

Foradil[®] (formoterol fumarate inhalation powder)

FDA Advisory Committee Meeting on the safety of long-acting beta₂-agonists for the treatment of asthma in adults and children (December 10-11, 2008)

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List of abbreviations

AE	Adverse event
AUC	Area under the curve
BHR	Bronchial hyper-responsiveness
BID	Twice daily
CI	Confidence Interval
CDC	Center for Disease Control
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
HCP	Healthcare Provider
ICS	Inhaled corticosteroid
MedDRA	Medical Dictionary for Regulatory Activities
MDDPI	Multi-dose dry powder inhaler
MDI	Metered dose inhaler
NHLBI	National Heart, Lung, and Blood Institute
OR	Odds ratio
PADAC	Pulmonary-Allergy Drugs Advisory Committee
PC ₂₀	provocation concentration required to cause a 20% fall in FEV ₁ (after methacholine challenge)
PEF	Peak expiratory flow
PMS	Post-marketing surveillance
QID	Four times a day
SAE	Serious adverse event
SMQ	Standardized Medical Queries
SRS/AERS	Spontaneous reporting system/ Adverse events reporting system
TDD	Total daily dose
USA	United States of America
VGDS	Voluntary Genomic Data Submission

1 Executive summary

This briefing document provides background information for the members of the FDA Pulmonary-Allergy Drugs Advisory Committee, the Drug Safety and Risk Management Advisory Committee and the Pediatric Advisory Committee in advance of their joint committee meeting scheduled for December 10-11, 2008 to discuss the benefit:risk assessment of long-acting beta₂-agonists for the treatment of asthma in adults and children. This document presents the analysis and perspective of Novartis on the benefit:risk profile of Foradil® Aerolizer® (formoterol fumarate inhalation powder) 12 mcg twice daily (BID) (24 mcg total daily dose [TDD] approved in USA) in children and adults and an assessment of the risk of serious asthma exacerbations, including events resulting in death, intubation or hospitalization.

Safety - Clinical Trial Database

In the pooled analyses of Novartis-sponsored, blinded, controlled asthma studies, a total of 8,369 subjects were enrolled in 45 trials, including 3,129 patients treated with formoterol 24 mcg TDD, 2026 patients receiving placebo, and 976 patients treated with regularly dosed (four times a day [QID]) albuterol. Other formoterol doses analyzed include formoterol 12 mcg TDD (n=585) and formoterol 48 mcg TDD (n=1,515). Analyses in this document focus on comparisons between the approved dose of formoterol (24 mcg TDD), placebo and albuterol.

There were no deaths or intubations among the 1,744 pediatric subjects (ages 5–18). Among the 6,625 subjects older than 18 years of age, one asthma-related death occurred in a 66-year-old woman who had received formoterol 48 mcg TDD (twice the daily US approved dose) with no reported use of concomitant inhaled corticosteroids (ICS).

The overall analysis of serious asthma exacerbations revealed an increase among patients randomized to formoterol 24 mcg TDD versus placebo, demonstrating a point estimate of 1.8 that was not statistically significant (odds ratio [OR] 1.8, 95% CI 0.8–4.0). The number of events per 100 patient years was 2.7 (formoterol) versus 1.4 (placebo) versus 4.5 (albuterol).

In pediatric patients 5–12 years of age, the rate of serious asthma exacerbations among patients treated with formoterol was significantly higher than the rate among patients treated with placebo (OR 8.4, 95% CI 1.1–65.3). The number of events per 100 patient years was 5.4 (formoterol) versus 0.6 (placebo) versus 16.2 (albuterol). Most of the pediatric data was obtained from a 1-year trial conducted during the period of 1996–1998 that is described in the current Foradil Aerolizer label.

The number of pediatric patients 13–18 years of age was small (n=512). Those randomized to formoterol did not demonstrate a significant increase of serious asthma exacerbations versus placebo.

In patients older than 18 years of age, the OR versus placebo was 1.3 (95% CI 0.4–3.7) with an event rate of 1.9 per 100 patient years versus 1.4 for placebo and 3.1 for albuterol.

In all age groups, patients treated with formoterol demonstrated fewer serious asthma exacerbations compared to patients treated with albuterol administered QID.

None of the trials included in these analyses was designed to assess the effect of concomitant inhaled corticosteroids on serious asthma exacerbations. Furthermore, in only one study was inhaled corticosteroid use randomized; therefore, the question of whether inhaled corticosteroids mitigate the risk of serious asthma exacerbations in patients on formoterol cannot be definitively answered by these analyses. Among patients 13 – 18 years of age and greater than 18 years of age, there was a trend towards fewer serious asthma exacerbations in subjects reporting the use of concomitant inhaled corticosteroids (13–18 years: OR 0.8, 95% CI 0.1–12.3; >18 years: OR 0.6, 95% CI 0.2 –2.2). In patients 5–12 years of age, the impact of concomitant use of inhaled corticosteroids appears to be less (OR 7.8, 95% CI 1.0–61.3).

Safety – Post-marketing data

Asthma-related mortality has steadily declined from 2000 until 2004, the last year for which CDC data is available. At that time, asthma mortality was 1.9 per 10,000 patients with asthma. Foradil was introduced to the US market in 2001. Since approval, an estimated 4.6 million prescriptions have been filled. Although post-marketing data from the FDA Spontaneous Reporting System and Adverse Event Reporting System (SRS/AERS) database is limited, analysis of the available information on US cases from 2001-2008 indicates that the number of asthma-related serious adverse events (SAEs) for Foradil is 2.1 per 100,000 prescriptions (97 cases) and 0.17 per 100,000 prescriptions for asthma-related death. During this time, there have been no confirmed spontaneous reports of fatal asthma exacerbations among children (< 18 years of age), and six fatal reports in adults older than 18 years. Two fatal events have been reported in patients of unknown age.

The Novartis safety database captures global spontaneous reports. During the 3-year period from June 1, 2005 to May 31, 2008, there have been approximately 3.5 million patient years of treatment with Novartis formoterol products. During this period, there have been 72 spontaneous cases of asthma-related SAEs reported. Of these, 3 cases had a fatal outcome, none of which were attributed to asthma.

Efficacy

In children and adults, formoterol has been demonstrated to improve lung function and decrease symptoms, the need for rescue medication use and the rate of mild exacerbations, including exacerbations requiring treatment with systemic corticosteroids. The addition of formoterol to inhaled corticosteroids has been shown to confer clinical benefits compared to inhaled corticosteroids alone. Foradil provides physicians and patients with the flexibility to add formoterol delivered via a dry powder inhaler to any inhaled corticosteroids over the range of approved doses in accordance with current treatment guidelines.

Conclusion

Novartis believes that based on the data from these analyses alone, there is evidence of an increased risk of non-fatal serious asthma exacerbations in subjects taking formoterol when

compared with placebo among children ages 5-12 years. These results should be considered in the context that the majority of the placebo-controlled data for this age group are from a single study conducted from 1996 to 1998, when the standard of care for the treatment of asthma differed from current treatment standards. In addition, this increased risk has not been observed in more recent studies in the literature nor in post-marketing experience. In patients 13 years of age and older, the data do not demonstrate an excess risk. Given the benefits associated with long-acting beta₂-agonist use in asthma, Novartis believes that the benefit:risk ratio is in favor of formoterol use as currently reflected in labeling and treatment guidelines. Long-acting beta₂-agonists, including formoterol, remain an important therapeutic option in the treatment of patients with asthma.

2 Introduction

Asthma is a chronic inflammatory disorder of the airways in children and adults that is characterized by variable and recurring symptoms, airflow obstruction that is typically reversible, and bronchial hyper-responsiveness to inhaled allergens and a variety of other stimuli (NHLBI Expert Panel 3 2007). The pathogenesis of the disease is complex and the etiology considered to be polygenetic with gene–environmental interactions.

A recent survey reported that 20 million people in the USA have a current diagnosis of asthma. Of these, 6.2 million were children (prevalence of 8.5%) and 13.8 million were adults (prevalence of 6.7%) (Moorman et al. 2007). While the prevalence of asthma in children and adults increased substantially from 1980 to 2001, a recent survey did not show an increase in prevalence of asthma from 2001 to 2004 (Moorman et al. 2007). The burden of asthma includes missed days of school and work, decreased productivity, emergency department visits and hospitalizations (CDC/NIH 2008). Asthma-related death remains a devastating consequence of the disease with 3,884 deaths reported per year, 134 of which occur in children under the age of 15 (Moorman et al. 2007). The number of asthma deaths increased in the USA in the 1980s and 1990s; however, the number of asthma deaths reported annually from the time Foradil was approved and made available in the USA in 2001 until the last available data in 2004 is lower than in the 1990s (Moorman et al. 2007).

