide group comprises both bid and qd dose groups.

Appendix E: Review of published literature

Sears et al 2008

An analysis of all AstraZeneca-sponsored randomized, controlled, parallel-group asthma trials of 3 to 12 months duration involving formoterol was published in September 2008 ([Sears et al 2008](#)). The analysis examined whether asthma-related, cardiac-related or all-cause mortality or morbidity were increased with formoterol use. Despite data on over 68 000 patients, there was insufficient evidence to conclude whether formoterol has any effect on asthma mortality. However, asthma-related serious adverse events (SAEs) were significantly reduced with formoterol, and cardiac-related SAEs were not increased, compared with non-LABA treatment. Note that this dataset included open-label studies and was therefore considerably more extensive than the dataset that is the basis for presentations given in this briefing document (see Section [2.2.1](#) for details regarding trials requested by FDA).

Bateman et al 2008

A recently published summary of 66 GlaxoSmithKline trials with almost 21 000 participants evaluated the incidences of severe asthma-related events (intubations, deaths and severe exacerbations) in persons receiving salmeterol plus ICS compared with ICS alone ([Bateman et al 2008](#)). There was one asthma-related death and one asthma-related intubation in patients receiving both salmeterol and ICS, compared with no such events in patients on ICS alone. No difference in risk of asthma-related hospitalizations was seen; however, in a subset of 24 trials, the risk of severe exacerbations was decreased with salmeterol and ICS compared with ICS alone.

Jaeschke et al 2008a and 2008b

A further systematic review and meta-analysis was published in September 2008, evaluating the impact of LABA on asthma-related and total morbidity and mortality in patients concomitantly using ICS ([Jaeschke et al 2008a](#)). Based on 62 studies with over 29 000 participants, it was concluded that in patients with asthma using ICS, LABA use did not increase the risk of asthma-related hospitalizations. Asthma-related deaths and intubations were too infrequent to establish LABA's relative effect on these outcomes.

A further review by the same authors ([Jaeschke et al 2008b](#)) studied the safety of formoterol more specifically, in a subset of the above data. In 16 trials with over 10 000 participants, of whom 5996 on formoterol, there were 2 asthma-related deaths and no asthma-related non-fatal intubations. The risk of asthma-related hospitalizations and asthma-related serious adverse events was statistically significantly lower in patients with formoterol and ICS than patients with ICS alone.

OHSU 2008 (draft review)

A draft drug class review on controller medications for asthma was made available for public comment in September 2008 by the Oregon Health and Science University (OHSU). With regard to the safety of LABAs, the report concludes that LABAs should not be used as monotherapy because they increase the risk of asthma-related deaths. Indirect evidence

suggests that the potential for increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline. The review points out that published pediatric data (ie, for patients under 12 years) are limited, and that results for older age groups are not necessarily applicable to pediatric populations.

Cates and Cates 2008a and b

A Cochrane review was published in 2008 ([Cates and Cates 2008a](#)) of serious adverse events during regular treatment with salmeterol versus placebo or short-acting β_2 -agonists, excluding trials that included randomization to treatment containing ICS. An increased risk of serious adverse events was reported with regular salmeterol compared with placebo and an increase in risk of asthma-related mortality in patients not using ICS was reported, based on the SNS study and Salmeterol Multi-centre Asthma Research Trial. The increase in asthma-related mortality was smaller in patients taking ICS at baseline, but it could not be concluded that ICS abolished the risks of regular salmeterol.

A corresponding review of formoterol was also published in 2008 ([Cates and Cates 2008b](#)) of serious adverse events during regular treatment with formoterol versus placebo or short-acting β_2 -agonists, and excluding trials that included randomization to treatment containing ICS. Three deaths were identified on formoterol treatment compared with none on placebo; the difference was not statistically significant. Non-fatal serious adverse events were significantly increased when formoterol was compared with placebo, but not compared with regular albuterol or terbutaline.

It can be noted that both of the above Cochrane reviews ([Cates and Cates 2008a](#), [Cates and Cates 2008b](#)) are based on previously published data, and thus do not contribute anything substantially new. The conclusion in these reviews that ICS does not appear to abolish the increased risk of serious adverse events seems poorly grounded, because the reviews excluded all trials in which patients were randomized to ICS-containing treatment.

Lasserson et al 2008

A further Cochrane review ([Lasserson et al 2008](#)) compared fixed-dose treatment with budesonide/formoterol and salmeterol/fluticasone with regard to exacerbations requiring oral steroid treatment, hospital admission and serious adverse events. No statistically significant differences were found between treatments.

Meta-analysis by Salpeter and colleagues

A meta-analysis was published in 2006 concluding that LABAs have been shown to increase severe and life-threatening asthma exacerbations, as well as asthma-related deaths ([Salpeter et al 2006](#)). It was further speculated that of the 5000 annual asthma deaths in the US, 4000 might be due to the introduction of LABAs (see Section 1.4.3 for comment on epidemiology and changes in methods for calculation of asthma mortality over this period). Extensive criticism of the meta-analysis has appeared on the website for letters to the journal in which it was published and in subsequent publications (eg, [Chinchilli 2007](#)). AstraZeneca's major concerns with regard to this publication are as follows:

- Of the 19 trials included, most of the data (26 353 of 33 826 patients) originate from the Salmeterol Multi-Center Asthma Research Trial.
- The majority of patients (78%) were on salmeterol. Less than 3000 patients were on formoterol, whereof less than 500 on OXIS; thus less than 1% of the safety data collected by AstraZeneca for formoterol were included in this meta-analysis.
- No patients on fixed ICS/LABA combination were included in the analysis, and several landmark studies with data evaluating the benefit of adding a LABA to an ICS, (eg, [Pauwels et al 1997](#)) were omitted.
- In order to be included in the meta-analysis, the trial publication had to present data on asthma-related SAEs. It is more likely that this information is included in the publication when the number of such events is high (especially on active treatment), and less likely when no or very few such events occurred.

Since the results for the meta-analysis by Salpeter and colleagues is dominated by data from the Salmeterol Multi-Center Asthma Research Trial ([Nelson et al 2006](#)), some further comments will be made regarding this study.

It has been suggested that poorer outcome in African Americans that participated in the Salmeterol Multicenter Asthma Research Trial could be due to genetic reasons, since several studies suggest that Arg-Arg homozygotes fail to respond to regular short-acting β_2 -agonist or long-acting β_2 -agonist therapy, and this genotype is over-represented in the African American population. However, extensive pharmacogenetic data from SYMBICORT studies ([Bleecker et al 2007a](#)) provide no support for the hypothesis that β_2 -adrenoceptor polymorphism affects the safety or efficacy of formoterol when used in combination with budesonide as therapy for asthma patients.

It cannot be excluded that other genetic factors may affect response to β_2 -agonists; but we believe the more important factor in the Salmeterol Multicenter Asthma Research Trial was the level of ICS use. African Americans enrolled in this study used less ICS than Caucasians (38% versus 49%), despite baseline data indicating that they had more severe asthma than the study population as a whole. The relatively low use of ICS in African American asthma patients in the US has also been observed in other clinical trials, which have also shown that the lower use of inhaled corticosteroid in African Americans is paralleled by inferior asthma control ([Krishnan et al 2006](#), [LeNoir 1999](#), [Lieu et al 2002](#), [Mannino et al 2002](#), [Shireman et al 2002](#), [Zoratti et al 1998](#)). AstraZeneca therefore consider it likely that the increased risk seen in African Americans in the Salmeterol Multicenter Asthma Research Trial is related to underlying socio-economic differences that are manifested in low use of ICS in this subpopulation, despite the African American study subjects having more severe asthma.