Inhaled corticosteroids are the foundation of step-up asthma therapy (GINA 2007, NHLBI Expert Panel 3 2007). Short-acting beta₂-agonists should be used only as rescue therapy for symptoms, and regular use of short-acting beta₂-agonists is not recommended. Increased usage of short-acting beta₂-agonists has been shown to be associated with increased mortality in asthma (Suisa et al. 1994, Lanes et al. 2002). In previous Food and Drug Administration (FDA) Public Health Advisories (FDA Public Health Advisory 2005, updated FDA Public Health Advisory 2006) and treatment guidelines, long-acting beta₂-agonists are not recommended for initiation of therapy or as monotherapies. In a significant number of patients, however, treatment with moderate-to-high doses of inhaled corticosteroids does not lead to control of asthma symptoms (Bateman et al. 2004). These patients have been shown to benefit from the addition of long-acting beta₂-agonists to inhaled corticosteroids.

Recently updated evidence-based guidelines from the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report 3 (NHLBI Expert Panel 3 2007) recommend a stepwise approach to pharmacologic therapy for patients of all ages to gain control of asthma.

Long-acting beta₂-agonists are recommended as add-on therapy for those patients not controlled by inhaled corticosteroids alone (NHLBI Expert Panel 3 2007). In children aged 5–11 years, for those patients not controlled on low-dose inhaled corticosteroids, the EPR-3 recommends medium-strength inhaled corticosteroids or the addition of long-acting beta₂-agonists, leukotriene antagonists or theophylline to low-dose inhaled corticosteroids. Particularly in children who complain of asthma-related symptoms or increased impairment on low-to-medium doses of inhaled corticosteroids, there is evidence to suggest that long-acting beta₂-agonists are appropriate add-on therapy (NHLBI Expert Panel 3 2007, Zimmerman et al. 2004). In adolescents 12–18 years of age and adults, for those patients not controlled on low-dose inhaled corticosteroids, the EPR-3 recommends medium-strength inhaled corticosteroids or the addition of long-acting beta₂-agonists to low-dose inhaled corticosteroids. For patients with symptoms on medium- or high-strength inhaled corticosteroids, long-acting beta₂-agonists are the preferred treatment option based on evidence that the concomitant use of long-acting beta₂-agonists and inhaled corticosteroids provides greater improvement in lung function and other measures of asthma control compared with doubling the dose of inhaled corticosteroids or adding theophylline or leukotriene receptor antagonists (Evans 1997, Ram et al 2005). Once asthma is well controlled in patients of all ages, appropriate adjustments should be made to step down therapy to identify the minimum medication necessary to maintain control, including consideration of long-acting beta₂-agonist discontinuation.

Since the initial results of the Salmeterol Multi-center Asthma Research Trial (SMART) became available in 2003, and the first public health advisory on long-acting beta₂-agonist risks in 2005, a number of meta-analyses and systematic reviews have evaluated potential excess risks of severe asthma morbidity and mortality based on accumulated clinical trial experience with long-acting beta₂-agonists (Salpeter et al. 2006, Cates & Cates 2008, Cates et al. 2008, Bateman et al. 2008, Sears et al. 2008). Some of these analyses (Salpeter et al. 2006, Cates & Cates 2008) include the large database from SMART (Nelson et al. 2006), and are thus mostly represented by data from SMART because of the large sample size of this study.

Other analyses that include data from more recently conducted trials are not consistent in their conclusions with respect to the potential excess risk of serious asthma exacerbations with long-acting beta₂-agonists. A Cochrane systematic review of formoterol (Cates et al. 2008) found an excess risk of non-fatal SAEs compared with placebo (odds ratio [OR] 1.6; 95% CI 1.15–2.4). The risk of non-fatal SAEs appeared to be greater in children than adults, but this difference was not significant. It was not possible to assess disease-specific mortality since there were few deaths in the 8,032 patients in this review. Bateman's meta-analysis of 66 trials comparing salmeterol plus inhaled corticosteroids with inhaled corticosteroids alone found no excess risk of asthma-related hospitalizations. A sub-group analysis of 26 trials longer than 12 weeks that collected asthma-related exacerbation data found no excess risk (risk difference - 0.025; CI - 0.036 to - 0.014; $p < 0.001$) (Bateman et al. 2008). A meta-

analysis by Jaeschke also demonstrated no increase in serious asthma exacerbations in patients treated with long-acting beta₂-agonists and inhaled corticosteroids (Jaeschke 2008).

Other meta-analyses that have not found an increased risk of serious asthma exacerbations among patients treated with formoterol include a meta-analysis of 64 trials of formoterol/budesonide or formoterol, which showed no excess risk of asthma-related exacerbations (Sears et al. 2008). An analysis of children ages 4-17 years demonstrated similar findings (Price et al 2008).

In 2005, after the Pulmonary-Allergy Drugs Advisory Committee met to discuss the safety of long-acting beta₂-agonists, a public health advisory was released stating that salmeterol and formoterol may increase the chance of serious asthma worsening, including death. This meeting was called following release of the results of a large placebo-controlled trial in which there was an increase in asthma-related deaths in patients receiving salmeterol (Nelson et al. 2006). On June 19, 2006, the FDA approved new labeling and a Medication Guide for patients using Foradil Aerolizer, including class labeling reflecting the possibility of an increased risk of asthma-related death.

At a November 2007 Pediatric Advisory Committee meeting, further concerns were raised regarding serious asthma exacerbations in children.

In January 2008, the FDA requested manufacturers of Advair Diskus, Advair HFA, Brovana Inhalation Solution, Foradil Aerolizer, Perforomist Inhalation Solution, Serevent Diskus, and Symbicort Inhalation Aerosol to provide information regarding controlled clinical studies conducted with these products in order to evaluate further the safety of long-acting beta₂-agonists when treating asthma. This briefing document summarizes the Foradil data submitted to the FDA in support of the joint meeting of the Pediatric, Drug Safety and Risk Management, and Pulmonary-Allergy Drugs Advisory Committees scheduled for December 10-11, 2008.

3 Regulatory history

In the US, Foradil® Aerolizer® (formoterol fumarate inhalation powder) 12 mcg (NDA 20-831) was approved in February 2001 and Foradil® Certihaler® (formoterol fumarate inhalation powder) 10 mcg (NDA 21-592) was approved in December 2006 for the BID maintenance treatment of asthma in adults and children 5 years of age and older.

Foradil Aerolizer is also approved for the maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, and for the treatment of exercise-induced bronchospasm on an occasional, as-needed basis in adults and children 5 years of age and older. Foradil Aerolizer consists of dry powder capsules for oral inhalation intended for use with the Aerolizer Inhaler.

In addition, Foradil (formoterol) inhalation capsules and Miflonide® (budesonide) inhalation capsules to be administered by the Aerolizer inhaler are sold together as Foraseq in Brazil, and by other names in Turkey and Venezuela for the maintenance treatment of asthma patients 6 years of age and older. In this document, Foraseq is used to denote the combined packaging of these products.

3.1 Labeling update

On June 19, 2006, the FDA approved new labeling and a Medication Guide for patients for Foradil Aerolizer. The labeling was revised to include class-labeling based on results of the SMART trial, a large, placebo-controlled trial in which there was an increase in asthma-related deaths in patients receiving salmeterol compared to placebo and to include additional data from formoterol trials regarding serious asthma exacerbations.

3.1.1 Possible increased risk of asthma-related death

The following boxed warning was added to the label regarding the possible increased risk of asthma-related death:

WARNING: Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, FORADIL AEROLIZER should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including FORADIL AEROLIZER. 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), the active ingredient in FORADIL AEROLIZER (see WARNINGS).

Revisions also included that when treating patients with asthma, Foradil Aerolizer should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

Use of Anti-inflammatory Agents

For the treatment of asthma, FORADIL AEROLIZER should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose ICS) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including FORADIL AEROLIZER. There are no data demonstrating that FORADIL has any clinical anti-inflammatory effect and therefore it cannot be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating FORADIL AEROLIZER. Any change in corticosteroid dosage, in particular a reduction, should be made ONLY after clinical evaluation (see PRECAUTIONS, Information for Patients).

3.1.2 Asthma-related exacerbations

The following information was added to the label to describe the incidence of asthma-related exacerbations from the three pivotal trials (two in adults and one pediatric) and the Phase IV study conducted to investigate the occurrence of asthma-related exacerbations.

In two 12-week controlled trials (Studies 40 and 41) with combined enrollment of 1095 patients 12 years of age and older, FORADIL AEROLIZER 12 mcg twice daily was compared to FORADIL AEROLIZER 24 mcg twice daily, albuterol 180 mcg four times daily, and placebo. Serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with FORADIL AEROLIZER 24 mcg twice daily than with the recommended dose of FORADIL AEROLIZER 12 mcg twice daily, albuterol, or placebo. The results are shown in the following table.

Number and frequency of serious asthma exacerbations in Patients 12 years of age and older from two 12-week controlled clinical trials

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Albuterol four times daily	Placebo
Trial #1				
Serious asthma exacerbations	0/136 (0)	4/135 (3.0%) ¹	2/134 (1.5%)	0/136 (0)
Trial #2				
Serious asthma exacerbations	1/139 (0.7%)	5/136 (3.7%) ²	0/138 (0)	2/141 (1.4%)

¹ One patient required intubation

² Two patients had respiratory arrest, one of the patients died

In a 16-week, randomized, multi-center, double-blind, parallel-group trial (Study 2307), patients who received either 24 mcg twice daily or 12 mcg twice daily doses of FORADIL AEROLIZER experienced more serious asthma exacerbations than patients who received placebo (see CLINICAL TRIALS). The results are shown in the following table.

Number and frequency of serious asthma exacerbations in patients 12 years of age and older from a 16-week trial

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Placebo
Serious asthma exacerbations	3/527 (0.6%)	2/527 (0.4%)	1/514 (0.2%)

Experience in Children with Asthma

The safety of FORADIL AEROLIZER 12 mcg twice daily compared to FORADIL AEROLIZER 24 mcg twice daily and placebo was investigated in

one large, multi-center, randomized, double-blind, 52-week clinical trial (Study 49) in 518 children with asthma (ages 5-12 years) in need of daily bronchodilators and anti-inflammatory treatment. More children who received FORADIL AEROLIZER 24 mcg twice daily than children who received FORADIL AEROLIZER 12 mcg twice daily or placebo experienced serious asthma exacerbations, as shown in the next table.

Number and frequency of serious asthma exacerbations in patients 5-12 years of age from a 52-week trial

	Foradil 12 mcg twice daily	Foradil 24 mcg twice daily	Placebo
Serious asthma exacerbations	8/171 (4.7%)	11/171 (6.4%)	0/176 (0)

4 Trials included in current analysis

At the request of the FDA, data from all Novartis-sponsored, blinded, randomized, controlled trials conducted with formoterol dry powder delivered via Aerolizer and Certihaler inhalers as an investigational treatment, or protocols with Foradil as an active comparator (Novartis studies only) in patients with asthma were included in the pooled database for analysis. As per the FDA inclusion criteria, trials in which formoterol was administered as randomized treatment, either with or without an ICS or other adjunct therapy, were considered for the current analysis. Both placebo-controlled and active-controlled trials were considered for inclusion. Parallel-arm and cross-over trials were included.

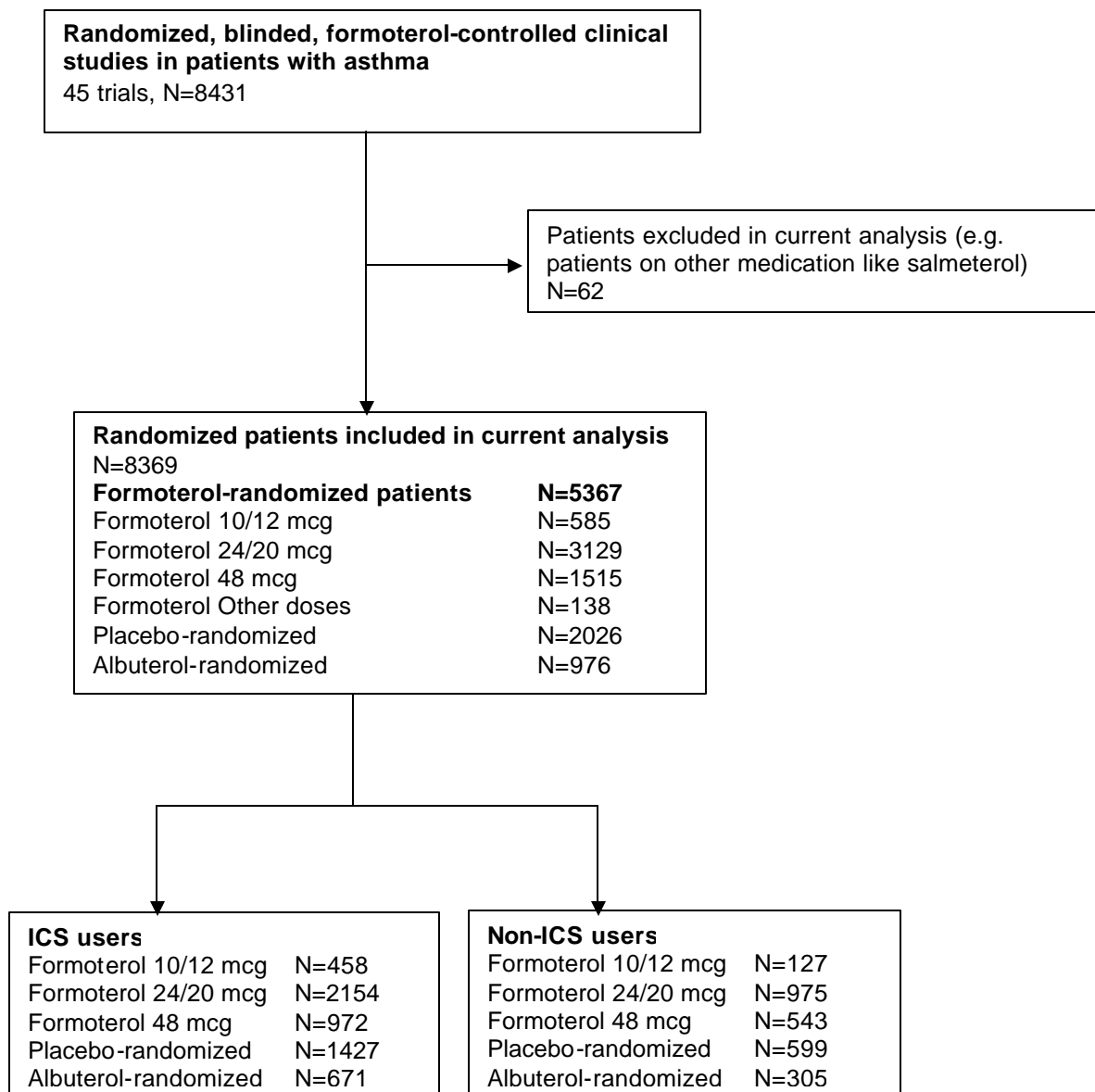
Trials that were uncontrolled, open-label, or conducted for indications other than asthma, such as COPD or exercise-induced bronchospasm, were not included in the current analysis. Trials that were primarily designed to obtain pharmacology data (Phase I studies) were not included.

4.1 Integrated database of Novartis clinical trials

Trials meeting FDA definition

Forty-five Novartis-sponsored asthma clinical studies met the FDA inclusion criteria and data from 8,369 randomized patients from these studies were enrolled in these trials. Figure 4-1 below gives an overview of the number of patients involved in Novartis Foradil clinical trials included in the current safety analysis.

Figure 4-1 Flowchart of patients involved in the Novartis formoterol trials included in the analysis



As per the FDA request, in the case of cross-over studies, only data from the first treatment period were included in the current database and analyses. In addition, patients (N=62) who were on randomized treatment other than formoterol, placebo or albuterol were not included in the analysis (e.g. patients on other medications, such as salmeterol, were excluded).