Results from the Salmeterol Nationwide Surveillance study ([Castle et al 1993](#)) were one of the reasons for initiating the Salmeterol Multicenter Asthma Research Trial. In this 16-week trial, the incidence of asthma-related deaths was numerically higher (12 vs 2, ie, 0.07% vs 0.02%), although not statistically significantly so, in patients treated with salmeterol 50 μ g twice daily

than in patients treated with albuterol 200 µg 4 times daily, both as additions to the patients' usual asthma therapy. Patients without anti-inflammatory therapy were allowed to participate, making up approximately 25% of the study population. According to the publication, "for 10 of the patients who died from asthma, the independent consultants considered that their asthma could possibly have been more appropriately treated by earlier or higher doses of inhaled corticosteroid." This strengthens the conclusion of the importance of an adequate ICS dose in patients using a LABA.

It should be noted that AstraZeneca has not conducted any trial with formoterol comparable to the Salmeterol Multicenter Asthma Research Trial, ie, where patients with persistent asthma were not required to use concomitant ICS. Due to the importance of concomitant anti-inflammatory treatment, the great majority of patients receiving formoterol in AstraZeneca trials have received concomitant anti-inflammatory treatment, usually ICS.

**Appendix F
Symbicort Package and Insert Medication Guide**

SYMBICORT® 80/4.5

31152-05 267077

CLINICAL PHARMACOLOGY

1

(budesonide 80 mcg and formoterol fumarate dihydrate* 4.5 mcg)

Inhalation Aerosol

SYMBICORT® 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate* 4.5 mcg)

Inhalation Aerosol

*3.7 mcg formoterol as the free base, equivalent to 4.5 mcg formoterol fumarate dihydrate

For Oral Inhalation Only

Rx only

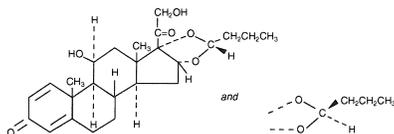
WARNING

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (eg, low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta₂-adrenergic agonist), one of the active ingredients in SYMBICORT (see **WARNINGS**).

DESCRIPTION

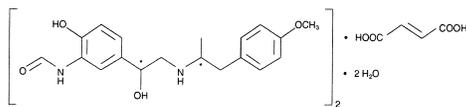
SYMBICORT 80/4.5 and SYMBICORT 160/4.5 each contain micronized budesonide and micronized formoterol fumarate dihydrate for oral inhalation only.

One active component of SYMBICORT is budesonide, a corticosteroid designated chemically as (RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder which is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6 x 10³.

The other active component of SYMBICORT is formoterol fumarate dihydrate, a selective beta₂-agonist designated chemically as (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butenedioate(2:1), dihydrate. The empirical formula of formoterol is C₂₂H₂₆N₂O₁₄ and its molecular weight is 840.9. Its structural formula is:



Formoterol fumarate dihydrate is a powder which is slightly soluble in water. Its octanol-water partition coefficient at pH 7.4 is 2.6. The pKa of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.

Each SYMBICORT 80/4.5 and SYMBICORT 160/4.5 canister is formulated as a hydrofluoroalkane (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled pressurized metered dose inhaler containing either 60 or 120 actuations (see **HOW SUPPLIED**). After priming, each actuation meters either 91/5.1 mcg or 181/5.1 mcg from the valve and delivers either 80/4.5 mcg or 160/4.5 mcg (budesonide micronized/formoterol fumarate dihydrate micronized) from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. SYMBICORT also contains povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant.

SYMBICORT should be primed before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well for 5 seconds before each spray and releasing two test sprays into the air away from the face.

Mechanism of Action

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the mechanisms of action described below for the individual components apply to SYMBICORT. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting selective beta₂-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

Budesonide

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses of budesonide. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85%-95%), and the low potency of formed metabolites.

Formoterol

Formoterol fumarate is a long-acting selective beta₂-adrenergic agonist (beta₂-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at beta₂-receptors than at beta₁-receptors. The *in vitro* binding selectivity to beta₂- over beta₁-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta₂-selectivity ratio than formoterol.

Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, there are also beta₂-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

Animal Pharmacology

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

SYMBICORT

In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak plasma concentrations for budesonide of 4.5 nmol/L occurred at 20 minutes following dosing and peak concentrations for formoterol of 136 pmol occurred at 10 minutes following dosing. Approximately 8% of the delivered dose of formoterol was recovered in the urine as unchanged drug. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler (DPI) at the same delivered dose. Following administration of SYMBICORT, the half-life of the budesonide component was 4.7 hours and for the formoterol component was 7.9 hours.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak plasma concentrations of budesonide (1.2 nmol/L) and formoterol (28 pmol/L) occurred at 21 and 10 minutes, respectively, in asthma patients. Peak plasma concentrations for budesonide and formoterol were about 30% to 40% higher in healthy subjects, compared to that in asthma patients. However, the total systemic exposure was comparable to that in asthma patients.

Following administration of SYMBICORT (160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentrations of budesonide and formoterol generally increased in proportion to dose. Additionally in this study, the accumulation index for the group

that received two inhalations twice daily was 1.32 for budesonide and 1.77 for formoterol.

Special Populations

Geriatric

The pharmacokinetics of SYMBICORT in geriatric patients have not been specifically studied.

Pediatric

Plasma concentrations of budesonide were measured following administration of four inhalations of SYMBICORT 160/4.5 mcg in a single-dose study in pediatric patients with asthma, 6-11 years of age. Urine was collected for determination of formoterol excretion. Peak budesonide concentrations of 1.4 nmol/L occurred at 20 minutes post-dose. Approximately 3.5% of the delivered formoterol dose was recovered in the urine as unchanged formoterol. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler which was also evaluated at the same delivered dose.

Gender/Race

Specific studies to examine the effects of gender and race on the pharmacokinetics of SYMBICORT have not been conducted. Population PK analysis of the SYMBICORT data indicates that gender does not affect the pharmacokinetics of budesonide and formoterol. No conclusions can be drawn on the effect of race due to the low number of non-Caucasians evaluated for PK.

Renal or Hepatic Insufficiency

There are no data regarding the specific use of SYMBICORT in patients with hepatic or renal impairment. Reduced liver function may affect the elimination of corticosteroids. Budesonide pharmacokinetics was affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous budesonide pharmacokinetics was, however, similar in cirrhotic patients and in healthy subjects. Specific data with formoterol is not available, but because formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment.

Drug-Drug Interactions

A single-dose crossover study was conducted to compare the pharmacokinetics of eight inhalations of the following: budesonide, formoterol, and budesonide plus formoterol administered concurrently. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between the two components of SYMBICORT.

Ketoconazole, a potent inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide. At recommended doses, cimetidine had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide. Specific drug-drug interaction studies with formoterol have not been performed.

Budesonide

Absorption

Orally inhaled budesonide is rapidly absorbed in the lungs, and peak concentration is typically reached within 20 minutes. After oral administration of budesonide, peak plasma concentration was achieved in about 1 to 2 hours, and the absolute systemic availability was 6%-13% due to extensive first pass metabolism. In contrast, most of the budesonide delivered to the lungs was systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lung (as assessed by plasma concentration method and using a budesonide-containing dry powder inhaler) with an absolute systemic availability of 39% of the metered dose. Peak steady-state plasma concentrations of budesonide administered by DPI in adults with asthma averaged 0.6 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice daily, respectively.

In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both a single dose and repeated dosing of inhaled budesonide.

Distribution

The volume of distribution of budesonide was approximately 3 L/kg. It was 85%-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended inhaled doses. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism

In vitro studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16 α -hydroxy-prednisolone and 6 β -hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion/Elimination

Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine. The 22R form of budesonide was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose.

Special Populations

Nursing Mothers

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum concentration of budesonide for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide levels in plasma samples obtained from five infants at about 90 minutes after breastfeeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant) (see **PRECAUTIONS, Nursing Mothers**).

Formoterol

Absorption

Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

Over the concentration range of 10-500 nmol/L, plasma protein binding for the RR and SS enantiomers of formoterol was 46% and 58%, respectively. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54-mcg dose.

Metabolism and Excretion

The metabolism and excretion of formoterol were studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces. The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.