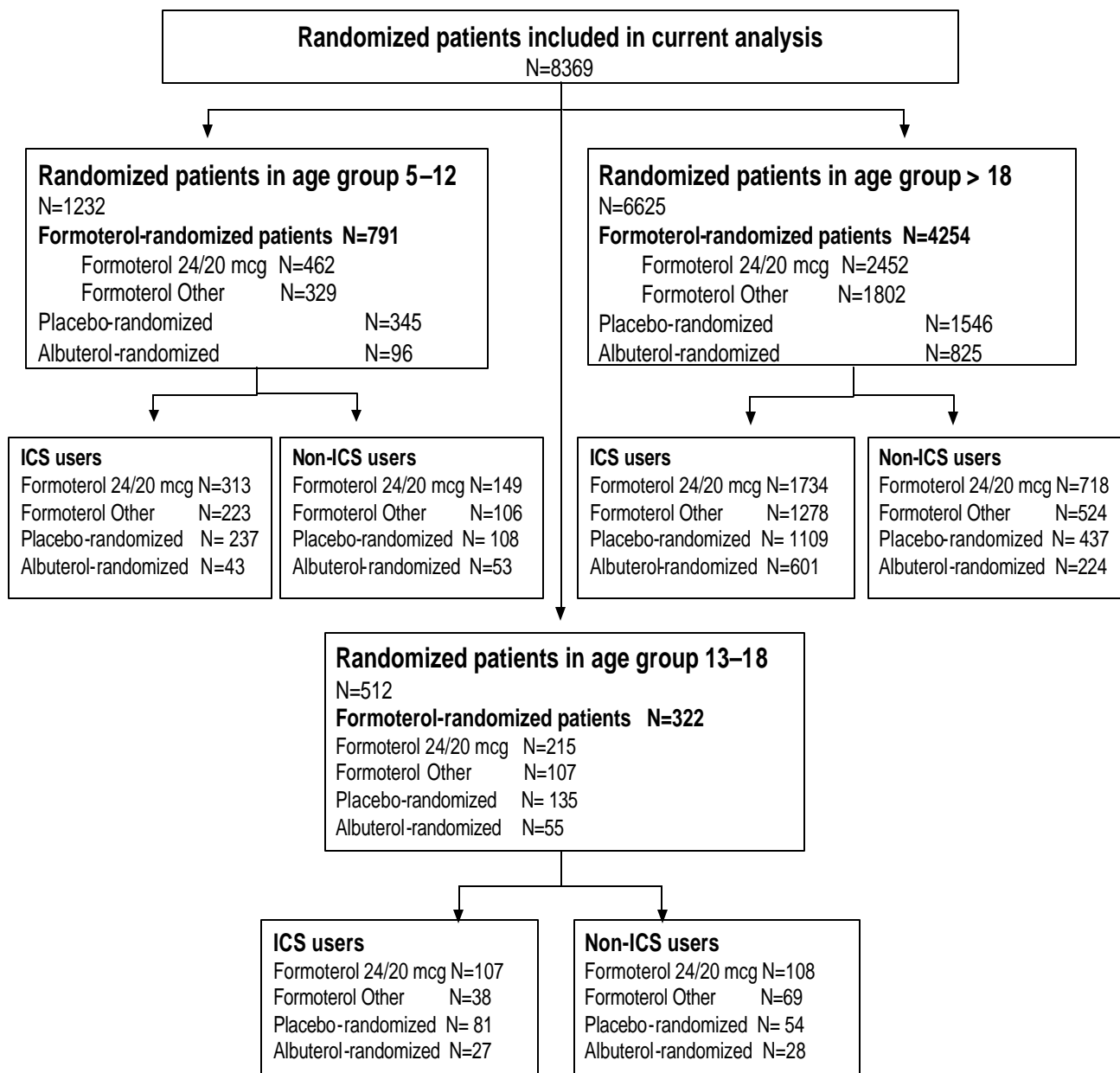
Of the 8369 randomized patients, 5367 were randomized to formoterol, 2026 patients to placebo and 976 patients to albuterol. Of the total 5367 patients treated with formoterol, 3,129 were on the approved Foradil Aerolizer 24 mcg TDD or Foradil Certihaler 20 mcg TDD. A total of 2,238 patients were on other total daily doses of formoterol (12 mcg, 48 mcg,

96 mcg etc.). The majority of safety summaries presented in this document focus on comparisons of patients treated with the approved formoterol dose of 24/20 mcg TDD versus placebo and/or albuterol. However, overall results of safety analyses for other formoterol doses are also presented in Section 5.8.

The majority of the randomized patients used ICS (all = 5,682, formoterol = 2,154, placebo = 1,427), either as baseline or as concomitant treatment during the study.

Figure 4-2 gives an overview of the distribution of patients by three age categories (5–12, 13–18 and >18 years) and ICS use.

Figure 4-2 Patient distribution by age and category



In adults and adolescents, there were 25 (14 multiple-dose and 11 single-dose) randomized, controlled, blinded studies in which Foradil Aerolizer was used and five (four multiple-dose and one single-dose) studies with Foradil Certihaler as an investigational treatment arm. There were five studies (one multiple-dose and four single-dose) with Foradil Aerolizer as an active comparator. For two studies, only limited information was available.

In pediatric patients (5–12 years), there were seven studies: five (three multiple-dose and two single-dose) randomized, controlled, blinded studies with Foradil Aerolizer and two (both multiple-dose) studies with Foradil Certihaler as an investigational treatment arm. One study had Foradil Aerolizer as an active comparator. No studies were conducted in children younger than 5 years of age.

The list of Foradil trials included in the analyses is provided in Appendix 1.

4.2 Definitions

Events of interest analyzed from the pooled data were defined by the FDA and include: (1) asthma deaths; (2) asthma-related intubations; and (3) asthma-related hospitalizations. These events were identified through a blinded physician review of the clinical and safety databases and are termed ‘serious asthma exacerbations’ in the analyses. Per the FDA definition, the search period for inclusion of events was defined as the beginning of treatment to the end of blinded treatment. Events occurring after the end of blinded treatment were therefore excluded from the current analyses.

The definition of ‘asthma-related’ is based on the asthma-related standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ) narrow terms. The MedDRA 10.1 (the SMQ narrow terms) preferred terms include: ‘analgesic asthma syndrome’, ‘asthma’, ‘asthma exercise induced’, ‘asthma late onset’, ‘asthmatic crisis’, ‘bronchial hyperreactivity’, ‘bronchospasm’, ‘infantile asthma’, and ‘status asthmaticus’.

4.3 Data analyses

In the analysis, formoterol doses are described in terms of ‘total daily dose’ (TDD), which is the sum of daily dosing: for example, 24 mcg TDD is a BID dose of 12 mcg or the dose of a single inhalation in single-dose studies.

Three formoterol treatment groups have been analyzed. The 12/10 mcg TDD refers to studies examining a dose of Foradil 6 mcg BID via Aerolizer (a single-dose dry powder inhaler), Foradil 5 mcg BID via Certihaler (a multi-dose dry powder inhaler) or a single dose of 12 mcg or 10 mcg from the Aerolizer or Certihaler, respectively.

Similarly, the 24/20 mcg TDD describes BID doses of 12 mcg via Aerolizer and 10 mcg via Certihaler. Separate work has shown that the delivered doses of 12 mcg via Aerolizer and 10 mcg via Certihaler are similar in terms of delivered dose and therapeutic effect.

The 48 mcg TDD refers to a twice-daily dose of 24 mcg via Aerolizer.

The 12/10 mcg TDD is not approved for use, and is not regarded as effective. It was used in single-dose studies in which patients received a single daily 12 mcg dose (19 studies), in dose ranging studies and in studies dating back to the early 1990s as a sub-therapeutic dose of 6 mcg BID because of regional ethical issues concerning design or conduct of placebo-controlled trials in children.

The albuterol treatment group in the present analysis includes albuterol doses (TDD) of 400 mcg (eight studies), 800 mcg (six studies), 1,200 mcg (one study), and 1,600 mcg (three studies).

Events are presented for each patient group of interest as number and percentage of patients with events ('incidence') and as number of events per 100 patient treatment years ('rate'). Crude ORs and 95% CI are calculated between any of the treatments and placebo. Alternatively, ORs and 95% CI are estimated by the exact method for a stratified OR (stratified by trials) using StatXact (Cytel 2005). Odds ratios and 95% CIs are also calculated using a stratified Poisson model for person-years data (Cytel 2005).

5 Safety—summary of serious asthma exacerbations in formoterol controlled trials

5.1 Demographics and baseline characteristics

Among studies pooled for these analyses, most demographic characteristics and baseline disease variables were balanced between the treatment groups with the exception of national origin (USA versus non-USA).

Among all subjects, the mean age was 37.2 years. Approximately half the subjects in each treatment group were female. In each treatment arm, >80% of patients were White. Among patients of all ages, subjects randomized at sites in the USA and those outside the USA were balanced across treatment arms. In children aged 5–12 years, however, more placebo patients were enrolled in sites in the USA (73%) compared with 4.2% of the albuterol-treated patients and 58% of the formoterol-treated patients. The reluctance of ethic committees outside the USA to approve placebo-controlled asthma studies in children is the reason for this imbalance.

The mean baseline FEV₁ was 2.2 L (68.3% predicted normal) for patients of all ages and was balanced across the treatment groups. In the 5–12 years age group, the mean baseline FEV₁ was 1.6 L, which was 74.3% predicted normal for the formoterol-treated patients, 72.4% predicted normal for placebo-treated patients and 80.3% for albuterol-treated patients. Approximately 70% of patients reported using ICS at some point during the clinical trial. Among children randomized to formoterol, 67.7% of subjects reported the use of ICS compared with 68.7% randomized to placebo and 44.8% randomized to albuterol.