Pharmacodynamics

SYMBICORT

In a single-dose cross-over study involving 201 patients with persistent asthma, single-dose treatments of 4.5, 9, and 18 mcg of formoterol in combination with 320 mcg of budesonide delivered via SYMBICORT were compared to budesonide 320 mcg alone. Dose-ordered improvements in FEV₁ were demonstrated when compared with budesonide. ECGs and blood samples for glucose and potassium were obtained postdose. For SYMBICORT, small mean increases in serum glucose and decreases in serum potassium (+0.44 mmol/L and -0.18 mmol/L at the highest dose, respectively) were observed with increasing doses of formoterol, compared to budesonide. In ECGs, SYMBICORT produced small dose-related mean increases in heart rate (approximately 3 bpm at the highest dose), and QTc intervals (3-6 msec) compared to budesonide alone. No subject had a QT or QTc value \geq 500 msec.

In the United States, five 12-week, active- and placebo- controlled studies evaluated 2152 patients aged 12 years and older with asthma. Systemic pharmacodynamic effects of formoterol (heart/pulse rate, blood pressure, QTc interval, potassium, and glucose) were similar in patients treated with SYMBICORT, compared with patients treated with formoterol dry inhalation powder 4.5 mcg, two inhalations twice daily. No patient had a QT or QTc value \geq 500 msec during treatment.

In three placebo-controlled studies in adolescents and adults with asthma, aged 12 years and older, a total of 1232 patients (553 patients in the SYMBICORT group) had evaluable continuous 24-hour electrocardiographic monitoring. Overall, there were no important differences in occurrence of ventricular or supraventricular ectopy and no evidence of increased risk for clinically significant dysrhythmia in the SYMBICORT group compared to placebo.

Overall, no clinically important effects on HPA axis, as measured by 24-hour urinary cortisol, were observed for SYMBICORT-treated adult or adolescent patients at doses up to 640/18 mcg/day compared to budesonide.

Budesonide

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide, despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Inhaled budesonide has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in patients with hyperreactive airways. The clinical relevance of these models is not certain.

Pretreatment with inhaled budesonide, 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV₁ following inhaled allergen challenge.

The systemic effects of inhaled corticosteroids are related to the systemic exposure to such drugs. Pharmacokinetic studies have demonstrated that in both adults and children with asthma the systemic exposure to budesonide is lower with SYMBICORT compared with inhaled budesonide administered at the same delivered dose via a dry powder inhaler (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, SYMBICORT**). Therefore, the systemic effects (HPA axis and growth) of budesonide delivered from SYMBICORT would be expected to be no greater than what is reported for inhaled budesonide when administered at comparable doses via the dry powder inhaler (see **PRECAUTIONS, Pediatric Use**).

The effects of inhaled budesonide administered via a dry powder inhaler on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with budesonide treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 6%, and 13%, respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short-cosyntropin test) as compared to 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800, and 1600 mcg of inhaled budesonide twice daily for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6-hour ACTH infusion) while 10-mcg prednisone resulted in a 35% reduction. In this study, no patient on budesonide at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated-cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal- and stimulated-plasma cortisol) of budesonide when administered at recommended doses. In patients who had previously been oral-steroid-dependent, use of budesonide in recommended doses was associated with higher stimulated-cortisol response compared to baseline following 1 year of therapy.

Formoterol

While the pharmacodynamic effect is via stimulation of beta-adrenergic receptors, excessive activation of these receptors commonly leads to skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose. Inhaled formoterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see **PRECAUTIONS, General**). For SYMBICORT, these effects are detailed in the **CLINICAL PHARMACOLOGY, Pharmacodynamics, SYMBICORT** section.

Use of long-acting beta₂-adrenergic agonist drugs can result in tolerance to bronchoprotective and bronchodilatory effects.

Rebound bronchial hyperresponsiveness after cessation of chronic long-acting beta-agonist therapy has not been observed.

Clinical Studies

SYMBICORT has been studied in patients with asthma 12 years of age and older. In two clinical studies comparing SYMBICORT with the individual components, improvements in most efficacy end points were greater with SYMBICORT than with the use of either budesonide or formoterol alone. In addition, one clinical study showed similar results between SYMBICORT and the concurrent use of budesonide and formoterol at corresponding doses from separate inhalers.

The safety and efficacy of SYMBICORT were demonstrated in two randomized, double-blind, placebo-controlled US clinical studies involving 1076 patients 12 years of age and older. Fixed SYMBICORT dosages of 160/9 mcg, and 320/9 mcg twice daily (each dose administered as two inhalations of the 80/4.5- and 160/4.5-mcg strengths, respectively) were compared with the monocomponents (budesonide and formoterol) and placebo to provide information about appropriate dosing to cover a range of asthma severity.

Study 1: Clinical Study with SYMBICORT 160/4.5

This 12-week study evaluated 596 patients 12 years of age and older by comparing SYMBICORT 160/4.5 mcg, the free combination of budesonide 160 mcg plus formoterol 4.5 mcg in separate inhalers, budesonide 160 mcg, formoterol 4.5 mcg, and placebo; each administered as two inhalations twice daily. The study included a 2-week run-in period with budesonide 80 mcg, two inhalations twice daily. Most patients had moderate to severe asthma and were using moderate to high doses of inhaled corticosteroids prior to study entry. Randomization was stratified by previous inhaled corticosteroid treatment (71.6% on moderate- and 28.4% on high-dose inhaled corticosteroid). Mean percent predicted FEV₁ at baseline was 68.1% and was similar across treatment groups. The coprimary efficacy end points were 12-hour-average postdose FEV₁ at week 2, and predose FEV₁ averaged over the course of the study. The study also required that patients who satisfied a predefined asthma worsening criterion be withdrawn. The predefined asthma-worsening criteria were a clinically important decrease in FEV₁ or peak expiratory flow (PEF), increase in rescue albuterol use, nighttime awakening due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other asthma-worsening criteria were met. The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 1.

Table 1 – The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 1)

	SYMBICORT 160/4.5 (n=124)	Budesonide 160 mcg plus Formoterol 4.5 mcg (n=115)	Budesonide 160 mcg (n=109)	Formoterol 4.5 mcg (n=123)	Placebo (n=125)
Patients withdrawn due to predefined asthma event*	13 (10.5)	13 (11.3)	22 (20.2)	44 (35.8)	62 (49.6)
Patients with a predefined asthma event*†	37 (29.8)	24 (20.9)	48 (44.0)	68 (55.3)	84 (67.2)
Decrease in FEV ₁	4 (3.2)	8 (7.0)	7 (6.4)	15 (12.2)	14 (11.2)
Rescue medication use	2 (1.6)	0	3 (2.8)	3 (2.4)	7 (5.6)
Decrease in AM PEF	2 (1.6)	5 (4.3)	5 (4.6)	17 (13.8)	15 (12.0)
Nighttime awakening‡	24 (19.4)	11 (9.6)	29 (26.6)	32 (26.0)	49 (39.2)
Clinical exacerbation	7 (5.6)	6 (5.2)	5 (4.6)	17 (13.8)	16 (12.8)

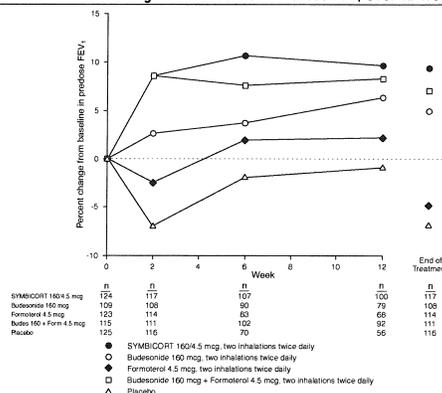
* These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV₁, which was assessed at each clinic visit.

† Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.

‡ For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in FEV₁ measured immediately prior to dosing (predose) over 12 weeks is displayed in Figure 1. Because this study used predefined withdrawal criteria for worsening asthma, which caused a differential withdrawal rate in the treatment groups, predose FEV₁ results at the last available study visit (end of treatment, EOT) are also provided. Patients receiving SYMBICORT 160/4.5 mcg had significantly greater mean improvements from baseline in predose FEV₁ at the end of treatment (0.19 L, 9.4%), compared with budesonide 160 mcg (0.10 L, 4.9%), formoterol 4.5 mcg (-0.12 L, -4.8%), and placebo (-0.17 L, -6.9%).