Table 5-1 Demographics in Foradil controlled asthma trials summarized by treatment groups and age groups

	Formoterol 24/20 mcg TDD	Placebo	Albuterol QID
Age 5–12 years inclusive			
Age, mean (SD)	9.4 (2.00)	9.6 (2.03)	9.3 (1.99)
Gender, % (M/F)	67.1/32.9	63.8/36.2	62.5/37.5
Location, % (US/Ex-US)	58.2/41.8	73.0/27.0	4.2/95.8
Race, n (%)			
White	289 (78.7)	273 (80.3)	3 (75.0)
Black	48 (13.1)	35 (10.3)	1 (25.0)
Asian	2 (0.5)	4 (1.2)	0 (0.0)
Other	28 (7.6)	28 (8.2)	0 (0.0)
Baseline FEV ₁ , mean (L/% predicted)	1.6/74.3	1.6/72.4	1.6/80.3
Concomitant ICS use %	67.7/32.3 (n=462)	68.7/31.3 (n=345)	44.8/55.2
BMI at baseline, mean	18.7	20.0	17.3
Age 13–18 years inclusive			
Age, mean (SD)	15.0 (1.70)	15.3 (1.71)	15.2 (1.80)
Gender, % (M/F)	67.0/33.0	63.0/37.0	54.5/45.5
Location, % (US/Ex-US)	88.4/11.6	89.6/10.4	89.1/10.9
Race, n (%)			
White	159 (79.5)	101 (80.2)	44 (89.8)
Black	20 (10.0)	13 (10.3)	3 (6.1)
Asian	6 (3.0)	2 (1.6)	0 (0.0)
Other	15 (7.5)	10 (7.9)	2 (4.1)
Baseline FEV ₁ , mean (L/% predicted)	2.7/70.9	2.7/72.8	2.4/68.8
Concomitant ICS use %	49.8/50.2	60.0/40.0	49.1/50.9
BMI at baseline, mean	22.7	22.5	24.2
>18 years			
Age, mean (SD)	44.2 (15.13)	42.3 (14.31)	45.0 (16.04)
Gender, % (M/F)	47.6 (52.4)	42.7 (57.3)	43.3 (56.7)
Location, % (US/Ex-US)	51.8/48.2	53.6/46.4	46.8/53.2
Race, n (%)			
White	1245 (81.0)	804 (82.0)	332 (86.0)
Black	152 (9.9)	91 (9.3)	22 (5.7)
Asian	24 (1.6)	18 (1.8)	3 (0.8)
Other	116 (7.5)	68 (6.9)	29 (7.5)
Baseline FEV ₁ , mean (L/% predicted)	2.2 /66.7	2.3/68.4	2.1/66.1
Concomitant ICS use %	70.7/29.3	71.7/28.3	72.8/27.2
BMI at baseline, mean	25.9	26.4	26.3

5.2 Asthma-related and all-cause mortality

In 8,369 patients across all 45 trials, there were two deaths among patients treated with Foradil, with no new deaths reported since the 2005 PADAC. A 66-year old female died 19 days after randomization to formoterol 48 mcg TDD. She did not report the use of concomitant ICS. There was one other death (a 26-year-old female) due to hemorrhagic pancreatitis in the albuterol group.

In the 30-day period following study completion or study discontinuation there was one death (a 47-year-old female, respiratory arrest) reported in the placebo group. In a single-dose cross-over study, a patient died (a 60-year-old male, probable myocardial infarction) 3 days after treatment with placebo.

Three deaths were reported more than 30 days after the last dose of blinded medication, one each in formoterol 24 mcg TDD (a 56-year-old male, squamous cell carcinoma of lung), albuterol (a 69-year old male, carcinoma bronchus) and placebo (a 41-year-old male, metastatic colon cancer) groups.

There was one death reported in an open-label, follow-up period in the formoterol 24 mcg TDD treatment group (a 72-year-old male, myocardial infarction).

Table 5-2 Details of asthma-related and all cause deaths

Treatment	Age	Sex	Cause of Death	Comments
Death during randomized double blind treatment period				
Formoterol 48ug TDD	66	Female	Asthma Exacerbation	46 years of history of asthma, Baseline FEV1 1.55L (62% predicted normal)
Albuterol	26	Female	Hemorrhagic Pancreatitis	
Death within 30 days after study discontinuation/ study completion or after a treatment period in a crossover study				
Placebo	47	Female	Respiratory arrest	Completed study. Baseline FEV1 1.39L (51% of predicted normal)
Placebo	60	Male	Probable Myocardial Infarction	Single dose cross over study. Patient died 3 days after placebo treatment.
Death after 30 days after study discontinuation/ study completion				
Formoterol 24ug TDD	56	Male	Squamous cell carcinoma lung	Completed study
Albuterol	69	Male	Carcinoma Bronchus	Discontinued from study
Placebo	41	Male	Metastatic colon cancer	Completed study
Death during open label follow-up period				
Formoterol 24ug TDD	72	Male	Myocardial infarction	Past history of cerebrovascular accidents. During blinded phase of treatment no adverse events reported

5.3 Serious asthma exacerbations summarized by age and treatment

Table 5-3 and Figure 5-1 describe serious asthma exacerbations summarized by age and study treatment.

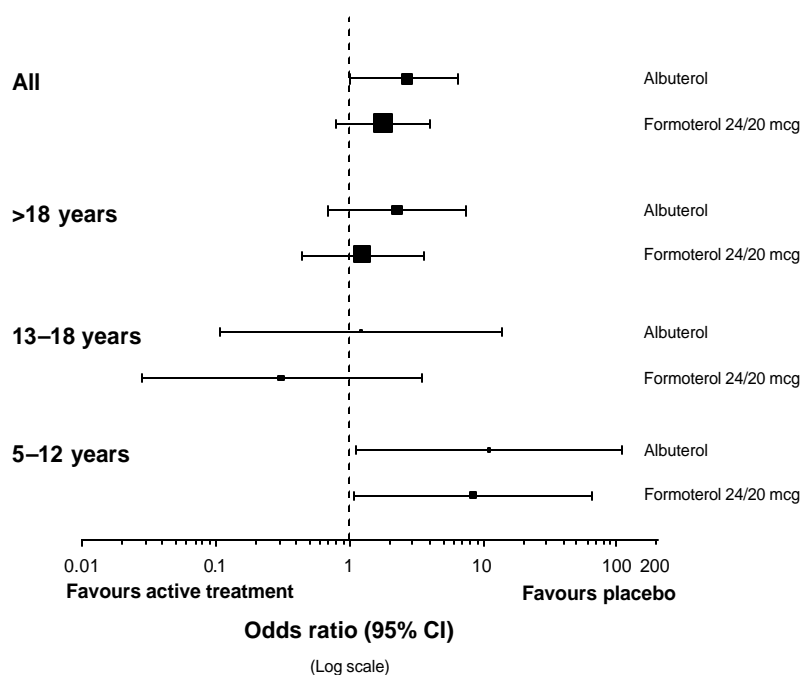
Table 5-3 Serious asthma exacerbations in Foradil controlled asthma trials summarized by treatment groups and age groups

	Formoterol 24/20 mcg TDD	Placebo	Albuterol QID
All patients, N	3129	2026	976
Serious exacerbations, n (%)	22 (0.7)	8 (0.4)	10 (1.0)
Serious exacerbations/100 yrs	2.7	1.4	4.5
Odds ratio vs placebo (95% CI)*	1.8 (0.8, 4.0)	—	2.6 (1.0, 6.6)
Age 5–12 yrs inclusive, N	462	345	96
Serious exacerbations, n (%)	11 (2.4)	1 (0.3)	3 (3.1)
Serious exacerbations/100 yrs	5.4	0.6	16.2
Odds ratio vs placebo (95% CI)	8.4 (1.1, 65.3)	—	11.1 (1.1, 107.9)
Age 13–18 yrs inclusive, N	215	135	55
Serious exacerbations, n (%)	1 (0.5)	2 (1.5)	1 (1.8)
Serious exacerbations/100 yrs	1.8	6.1	8.4
Odds ratio vs placebo (95% CI)	0.3 (0.03, 3.5)	—	1.2 (0.1, 13.9)
>18 yrs N	2452	1546	825
Serious exacerbations, n (%)	10 (0.4)	5 (0.3)	6 (0.7)
Serious exacerbations/100 yrs	1.9	1.4	3.1
Odds ratio vs placebo (95% CI)	1.3 (0.4, 3.7)	—	2.3 (0.7, 7.4)

*Odds ratio (95% CI) based on stratified exact method is 1.3 (0.5, 3.7) for formoterol 24 mcg versus placebo and 1.5 (0.4, 7.1) for albuterol versus placebo. OR (95% CI) based on Poisson model is 1.4 (0.5, 3.8) for formoterol 24 mcg versus placebo and 1.5 (0.4, 7.4) for albuterol versus placebo.

Overall, there was an increase in serious asthma exacerbations among patients treated with formoterol. The increase was greatest among patients 5–12 years of age. Among children 13–18 years and adults greater than 18 years of age, the rate of serious asthma exacerbations was similar to placebo. For patients of all ages, there were more serious asthma exacerbations among patients receiving albuterol compared to formoterol or placebo.

Figure 5-1 Odds ratios (95% CIs) and incidences for serious asthma exacerbations in Foradil controlled asthma trial summarized by treatment group and age



5.4 Serious asthma exacerbations summarized by age and ICS use

In all of the 45 trials included in the pooled analyses, the concomitant use of an anti-inflammatory medication was permitted; however, the type of medication used was not specified. A total of 69% of patients reported the use of ICS either prior to randomization or during the course of the study. Patients were not randomized by ICS use.

Among patients 13 – 18 years of age and greater than 18 years of age, there was a trend (non-significant) towards fewer serious asthma exacerbations in subjects reporting the use of concomitant inhaled corticosteroids. In patients 5–12 years of age, the impact of concomitant use of inhaled corticosteroids appears to be less.

Figure 5-2 Odds ratios (95% CIs) and incidences for serious asthma exacerbations in Foradil controlled asthma trials summarized by treatment group, age and ICS use

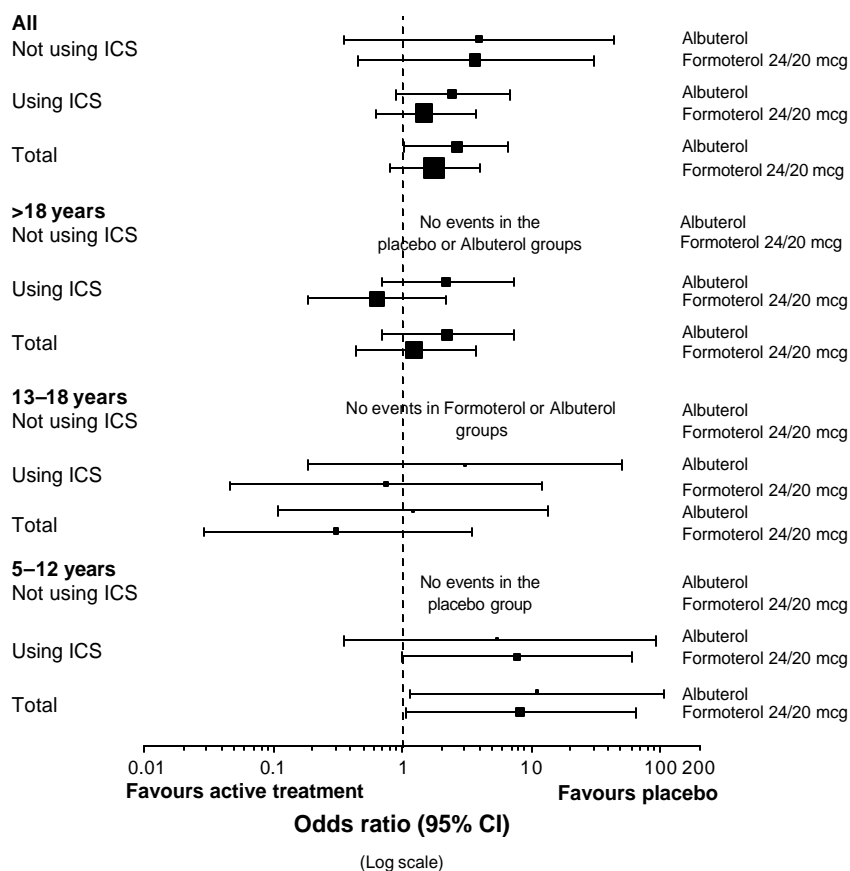


Table 5-4 **Serious asthma exacerbations in Foradil controlled asthma trials summarized by treatment groups and ICS usage and age 5–12 years**

	Formoterol 24/20 mcg TDD	Placebo	Albuterol QID
Using ICS, N	313	237	43
Serious exacerbations, n (%)	10 (3.2)	1 (0.4)	1 (2.3)
Serious exacerbations/100 yrs	6.9	0.8	9.6
Odds ratio vs placebo (95% CI)	7.8 (1.0, 61.3)	—	5.6 (0.3, 91.6)
Not using ICS, N	149	108	53
Serious exacerbations, n (%)	1 (0.7)	0	2 (3.8)
Serious exacerbations/100 yrs	1.7	0	24.5
Odds ratio vs placebo (95% CI)	—	—	—

Table 5-5 **Serious asthma exacerbations in Foradil controlled asthma trials summarized by treatment groups and ICS usage and age 13–18 years**

	Formoterol 24/20 mcg TDD	Placebo	Albuterol QID
Using ICS, N	107	81	27
Serious exacerbations, n (%)	1 (0.9)	1 (1.2)	1 (3.7)
Serious exacerbations/100 yrs	3.4	5.0	17.7
Odds ratio vs placebo (95% CI)	0.8 (0.05, 12.3)	—	3.1 (0.2, 50.9)
Not using ICS, N	108	54	28
Serious exacerbations, n (%)	0	1 (1.9)	0
Serious exacerbations/100 yrs	0	7.7	0
Odds ratio vs placebo (95% CI)	—	—	—

Table 5-6 Serious asthma exacerbations in Foradil controlled asthma trials summarized by treatment groups and ICS usage and age >18 years

	Formoterol 24/20 mcg TDD	Placebo	Albuterol QID
Using ICS, N	1734	1109	601
Serious exacerbations, n (%)	5 (0.3)	5 (0.5)	6 (1.0)
Serious exacerbations/100 yrs	1.2	1.9	4.1
Odds ratio vs placebo (95% CI)	0.6 (0.2, 2.2)	—	2.2 (0.7, 7.3)
Not using ICS, N	718	437	224
Serious exacerbations, n (%)	5 (0.7)	0	0
Serious exacerbations/100 yrs	3.5	0	0
Odds ratio vs placebo (95% CI)	—	—	—

5.5 Serious asthma exacerbations summarized by treatment and baseline lung function

Among patients of all ages, 1,725 had a baseline FEV₁ less than 60% of predicted normal. 3,286 subjects had a baseline FEV₁ between 60 and 80% of predicted normal and 1,095 patients with a baseline FEV₁ greater than 80% of predicted normal. There was no clear association of serious asthma exacerbations with baseline lung function.

Table 5-7 Summary of serious asthma adverse exacerbations (%) by baseline and FEV₁ (% predicted)

	Formoterol 24/20 mcg TDD	Placebo	Albuterol QID
FEV ₁ <60% predicted, N	906	514	305
Serious exacerbations, n (%)	7 (0.8)	2 (0.4)	3 (1.0)
Serious exacerbations/100 yrs	3.7	1.5	4.7
Odds ratio vs placebo (95% CI)	2.0 (0.4, 9.6)	—	2.5 (0.4, 15.3)
FEV ₁ 60–80% predicted, N	1670	1129	487
Serious exacerbations, n (%)	8 (0.5)	4 (0.4)	4 (0.8)
Serious exacerbations/100 yrs	1.7	1.2	3.6
Odds ratio vs placebo (95% CI)	1.4 (0.4, 4.5)	—	2.3 (0.6, 9.4)
FEV ₁ >80% predicted, N	544	378	173
Serious exacerbations, n (%)	7 (1.3)	2 (0.5)	3 (1.7)
Serious exacerbations/100 yrs	4.7	1.8	6.7
Odds ratio vs placebo (95% CI)	2.5 (0.5, 11.9)	—	3.3 (0.5, 20.0)

5.6 Serious asthma exacerbations summarized by location

Serious asthma exacerbations are summarized by treatment group and country in Table 5-8.

Among children 5–12 years of age, however, enrollment was imbalanced, with more placebo randomized subjects enrolled at sites in the US and more albuterol randomized subjects enrolled at non-US sites.

The incidence of serious asthma exacerbations for all treatment groups was lower for patients enrolled in sites in the USA.