Figure 1 - Mean Percent Change From Baseline in Predose FEV₁ Over 12 Weeks (Study 1)



The effect of SYMBICORT 160/4.5 mcg two inhalations twice daily on selected secondary efficacy variables, including morning and evening PEF, albuterol rescue use, and asthma symptoms over 24 hours on a 0-3 scale is shown in Table 2.

Table 2 - Mean values for selected secondary efficacy variables (Study 1)

Efficacy Variable	SYMBICORT 160/4.5 (n=124)	Budesonide 160 mcg plus Formoterol 4.5 mcg (n=115)	Budesonide 160 mcg (n=109)	Formoterol 4.5 mcg (n=123)	Placebo (n=125)
AM PEF (L/min)					
Baseline	341	338	342	339	355
Change from Baseline	35	28	9	-9	-18
PM PEF (L/min)					
Baseline	351	348	357	354	369
Change from Baseline	34	26	7	-7	-18
Albuterol rescue use					
Baseline	2.1	2.3	2.7	2.5	2.4
Change from Baseline	-1.0	-1.5	-0.8	-0.3	0.8
Average symptom score/day (0-3 scale)					
Baseline	0.99	1.03	1.04	1.04	1.08
Change from Baseline	-0.28	-0.32	-0.14	-0.05	0.10

* Number of patients (n) varies slightly due to the number of patients for whom data were available for each variable. Results shown are based on last available data for each variable.

The subjective impact of asthma on patients' health-related quality of life was evaluated through the use of the standardized Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). Patients receiving SYMBICORT 160/4.5 had clinically meaningful improvement in overall asthma-specific quality of life, as defined by a mean difference between treatment groups of >0.5 points in change from baseline in overall AQLQ score (difference in AQLQ score of 0.70 [95% CI 0.47, 0.93], compared to placebo).

Study 2: Clinical Study with SYMBICORT 80/4.5

This 12-week study was similar in design to Study 1, and included 480 patients 12 years of age and older. This study compared SYMBICORT 80/4.5 mcg, budesonide 80 mcg, formoterol 4.5 mcg, and placebo; each administered as two inhalations twice daily. The study included a 2-week placebo run-in period. Most patients had mild to moderate asthma and were using low to moderate doses of inhaled corticosteroids prior to study entry. Mean percent predicted FEV₁ at baseline was 71.3% and was similar across treatment groups. Efficacy variables and end points were identical to those in Study 1.

The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 3. The method of assessment and criteria used were identical to that in Study 1.

Table 3 - The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 2)

	SYMBICORT 80/4.5 (n=123)	Budesonide 80 mcg (n=121)	Formoterol 4.5 mcg (n=114)	Placebo (n=122)
Patients withdrawn due to predefined asthma event*	9 (7.3)	8 (6.6)	21 (18.4)	40 (32.8)
Patients with a predefined asthma event†‡	23 (18.7)	26 (21.5)	48 (42.1)	69 (56.6)
Decrease in FEV ₁	3 (2.4)	3 (2.5)	11 (9.6)	9 (7.4)
Rescue medication use	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)
Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)	14 (11.5)
Nighttime awakening‡	17 (13.8)	20 (16.5)	31 (27.2)	52 (42.6)
Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)	20 (16.4)

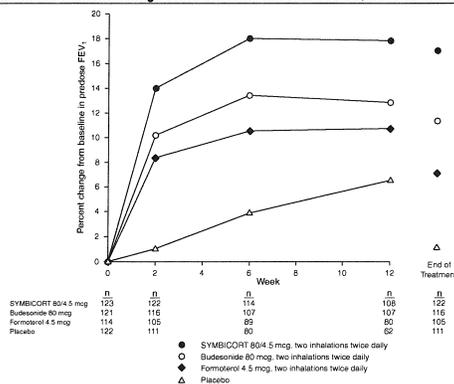
* These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV₁, which was assessed at each clinic visit.

† Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.

‡ For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in predose FEV₁ over 12 weeks is displayed in Figure 2.

Figure 2 - Mean Percent Change From Baseline in Predose FEV₁ Over 12 Weeks (Study 2)



Efficacy results for other secondary end points, including quality of life, were similar to those observed in Study 1.

Onset and Duration of Action and Progression of Improvement in Asthma Control

The onset of action and progression of improvement in asthma control were evaluated in the two pivotal clinical studies. The median time to onset of clinically significant bronchodilation (>15% improvement in FEV₁) was seen within 15 minutes. Maximum improvement in FEV₁ occurred within 3 hours, and clinically significant improvement was maintained over 12 hours. Figures 3 and 4 show the percent change from baseline in postdose FEV₁ over 12 hours on the day of randomization and on the last day of treatment for Study 1.

Reduction in asthma symptoms and in albuterol rescue use, as well as improvement in morning and evening PEF, occurred within 1 day of the first dose of SYMBICORT; improvement in these variables was maintained over the 12 weeks of therapy.

Following the initial dose of SYMBICORT, FEV₁ improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and was maintained through Week 12 for both studies.

No diminution in the 12-hour bronchodilator effect was observed with either SYMBICORT 80/4.5 mcg or SYMBICORT 160/4.5 mcg, as assessed by FEV₁, following 12 weeks of therapy or at the last available visit.

FEV₁ data from Study 1 evaluating SYMBICORT 160/4.5 mcg is displayed in Figures 3 and 4.

Figure 3 - Mean Percent Change From Baseline in FEV₁ on Day of Randomization (Study 1)

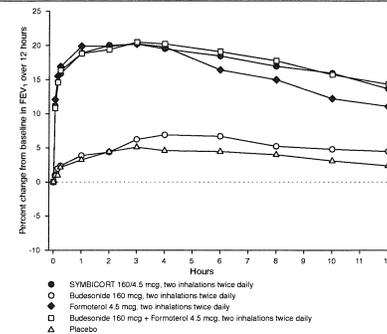
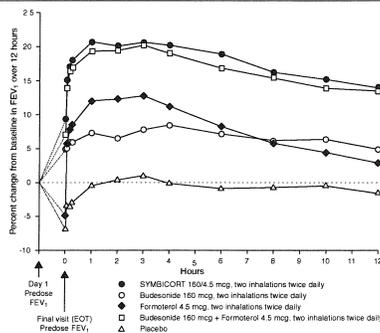


Figure 4 - Mean Percent Change From Baseline in FEV₁ At End of Treatment (Study 1)



INDICATIONS AND USAGE

SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death (see **WARNINGS**). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta₂-agonists.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

SYMBICORT is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients in SYMBICORT contraindicates its use.

WARNINGS

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

- A 28-week, placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta₂-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.

- Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

SYMBICORT Should Not Be Initiated In Patients During Rapidly Deteriorating Or Potentially Life-Threatening Episodes Of Asthma.

Do Not Use SYMBICORT to Treat Acute Symptoms. SYMBICORT should not be used to treat acute symptoms of asthma. An inhaled, short-acting beta₂-agonist (eg, albuterol), should be used to relieve acute asthma symptoms. Therefore, when prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SYMBICORT.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (eg, 4 times a day) should be instructed to discontinue the regular use of these drugs. For patients on SYMBICORT, short-acting, inhaled beta₂-agonists should only be used for symptomatic relief of acute asthma symptoms (see **PRECAUTIONS, Information for Patients**).

Watch for Increasing Use of Inhaled, Short-Acting Beta₂-Agonists, Which is a Marker of Deteriorating Asthma. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta₂-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in lung function, these may be markers of destabilization of asthma. In this setting, the patient requires immediate reevaluation and reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than two actuations twice daily (morning and evening) of SYMBICORT.