Table 5-8 Summary of serious asthma adverse exacerbations (%) by location (United States versus non-United States)

	Formoterol 24/20 mcg TDD	Placebo	Albuterol QID
US, N	1730	1201	439
Serious exacerbations, n (%)	7 (0.4)	3 (0.2)	3 (0.7)
Serious exacerbations/100 yrs	1.6	0.8	3.1
Odds ratio vs placebo (95% CI)	1.6 (0.4, 6.3)	—	2.7 (0.6, 13.7)
Non-US, N	1399	825	537
Serious exacerbations, n (%)	15 (1.1)	5 (0.6)	7 (1.3)
Serious exacerbations/100 yrs	4.6	2.4	5.6
Odds ratio vs placebo (95% CI)	1.8 (0.6, 4.9)	—	2.2 (0.7, 6.9)

5.7 Serious asthma exacerbations summarized by treatment groups and race

Race was not reported for 45% of subjects in the pooled data set. For those subjects whose race was reported, the great majority were White. For White subjects, there were eight serious asthma exacerbations among the 1,693 subjects (0.5%) randomized to formoterol compared with three serious asthma events among the 1,178 subjects (0.3%) randomized to placebo and three of 379 subjects (0.8%) randomized to albuterol. Three Black subjects experienced serious asthma exacerbations (1.4%); all were randomized to formoterol. There were no serious asthma exacerbations reported among subjects describing their race as Asian or Other.

Table 5-9 Summary of serious asthma adverse exacerbations (%) by race

	Formoterol 24/20 mcg TDD	Placebo	Albuterol QID
White, N	1693	1178	379
Serious exacerbations, n (%)	8 (0.5)	3 (0.3)	3 (0.8)
Serious exacerbations/100 yrs	1.6	0.8	3.6
Odds ratio vs placebo (95% CI)	1.9 (0.5, 7.0)	—	3.1 (0.6, 15.5)
Black/African-American, N	220	139	26
Serious exacerbations, n (%)	3 (1.4)	0	0
Serious exacerbations/100 yrs	6.5	0	0
Odds ratio vs placebo (95% CI)	—	—	—

There are insufficient numbers of non-White subjects to assess the effect of race on the risk of serious asthma exacerbations.

5.8 Serious asthma exacerbations summarized by treatment group and dose (approved and unapproved doses of formoterol fumarate)

Although not the focus of this briefing document, many trials contributing data to the pooled analyses included treatment arms in which subjects received formoterol at doses above and below the approved dose. Five-hundred-eighty-five (585) subjects in the pooled group were treated with 12/10 mcg TDD of formoterol. All trials incorporating this treatment arm were conducted outside the USA and many were single-dose trials. 48 mcg of formoterol delivered as 24 mcg BID is an approved dose in many countries. A total of 1115 patients in the pooled group received this dose.

Among patients of all ages, there is a higher OR of serious asthma exacerbations versus placebo for subjects treated with 12/10 mcg TDD and 48 mcg TDD compared with subjects treated with the approved US dose of 24/20 mcg TDD. The same pattern was observed in the pediatric and adult age groups.

Table 5-10 Summary of serious asthma exacerbations (%) by treatment group and age (approved and unapproved doses)

	Formoterol TDD			Placebo	Albuterol QID
	12/10 mcg	24/20 mcg	48 mcg		
All patients, N	585	3129	1515	2026	976
Serious exacerbations, n (%)	9 (1.5)	22 (0.7)	17 (1.1)	8 (0.4)	10 (1.0)
Serious exacerbations/100 yrs	10.8	2.7	3.8	1.4	4.5
Odds ratio vs placebo (95% CI)	3.9 (1.5, 10.3)	1.8 (0.8, 4.0)	2.9 (1.2, 6.6)	—	2.6 (1.0, 6.6)
5-12 yrs inclusive, N	103	462	188	345	96
Serious exacerbations, n (%)	5 (4.9)	11 (2.4)	8 (4.3)	1 (0.3)	3 (3.1)
Serious exacerbations/100 yrs	28.7	5.4	5.8	0.6	16.2
Odds ratio vs placebo (95% CI)	17.6 (2.0, 152.0)	8.4 (1.1, 65.3)	15.3 (1.9, 123.2)	—	11.1 (1.1, 107.9)
13-18 yrs inclusive, N	6	215	101	135	55
Serious exacerbations, n (%)	0	1 (0.5)	0	2 (1.5)	1 (1.8)
Serious exacerbations/100 yrs	0	1.8	0	6.1	8.4
Odds ratio vs placebo (95% CI)	—	0.3 (0.03, 3.5)	—	—	1.2 (0.1, 13.9)
> 18 yrs, N	476	2452	1226	1546	825
Serious exacerbations, n (%)	4 (0.8)	10 (0.4)	9 (0.7)	5 (0.3)	6 (0.7)
Serious exacerbations/100 yrs	6.2	1.9	3.1	1.4	3.1
Odds ratio vs placebo (95% CI)	2.6 (0.7, 9.8)	1.3 (0.4, 3.7)	2.3 (0.8, 6.8)	—	2.3 (0.7, 7.4)

5.9 Individual Study Results- Serious Asthma Exacerbations

The two studies described below are included in the pooled analyses, but are highlighted here because of their importance to the current safety assessment. Study 2307 was a post-approval commitment to the FDA to assess the incidence of asthma-related serious asthma exacerbations at the approved (24 mcg TDD) and higher doses (48 mcg TDD). Study 49 was a one-year study to assess long-term safety of formoterol in the treatment of children.

5.9.1 Study 2307: Serious Asthma Exacerbations Phase IV study in adolescent and adult patients

Study design and results

Study 2307 was a randomized, multicenter, placebo-controlled, parallel group Phase IV commitment study conducted in a total of 2,085 adolescent and adult patients with persistent stable asthma, including 314 patients 13–18 years of age. There were three double-blind

treatment groups: formoterol Aerolizer 12 mcg BID (24 mcg TDD), formoterol Aerolizer 24 mcg BID (48 mcg TDD), and placebo BID; and one open-label treatment group receiving formoterol Aerolizer 12 mcg BID with up to two additional doses per day of formoterol Aerolizer 12 mcg as needed for worsening of symptoms (24–48 mcg TDD). The duration of treatment was 16 weeks.

The primary endpoint was the percentage of patients with asthma-related serious adverse events, including events leading to emergency room visits, hospitalization, death or requiring urgent care to prevent one of these outcomes. An important secondary endpoint was asthma-related adverse events requiring oral corticosteroids. Serious asthma-related adverse events (the primary end-point) were reported by a total of 6 patients in the study, with 2 cases (0.9%) in the formoterol 24 mcg TDD group, 2 cases (0.4%) in the formoterol 48 mcg TDD group, 1 case (0.2%) in the formoterol 24 mcg TDD + prn group and 1 case (0.2%) in the placebo group. Two additional respiratory-related SAEs, both pneumonias, were reported in the 24 mcg TDD group. Premature discontinuations due to asthma-related AEs (serious or non-serious) occurred in a small and similar percentage in all treatment groups.

A total of 45 (8.8%) patients in the placebo group, 23 (4.4%) patients in formoterol prn group, 33 (6.3%) patients in the 48 mcg TDD group and 31 (5.9%) patients in the 24 mcg TDD group required systemic corticosteroids for asthma exacerbations.

This distribution, combined with the low number of events, points in the direction of a random effect. This conclusion is strengthened by the trend toward a higher frequency in the placebo group for patients who required oral steroids during the study.

5.9.2 Study 49: 12-month placebo-controlled study in children aged 5–12 years

Study design and results

Study 49 (Bensch et al. 2002) was a 12-month placebo-controlled study comparing the safety and efficacy of formoterol 24 mcg TDD and 48 mcg TDD in 512 patients aged 5–12 years. The study was conducted from 1996 until 1998 in five countries: the US, Spain, Russia, Argentina and Chile. The results of this trial are included in the pooled analyses described in previous sections; however, as this study provides the majority of placebo-controlled data in the pediatric age group, it is described here in greater detail.

At baseline, 75% of subjects reported using inhaled corticosteroids. The most commonly used ICS included beclomethasone dipropionate, budesonide, and triamcinolone acetate.

Of the 13 subjects experiencing serious asthma exacerbations, five were randomized to formoterol 24 mcg TDD and eight were randomized to 48 mcg TDD. None of the subjects randomized to placebo experienced serious asthma exacerbations. All serious asthma exacerbations were hospitalizations; no intubations or death occurred in these patients. A summary of the events is provided in Table 5-11. Serious asthma exacerbations occurred from 5 to 337 days after randomization, with the majority occurring after more than 2 months of treatment.

Table 5-11 Summary of subjects experiencing serious asthma exacerbations in Study 49

Country/Subject Number	Age	Formoterol TDD	Gender	Race	Adverse event onset (days)
Russia/4015	8	24 mcg	Male	White	98
Spain/2019	10	24 mcg	Female	White	166
Russia/4091	8	24 mcg	Male	White	313
USA/7060	7	24 mcg	Male	White	337
USA/7135	11	24 mcg	Female	White	233
Spain/2006	8	48 mcg	Male	White	5, 58*
Spain/2016	9	48 mcg	Female	White	50
Russia/4032	10	48 mcg	Female	White	61
USA/7112	8	48 mcg	Male	Black	78
USA/7117	10	48 mcg	Female	Black	81
USA/7451	10	48 mcg	Female	White	83
USA/7042	9	48 mcg	Male	White	211
Spain/2056	7	48 mcg	Female	White	216

* Two distinct serious asthma exacerbations events in one subject

5.10 Discussion

All Patient Data

Analyses of pooled data from 45 Novartis-sponsored studies demonstrate that, overall, the number of serious asthma exacerbations is increased among subjects randomized to formoterol compared with those randomized to placebo. The rate of events per 100 patient years is 2.7 among patients treated with formoterol 24 mcg TDD, compared with 1.4 for placebo and 4.5 for albuterol.