SYMBICORT Should Not be Used For Transferring Patients from Systemic Corticosteroid Therapy. Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months may be required for recovery of HPA function. Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although inhaled corticosteroid therapy may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Do Not Use an Inhaled, Long-Acting Beta₂-Agonist in Conjunction With SYMBICORT. Patients who are receiving SYMBICORT twice daily should not use additional formoterol or other long-acting inhaled beta₂-agonists (eg, salmeterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be gained from using supplemental formoterol or salmeterol for prevention of EIB since SYMBICORT already contains an inhaled, long-acting beta₂-agonist.

Do Not Exceed Recommended Dosage. SYMBICORT should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. In addition, data from clinical studies with formoterol dry powder inhaler suggest that the use of doses higher than recommended (24 mcg twice daily) is associated with an increased risk of serious asthma exacerbations. In a 52-week active-controlled safety study evaluating SYMBICORT 160/4.5, patients treated with twice the highest recommended dose of SYMBICORT demonstrated a similar safety profile to that of patients treated with the highest recommended dose.

Paradoxical Bronchospasm. As with other inhaled asthma medications, SYMBICORT may produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, treatment with SYMBICORT should be discontinued immediately and alternate therapy should be instituted.

Immediate Hypersensitivity Reactions. Immediate hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm may occur after administration of SYMBICORT.

Cardiovascular Disorders. SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Formoterol, a component of SYMBICORT, may produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of SYMBICORT at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown.

Discontinuation of Systemic Corticosteroids. Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids may unmask conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, eczema, and arthritis.

Immunosuppression. Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can

have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is unknown how the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient on immunosuppressant doses of corticosteroids is exposed to chicken pox, therapy with varicella zoster immune globulin (VZIG) or pooled intramuscular immunoglobulin (IG), as appropriate may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension (see **PRECAUTIONS, Drug Interactions**).

PRECAUTIONS

General

Sympathomimetic Effects. The cardiovascular and central nervous system effects seen with all sympathomimetic drugs (eg, increased blood pressure, heart rate, excitement) can occur after use of formoterol, a component of SYMBICORT, and may require discontinuation of SYMBICORT. SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, untreated hypokalemia, or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically important changes in electrocardiograms, systolic and/or diastolic blood pressure, and pulse rate were seen infrequently in individual patients during controlled clinical studies with SYMBICORT at recommended doses.

Metabolic and Other Effects. Long-term use of orally inhaled corticosteroids, such as budesonide, a component of SYMBICORT, may affect normal bone metabolism resulting in a loss of bone mineral density. In patients with major risk factors for decreased bone mineral content, such as tobacco use, advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants and corticosteroids), orally inhaled corticosteroids may pose an additional risk.

Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. High doses of beta-adrenergic agonist medications may produce significant hypokalemia in some patients, through intracellular shunting, which may have the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically important changes in blood glucose and/or serum potassium were seen rarely during clinical studies with SYMBICORT at recommended doses.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Budesonide, a component of SYMBICORT, will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active, patients should not exceed the recommended dosage of SYMBICORT. Individual patients should be titrated to the lowest effective dose in order to minimize HPA dysfunction. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing SYMBICORT.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, the total daily dose of SYMBICORT should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

Budesonide, a component of SYMBICORT, may cause a reduction in growth velocity when administered to pediatric patients. Patients should be maintained on the lowest dose of SYMBICORT that effectively controls their asthma (see **PRECAUTIONS, Pediatric Use**).

The long-term effects resulting from chronic use of budesonide on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown. The local and systemic effects of SYMBICORT in humans have been studied for up to one year (see **ADVERSE REACTIONS, Long Term Safety**).

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT.

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT. In the three placebo-controlled US clinical studies, the incidence of lower respiratory tract infections, including pneumonia, was low, with no consistent evidence of increased risk for SYMBICORT compared to placebo.

In clinical studies with SYMBICORT, localized infections with *Candida albicans* have occurred in

the mouth and pharynx. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing with SYMBICORT therapy, but at times, the dose of SYMBICORT may need to be temporarily decreased or interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill.

Patients being treated with SYMBICORT should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use the SYMBICORT inhaler device appropriately and how SYMBICORT should be used in relation to other asthma medications they are taking.

- Patients should be informed that long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death.** Patients should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, such as budesonide, the other component of SYMBICORT, or other asthma-controller therapy modifies this risk.
- Patients should be instructed that the correct dose of SYMBICORT is two puffs inhaled twice daily of the appropriate dosage strength, 80/4.5 or 160/4.5. They should take two puffs of SYMBICORT in the morning and two puffs in the evening every day. The maximum daily recommended dose is 640/18 mcg budesonide/formoterol (given as two inhalations of SYMBICORT 160/4.5 twice daily). Do not use more than twice daily or use a higher number of inhalations (more than two inhalations twice daily) of the prescribed strength of SYMBICORT as this will result in a daily dose of formoterol in excess of the dose determined to be safe. **Patients should also be instructed not to take SYMBICORT more often or use more puffs than you have prescribed.** If they miss a dose, they should be instructed to take their next dose at the same time they normally do.
- SYMBICORT is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose.** Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient on how it should be used).
- The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma:
 - Decreasing effectiveness of inhaled, short-acting beta₂-agonists
 - Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
 - Significant decrease in lung function as outlined by the physician
 - Marked change in symptoms
- When patients are prescribed SYMBICORT, other inhaled drugs and asthma medications should be used only as directed by a physician. Patients should be instructed about the differences between SYMBICORT and their other inhaled medications including the differences in intended use and physical appearance.
- Patients who are receiving SYMBICORT should not use formoterol or another long-acting inhaled beta₂-agonist for prevention of exercise-induced bronchospasm or maintenance treatment of asthma.
- Patients should not stop therapy with SYMBICORT without physician/provider guidance since symptoms may recur after discontinuation.
- Patients should be cautioned regarding common adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- Patients should be warned to avoid exposure to chicken pox or measles and if they are exposed, to consult their physician without delay.
- Long-term use of inhaled corticosteroids, including budesonide, a component of SYMBICORT, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
- If the patient is pregnant or nursing, the physician should be contacted about the use of SYMBICORT.
- Results of clinical trials indicate that in most patients, clinically significant improvement occurred within 15 minutes of beginning treatment with SYMBICORT. The maximum benefit may not be achieved for 2 weeks or longer after starting treatment. Individual patients may experience a variable time to onset and degree of symptom relief.
- The bronchodilation from a dose (two inhalations) of SYMBICORT has been shown to last up to 12 hours or longer. The recommended dosage should not be exceeded.
- The following measures should be observed when using SYMBICORT:
 - Patients should not attempt to take the inhaler apart.
 - SYMBICORT should be primed before using the first time and also when the inhaler has not been used for more than 7 days or when it has been dropped, by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray.
 - Patients should replace the mouthpiece cover after each use.
 - To remove any excess medication, patients should rinse their mouth with water after each dose (do not swallow) to decrease the risk of the development of oral candidiasis.

- Patients should clean the inhaler every 7 days by wiping the mouthpiece with a dry cloth.
- Use SYMBICORT only with the actuator supplied with the product.
- When the counter approaches the yellow zone, which shows that the inhaler is close to being empty, contact your healthcare provider for a refill of the inhaler. Discard the inhaler when the counter reaches zero ("0").
- Never try to remove the counter from the top of the metal canister.
- Never immerse the canister in water to determine the amount of drug remaining in the canister.
- Store in a dry place at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP] and out of the reach of children.

Drug Interactions

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta₂-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse events. No formal drug interaction studies have been performed with SYMBICORT.

Short-Acting Beta₂-Agonists: In three 12-week, placebo-controlled US clinical studies, the mean daily need for albuterol rescue use in 401 adult and adolescent patients using SYMBICORT twice daily was approximately 0.8 inhalations/day, and ranged from 0 to 14 inhalations/day. Approximately 2% (n=8) of the SYMBICORT patients in these studies averaged six or more inhalations per day. No cardiac adverse events were reported in these patients.

Methylxanthines and leukotriene modifying agents: The concurrent use of intravenously or orally administered methylxanthines (eg, aminophylline, theophylline) by patients receiving SYMBICORT has not been completely evaluated. In clinical trials with SYMBICORT, a limited number of patients received concurrent methylxanthines or leukotriene modifying agents, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Intranasal and systemic corticosteroids: Among adult and adolescent patients participating in active- and placebo-controlled US clinical trials, twice daily SYMBICORT was used concurrently with intranasal budesonide in 105 patients and with any intranasal corticosteroid in 585 patients. Two hundred seventeen patients used courses of systemic corticosteroids while taking SYMBICORT. There were no important differences noted in the adverse event profiles between these groups.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents: Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non-potassium-sparing diuretics.

Ketoconazole and Other Inhibitors of Cytochrome P450: The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known potent CYP3A4 inhibitors.

Varicella Vaccine: An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (ie, beta₂-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Budesonide

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum

recommended human daily inhalation dose on a mcg/m² basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m² basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m² basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis).

Formoterol

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of formoterol fumarate.

In a 24-month carcinogenicity study in CD-1 mice, formoterol at oral doses of 0.1 mg/kg and above (approximately 20 times the maximum recommended human daily inhalation dose on a mcg/m² basis) caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 15 mcg/kg (approximately 60 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No tumors were seen at 22 mcg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

Other beta-agonist drugs, have similarly demonstrated increases in leiomyomas of the genital tract in female rodents. The relevance of these findings to human use is unknown.

Formoterol was not mutagenic or clastogenic in Ames *Salmonella*/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, and rat micronucleus test.

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). In a separate study with male rats treated with an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No such effect was seen at 3 mg/kg (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No effect on fertility was detected in female rats at doses up to 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

Pregnancy

SYMBICORT

Teratogenic Effects: Pregnancy Category C

SYMBICORT has been shown to be teratogenic and embryocidal in rats when given at inhalation doses of 12/0.66 mcg/kg (budesonide/formoterol) and above (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). Umbilical hernia, a malformation, was observed for fetuses at doses of 12/0.66 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). No teratogenic or embryocidal effects were detected at 2.5/0.14 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis). There are no adequate and well-controlled studies in pregnant women. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Budesonide

Teratogenic Effects

As with other corticosteroids, budesonide has been shown to be teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) and 500 mcg/kg/day in rats (approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m² basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg/day (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to

physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Formoterol

Teratogenic Effects

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Umbilical hernia, a malformation, was observed in rat fetuses at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Brachygnathia, a skeletal malformation, was observed in rat fetuses at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Pregnancy was prolonged at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). In another study in rats, no teratogenic effects were seen at inhalation doses up to 1.2 mg/kg/day (approximately 500 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

Formoterol fumarate has been shown to be teratogenic in rabbits when given at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No teratogenic effects were observed at oral doses up to 3.5 mg/kg (approximately 3200 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

There are no adequate and well-controlled studies with formoterol in pregnant women.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Use in Labor and Delivery

There are no well-controlled human studies that have investigated the effects of SYMBICORT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers

Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother.

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Budesonide, Special Populations, Nursing Mothers**). For SYMBICORT, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

Pediatric Use

Safety and effectiveness of SYMBICORT in patients 12 years of age and older have been established in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age group compared with patients 18 years of age and older.

The effectiveness of SYMBICORT in patients 6 to <12 years of age has not been established.

Overall 1447 patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5–12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of 4 years, children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, each patient should be titrated to the lowest strength that effectively controls his/her asthma (see **DOSE AND ADMINISTRATION**).

Geriatric Use

In three 12-week, double-blind, placebo-controlled US clinical studies, 17 patients treated with SYMBICORT twice daily were 65 years of age or older, of whom two were 75 years of age or older. Of the total number of patients in clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom 25 were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients. As with other products containing beta₂-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric patients is warranted.

ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death (See **Boxed WARNING, WARNINGS, and PRECAUTIONS** sections).

The incidence of common adverse events in the table below is based upon three 12-week, double-blind, placebo-controlled US clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated twice daily with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5, budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebos (MDI and DPI).

Table 4 - Adverse Events (regardless of causality) Occurring at an Incidence of ≥3% and more Commonly than Placebo in any SYMBICORT Group

Treatment*	SYMBICORT		Budesonide HFA MDI		Formoterol DPI	Placebo MDI and DPI
	80/4.5 mcg n=277 (%)	160/4.5 mcg n=124 (%)	80 mcg n=121 (%)	160 mcg n=109 (%)		
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	77.7	73.8	77.0	71.4	62.4	55.9

* All treatments were administered as two inhalations twice daily.

The table above includes all events (whether or not considered drug-related by the investigators) that occurred at an incidence of ≥3% in any one SYMBICORT group and that were more common than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for unequal treatment duration.

The following additional adverse events occurred in patients ≥12 years of age in the active- and placebo-controlled clinical studies among 2344 patients treated with SYMBICORT twice daily with an incidence of ≥1% to <3%, regardless of relationship to treatment, and are listed in decreasing order of incidence: asthma, nausea, dysphonia, pyrexia, sinus headache, diarrhea, pharyngitis, tremor, lower respiratory tract infection, muscle spasms, urinary tract infection, rhinitis,

arthralgia, myalgia, dyspepsia, gastroenteritis viral, abdominal pain upper, dizziness, sinus congestion, rhinitis allergic, pain in extremity, palpitations, bronchitis acute, tension headache, migraine, postprocedural pain. Additionally, the incidence of cough, bronchitis, and viral upper-respiratory-tract infection was ≥3% (but each <4%) in this population but did not meet criteria for inclusion in the above table, as these data are not derived from placebo-controlled trials for subjects ≥12 years old.

The following adverse events occurred in this same population (patients ≥12 years of age) with an incidence <1%, and are listed because they have previously been reported during treatment with any formulation of inhaled SYMBICORT, budesonide and/or formoterol, regardless of the indication: immediate and delayed hypersensitivity reactions, eg, rash, pruritus, urticaria, angioedema; cardiac events, eg, tachycardia, coronary ischemia, atrial and ventricular tachyarrhythmias; variations in blood pressure, eg, hypotension, hypertension, hypertensive crisis; hypokalemia; hyperglycemia; taste disturbance; psychiatric symptoms, eg, irritability, anxiety, restlessness, nervousness, agitation, depression; skin bruising.

Long-Term Safety: Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Adverse Event Reports From Other Sources: Other relevant rare adverse events reported in the published literature, clinical trials or from worldwide marketing experience with any formulation of inhaled SYMBICORT, budesonide and/or formoterol, regardless of the indication include: immediate hypersensitivity reactions, such as anaphylactic reaction and bronchospasm; symptoms of hypocorticism and hypercorticism; glaucoma, cataracts; psychiatric symptoms, including aggressive reactions, behavioral disturbances, psychosis.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, a total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma and was well tolerated. In a long-term active-controlled safety study, SYMBICORT 160/4.5 was well tolerated for up to 12 months at doses up to twice the highest recommended daily dose.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarrh, redness of intact skin, abdominal respiration, vomiting, and salivation; in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation doses of 97 and 3 mg/kg, respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No deaths occurred in dogs given a combination of budesonide and formoterol at the acute inhalation doses of 732 and 22 mcg/kg, respectively (approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol on a mcg/m² basis).

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see **PRECAUTIONS**). Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

In mice, the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mcg/m² basis). In rats, there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m² basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta₂-agonists; therefore, the following adverse experiences may occur: angina, hypertension or hypotension, palpitations, tachycardia, arrhythmia, prolonged QTc-interval, headache, tremor, nervousness, muscle cramps, dry mouth, insomnia, fatigue, malaise, seizures, metabolic acidosis, hypokalemia, hyperglycemia, nausea and vomiting. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. Formoterol was well tolerated at a delivered dose of 90 mcg/day over 3 hours in adult patients with acute bronchoconstriction and when given three times daily for a total dose of 54 mcg/day for 3 days to stable asthmatics.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardio-selective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

In rats, the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Maximum nonlethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m² basis).

DOSAGE AND ADMINISTRATION

SYMBICORT should be administered by the orally inhaled route in patients with asthma 12 years of age and older. SYMBICORT should not be used for transferring patients from systemic corticosteroid therapy.

Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death (see **WARNINGS**). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT is not indicated for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled short-acting beta₂-agonists.

SYMBICORT is available in two strengths, SYMBICORT 80/4.5 and SYMBICORT 160/4.5, containing 80 and 160 mcg of budesonide, respectively, and 4.5 mcg of formoterol fumarate dihydrate per inhalation. Each dose is administered as two inhalations twice daily (in the morning and the evening) by the orally inhaled route only. Rinsing the mouth after every dose is advised.

For patients who are currently receiving medium to high doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is SYMBICORT 160/4.5, two inhalations twice daily.

For patients who are currently receiving low to medium doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is SYMBICORT 80/4.5, two inhalations twice daily.

For patients who are not currently receiving inhaled corticosteroid therapy, but whose disease severity clearly warrants initiation of treatment with two maintenance therapies, the recommended starting dose is SYMBICORT 80/4.5 or 160/4.5, two inhalations twice daily depending upon asthma severity.

If a previously effective dosage regimen of SYMBICORT fails to provide adequate control of asthma, the therapeutic regimen should be reevaluated and additional therapeutic options, eg, replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

The maximum daily recommended dose is 640/18 mcg budesonide/formoterol (given as two inhalations of SYMBICORT 160/4.5 twice daily) for patients 12 years of age and older. Do not use more than twice daily or use a higher number of inhalations (more than two inhalations twice daily) of the prescribed strength of SYMBICORT as this will result in a daily dose of formoterol in excess of the dose determined to be safe. For all patients, consideration should be given to titrating to the lowest effective strength after adequate asthma stability has been achieved.

SYMBICORT is not approved for the treatment or prevention of exercise-induced bronchospasm. Patients who are receiving SYMBICORT twice daily should not use formoterol or other long-acting beta₂-agonists for prevention of exercise-induced bronchospasm, or for any other reason. If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

In clinical studies, significant improvement in FEV₁ occurred within 15 minutes of beginning treatment with SYMBICORT in most patients, and improvement in asthma control (asthma symptoms, albuterol rescue use, PEF) occurred within 1 day. The maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients may experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with SYMBICORT 80/4.5, replacing the strength with SYMBICORT 160/4.5 may provide additional asthma control.

SYMBICORT should be primed before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing two test sprays into the air away from the face.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see **PRECAUTIONS, Geriatric Use**) have been treated with SYMBICORT, efficacy and safety did not differ from that in younger patients. Based on available data for SYMBICORT and its active components, no dosage adjustment is recommended.

HOW SUPPLIED

SYMBICORT is available in two strengths and is supplied in the following package sizes:

Package Size	NDC
SYMBICORT 160/4.5, 120 inhalations	NDC 0186-0370-20
SYMBICORT 160/4.5, 60 inhalations (institutional pack)	NDC 0186-0370-28
SYMBICORT 80/4.5, 120 inhalations	NDC 0186-0372-20
SYMBICORT 80/4.5, 60 inhalations (institutional pack)	NDC 0186-0372-28

Each strength is supplied as a pressurized aluminum canister that has a shield component, and a red plastic actuator body with white mouthpiece and attached gray dust cap. Each 120 inhalation canister has a net fill weight of 10.2 grams and each 60 inhalation canister has a net fill weight of 6 grams (SYMBICORT 160/4.5) or 6.9 grams (SYMBICORT 80/4.5). Each canister is packaged in a foil overwrap pouch with desiccant sachet and placed into a carton. Each carton contains one canister and a Medication Guide.

The SYMBICORT canister should only be used with the SYMBICORT actuator, and the SYMBICORT actuator should not be used with any other inhalation drug product.

The correct amount of medication in each inhalation cannot be ensured after the counter reaches zero ("0"), even though the inhaler may not feel completely empty and may continue to operate. The inhaler should be discarded when the counter reaches zero ("0") (indicating that the labeled number of inhalations have been used) or within 3 months after removal from the foil pouch. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

Store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP]. Store the inhaler with the mouthpiece down.

For best results, the canister should be at room temperature before use. Shake well for 5 seconds before using.

Keep out of the reach of children. Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store near heat or open flame. Exposure to temperatures over 120°F may cause bursting. Never throw container into fire or incinerator.

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MEDICATION GUIDE

SYMBICORT® 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg)

Inhalation Aerosol

SYMBICORT® 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg)

Inhalation Aerosol

Read the Medication Guide that comes with SYMBICORT before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SYMBICORT?

- SYMBICORT contains 2 medicines:
 - Budesonide (the same medicine found in PULMICORT TURBUHALER®), an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
 - Formoterol (the same medicine found in FORADIL AEROLIZER®), a long-acting beta₂-agonist medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and may lead to death if not treated right away.
- **In patients with asthma, LABA medicines such as formoterol (one of the medicines in SYMBICORT) may increase the chance of death from asthma problems.** In a large asthma study, more patients who used another LABA medicine, died from asthma problems compared with patients who did not use that LABA medicine. Talk with your healthcare provider about this risk and the benefits of treating your asthma with SYMBICORT.
- **SYMBICORT does not relieve sudden symptoms. Always have an inhaled short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have this type of medicine, contact your healthcare provider to have one prescribed for you.**
- **Do not stop using SYMBICORT unless told to do so by your healthcare provider because your symptoms might get worse.**
- **SYMBICORT should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need two asthma-controller medicines.**
- **Call your healthcare provider if breathing problems worsen over time while using SYMBICORT. You may need different treatment.**
- **Get emergency medical care if:**
 - Breathing problems worsen quickly, and
 - You use your short-acting beta₂-agonist medicine, but it does not relieve your breathing problems.

What is SYMBICORT?

SYMBICORT combines an inhaled corticosteroid medicine, budesonide (the same medicine found in PULMICORT TURBUHALER), and a long-acting beta₂-agonist medicine (LABA), formoterol (the same medicine found in FORADIL AEROLIZER).

SYMBICORT is used long-term, twice a day, everyday to control symptoms of asthma, and prevent symptoms such as wheezing in patients 12 years of age and older.

SYMBICORT contains formoterol (the same medicine found in FORADIL AEROLIZER). Because LABA medicines such as formoterol may increase the chance of death from asthma problems, SYMBICORT is not for patients with asthma who:

- are well controlled with another asthma-controller medicine such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta₂-agonist medicines once in awhile

What should I tell my healthcare provider before using SYMBICORT?

Tell your healthcare provider about all of your health conditions, including if you:

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- have liver problems
- have osteoporosis
- have an immune system problem
- are pregnant or planning to become pregnant. It is not known if SYMBICORT may harm your unborn baby.
- are breastfeeding. It is not known if SYMBICORT passes into your milk and if it can harm your baby.
- are allergic to SYMBICORT or any other medicines
- are exposed to chicken pox or measles

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SYMBICORT and certain other medicines may interact with each other. This may cause serious side effects.

Know all the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

How do I use SYMBICORT?

See the step-by-step instructions for using SYMBICORT at the end of this Medication Guide. Do not use SYMBICORT unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Use SYMBICORT exactly as prescribed. **Do not use SYMBICORT more often than prescribed.** SYMBICORT comes in two strengths. Your healthcare provider has prescribed the strength that is best for you. Note the differences between SYMBICORT and your other inhaled medications, including the differences in prescribed use and physical appearance.
- SYMBICORT should be taken as two puffs in the morning and two puffs in the evening every day. If you miss a dose of SYMBICORT, you should take your next dose at the same time you normally do. Do not take SYMBICORT more often or use more puffs than you have been prescribed.
- Rinse your mouth with water after each dose (two puffs) of SYMBICORT.
- **While you are using SYMBICORT twice a day, do not use other medicines that contain a long-acting beta₂-agonist (LABA) for any reason, such as SEREVENT DISKUS (salmeterol xinafoate inhalation powder), ADVAIR DISKUS or ADVAIR HFA (fluticasone propionate and salmeterol), or FORADIL AEROLIZER (formoterol fumarate inhalation powder).**
- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.
- Make sure you always have a short-acting beta₂-agonist medicine with you. Use your short-acting beta₂-agonist medicine if you have breathing problems between doses of SYMBICORT.
- **Call your healthcare provider or get medical care right away if:**
 - your breathing problems worsen with SYMBICORT
 - you need to use your short-acting beta₂-agonist medicine more often than usual

continued

- your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms
- you need to use four or more inhalations of your short-acting beta₂-agonist medicine for 2 or more days in a row
- you use one whole canister of your short-acting beta₂-agonist medicine in 8 weeks' time
- your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
- your asthma symptoms do not improve after using SYMBICORT regularly for 1 week.

What are the possible side effects with SYMBICORT?

SYMBICORT contains formoterol. In patients with asthma, LABA medicines such as formoterol may increase the chance of death from asthma problems. See "What is the most important information I should know about SYMBICORT?"

Other possible side effects with SYMBICORT include:

- **serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems.** Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- **chest pain**
- **increased blood pressure**
- **a fast and irregular heartbeat**
- **headache**
- **tremor**
- **nervousness**
- **immune system effects and a higher chance for infections**
- **eye problems including glaucoma and cataracts.** Regular eye exams should be considered while using SYMBICORT.
- **lower bone mineral density.** This may be a problem for people who already have a higher chance for low bone mineral density (osteoporosis).
- **slowed growth in children.** A child's growth should be checked often.
- **throat irritation.**

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with SYMBICORT. Ask your healthcare provider or pharmacist for more information.

How do I store SYMBICORT?

- Store SYMBICORT at room temperature 68°F to 77°F (20°C to 25°C). Store with the mouthpiece down.
- The contents of your SYMBICORT canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120°F may cause the canister to burst.
- **Keep SYMBICORT and all medicines out of the reach of children.**

General Information about SYMBICORT

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use SYMBICORT for a condition for which it was not prescribed. Do not give your SYMBICORT to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about SYMBICORT. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SYMBICORT that was written for healthcare professionals. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You can also contact the company that makes SYMBICORT (toll free) at 1-800-236-9933 or visit our web site at www.MySymbicort.com.

HOW TO USE SYMBICORT

Follow the instructions below for using SYMBICORT. You will breathe-in (inhale) the medicine. If you have any questions, ask your doctor or pharmacist.

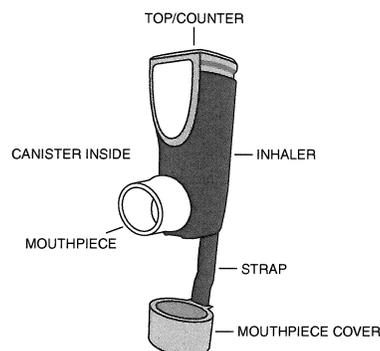


Figure 1

PREPARING YOUR INHALER FOR USE

1. Take your SYMBICORT inhaler out of the moisture-protective foil pouch before you use it for the first time and throw the foil away. Write the date that you open the foil pouch on the box.
2. A counter is attached to the top of the metal canister. The counter will count down towards zero ("0"). Each time you release a puff from the inhaler, the number will count down by 1. The arrow points to the number of inhalations (puffs) remaining in the canister. The counter will stop counting at zero ("0"). You should discard the inhaler when the counter reaches zero ("0"), indicating that the labeled number of inhalations have been used or within 3 months of opening the foil pouch.
3. Use the SYMBICORT canister only with the red SYMBICORT inhaler supplied with the product. Parts of the SYMBICORT inhaler should not be used with parts from any other inhalation drug product.
4. **SHAKE THE INHALER WELL** for 5 seconds right before each use. Remove the mouthpiece cover. Check the mouthpiece for foreign objects prior to use.
5. SYMBICORT should be primed before using it for the first time and also when the inhaler has not been used for more than 7 days or when it has been dropped. Prime the inhaler by shaking the inhaler well for 5 seconds and then releasing a test spray. Then shake the inhaler again and release a second test spray. Your inhaler is now primed and ready for use. After you have primed the inhaler for the first time, the counter will read either 120 or 60, depending on whether you have a filled prescription (120) or an institutional or sample pack (60).

Do not spray the medicine in your eyes during priming or use.

continued

WAYS TO HOLD THE INHALER FOR USE

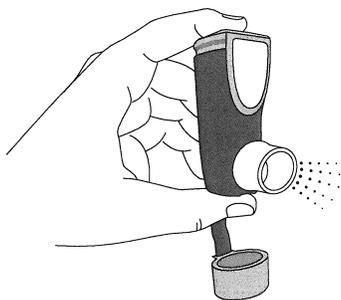


Figure 2

OR

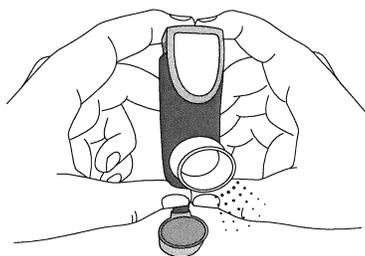


Figure 3

USING YOUR SYMBICORT INHALER

6. SHAKE THE INHALER WELL for 5 seconds. Remove the mouthpiece cover. Check the mouthpiece for foreign objects.
7. Breathe out fully (exhale). Raise the inhaler up to your mouth. Place the white mouthpiece fully into your mouth and close your lips around it. Make sure that the inhaler is upright and that the opening of the mouthpiece is pointing towards the back of your throat (see Figure 4).



Figure 4

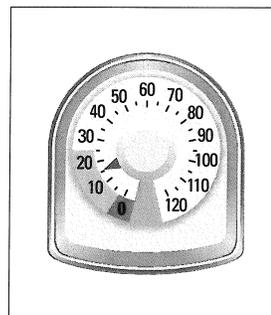
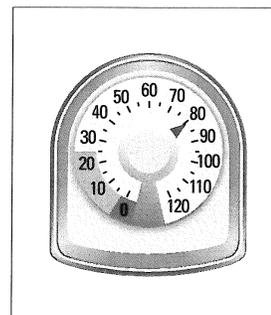
8. While breathing in deeply and slowly through your mouth, press down firmly and fully on the top of the counter on the inhaler to release the medicine (see Figures 2 and 3).
9. Continue to breathe in and hold your breath for about 10 seconds, or for as long as is comfortable. Before breathing out, release your finger from the top of the counter and remove the inhaler from your mouth while keeping the inhaler upright.
10. Shake the inhaler again for 5 seconds and repeat steps 7 through 9.

AFTER USING YOUR SYMBICORT INHALER

11. Replace the mouthpiece cover after use.
12. After you finish taking this medicine (two puffs), rinse your mouth with water. Spit out the water. Do not swallow it.

READING THE COUNTER

- The arrow on the counter on the top of the inhaler points to the number of inhalations (puffs) remaining in your inhaler.
- The counter will count down toward zero ("0") each time you release a puff of medicine (either when preparing your inhaler for use or when taking the medicine).
- When the arrow on the counter approaches 20, you will notice the beginning of a yellow colored zone, indicating that it is time to call for a refill.
- It is very important that you note the number of inhalations (puffs) remaining in your SYMBICORT inhaler by reading the counter. Discard SYMBICORT after the counter reaches zero ("0"), indicating that you have used the number of inhalations on the product label and box. Your inhaler may not feel empty and it may continue to operate, but you will not get the right amount of medicine if you keep using it.



OTHER IMPORTANT INFORMATION ABOUT YOUR SYMBICORT INHALER

SYMBICORT should be discarded within 3 months after it is taken out of its foil pouch.

- For best results, use and store at room temperature. Avoid exposing product to extreme heat and cold. Store with the mouthpiece down.

How to Clean your SYMBICORT Inhaler

Clean the white mouthpiece of the inhaler every 7 days. To clean the mouthpiece:

- Remove the grey mouthpiece cover
- Wipe the inside and outside of the white mouthpiece opening with a clean, dry cloth
- Replace the mouthpiece cover
- **Do not put the inhaler into water**
- Do not try to take the inhaler apart

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