Children 5–12 years of age

The increased rate of serious asthma exacerbations in patients of all ages is primarily driven by the rate among children between the ages of 5 and 12 years. In this population, the rate of serious asthma exacerbations was 5.4 events per 100 patient years for patients treated with formoterol compared with 0.6 events per 100 patient years among patients receiving placebo (OR 8.4; 95% CI 1.1–65.3). This imbalance is largely due to Study 49 as discussed above, in which five serious asthma exacerbations were reported among subjects randomized to formoterol 24 mcg TDD, nine were reported among subjects randomized to 48 mcg TDD, while no patients receiving placebo experienced a serious asthma exacerbation. Although the risk of serious asthma exacerbations in patients aged 5–12 years is increased, the magnitude of this increase is difficult to assess for reasons discussed below, including a rate of placebo exacerbations below expected, with a high rate of drop-outs among all treatment groups, compliance with ICS therapy and regional differences in events.

The absence of any serious asthma exacerbations in the placebo group is unusual based on the expected rate of exacerbations in patients of this age from health survey data and clinical trials. Data from the Center of Disease Control National Health Interview Survey and the National Hospital Discharge Survey, at the time this study was conducted, showed a 2.4% incidence of hospitalizations per year for children of this age. In the Childhood Asthma Research Program (CAMP) study, a 4–6 year study of 1,041 children 5–12 years of age, patients receiving placebo reported 4.4 hospitalizations per 100 patient–years, while patients treated with budesonide experienced 2.5 and patients treated with nedocromil reported 4.3 (CAMP Research Group 2000). The unexpected lack of placebo events makes the magnitude of the risk difficult to access.

As expected in a study of this duration, drop-out rates were high. Twenty three percent of subjects randomized to placebo discontinued the study compared to 22% and 19% in the formoterol 24 and 48 mcg TDD treatment groups. Follow-up was not obtained on patients who withdrew early. Although there is no clear differential drop among placebo-treated patients, high drop-out rates and lack of follow-up may have contributed to the absence of placebo hospitalizations observed in the trial.

Although the protocol stated that patients were to remain on a stable regimen of anti-inflammatory medications, concomitant inhaled corticosteroids were not considered study medications. Patients were responsible for obtaining and paying for the inhaled corticosteroids and compliance with these drugs was not measured. Compliance with the randomized study medications was high; the same assumption cannot be made for the concomitant therapies. In clinical practice, under-reporting the use of inhaled corticosteroids is common (Bender et al. 2007, Breekveldt-Postma et al. 2008, Conn et al. 2005). The FDA issued an advisory notice regarding the effect of ICS on childhood growth during the period of the study (FDA 1998) which may also have influenced the use of concomitant inhaled corticosteroids. It is unclear in this study whether all patients who reported using inhaled corticosteroids and other anti-inflammatory therapies at baseline continued using them, which may have increased the risk of serious asthma exacerbations in patients randomized to receive formoterol.

In the 5–12 year age group, the rate of serious asthma exacerbations was lower among patients enrolled in sites in the USA for all treatment groups. This difference may reflect regional treatment practices, including criteria for hospitalization, access to care, or severity of disease among subjects participating in clinical trials. Seventy three percent of placebo treated patients were enrolled at sites in the USA compared to 58% of the formoterol patients and 4% of albuterol treated patients. As the other large pediatric study (DP/PD2) was conducted outside of the USA without placebo control, more subjects on albuterol and formoterol were treated outside of the USA and therefore were more likely to experience serious asthma exacerbation. It is possible that regional differences in practice may be contributing to the increased numbers of serious asthma exacerbations among formoterol and albuterol treated subjects in the pooled analyses.

Recently published analyses of other formoterol formulations have not demonstrated differences in the rate of serious asthma exacerbations between children treated with formoterol and those treated with placebo. In an abstract presented at the European Respiratory Society in 2008, the frequency of asthma-related hospitalizations among 5,481

children between the ages of 4 and 11 years was 1.1% (38/3316) for those treated with formoterol versus 1.1% (23/2165) for patients randomized to non-long-acting beta₂-agonist treatment arms (Price et al. 2008).

The analyses of 1,232 subjects aged 5–12 years enrolled in Novartis-sponsored studies demonstrate an increased risk of serious asthma exacerbations among children treated with formoterol. Study 49 provides valuable information on the long-term efficacy and safety of formoterol in children; however, the magnitude of the observed imbalance in serious asthma exacerbations may have been influenced by the unexpected absence of serious asthma exacerbations in the placebo group, poor compliance with concomitant anti-inflammatory medications and regional treatment differences.

Children 13–18 years of Age and Adults

In patients 13-18 years of age and greater than 18 years of age who reported using inhaled corticosteroids, the rate of serious asthma exacerbations was lower in patients randomized to formoterol compared with those randomized to placebo (13–18 years: OR 0.8; 95% CI 0.05–12.3; >18 years: OR 0.6, 95% CI 0.2–2.2). Although this difference did not meet clinical significance, the apparent reduction in the risk of serious asthma exacerbations in patients using ICS is supported by the results of Study 2307, a Phase IV commitment designed specifically to address this question (Wolfe et al. 2006). A total of 2,085 subjects aged 12 years and older were randomized to receive formoterol 24 mcg TDD, 48 mcg TDD, a flexible dose (24 mcg up to 48 mcg TDD) or placebo. In each treatment group, subjects experienced a similar number of events: three events in the formoterol 24 mcg TDD group, two events in the formoterol 48 mcg TDD group, one event in the formoterol flexible dosing group and one in the placebo treated group. While patients 5–12 years of age treated with formoterol appear to have an increased risk of serious asthma exacerbations, in patients 13 – 18 years of age and adults, the risk is less and appears to be mitigated by concomitant ICS use.

6 Spontaneous reports

6.1 Post-marketing experience, spontaneous reports 1 June 2005–31 May 2008 (Novartis ARGUS safety database)

6.1.1 Introduction

This section reviews asthma-related SAEs and deaths reported spontaneously to the Novartis safety database (ARGUS) world-wide during the 3-year period from June 1, 2005 to May 31, 2008 for Foradil (all formulations, including Aerolizer dry powder capsules for inhalation, Certihaler dry powder inhaler, solution aerosol MDI, and HFA aerosol MDI) and for Foraseq (Foradil Aerolizer inhalation capsules sold together with Miflonide (budesonide) inhalation capsules). This 3-year period was chosen as it was the reporting period for a recent periodic safety update report for Foradil, and is relevant as it covers a period which includes the July 2005 FDA PADAC meeting which discussed long-acting beta₂-agonist safety, and during which the resulting modifications were made to the package insert and the global Basic Prescribing Information for Foradil.

Additionally, asthma-related deaths from solicited case reports and all-cause pediatric deaths reported world-wide during the 3-year period are summarized.

6.1.2 Marketing information for the 3-year period

An estimate of global patient exposure during the 3-year period was calculated from the number of canisters (about 100 puffs per canister, 1 puff containing formoterol fumarate 12 mcg) and the number of capsules (one capsule contains formoterol fumarate 12 mcg) sold during the 3-year period. It has been assumed that each patient used an average of 2 puffs daily. The sales figures in the 3-year period of approximately 4.3 million canisters and 1,797 million capsules corresponded to approximately 3.05 million patient years of treatment with Foradil. In addition, during the 3-year period, approximately 6.1 million packs of Foraseq were sold, each containing 60 capsules of Foradil (containing formoterol fumarate 12 mcg) and 60 capsules of budesonide. On the basis of 2 capsules per day, this corresponds to 0.5 million patient treatment years with Foraseq.

6.1.3 Asthma-related serious adverse events during the 3-year period (spontaneous reports)

A search was performed of the Novartis ARGUS safety database for spontaneously reported cases with at least one of the following terms as a preferred term (the narrow SMQ [Standardized MedDRA Query] for asthma/bronchospasm): Analgesic asthma syndrome, Asthma, Asthma exercise induced, Asthma late onset, Asthmatic crisis, Bronchial hyperreactivity, Bronchospasm, Infantile asthma, Status asthmaticus.

Foradil

For Foradil the search revealed 41 spontaneous reports, including 18 non-health care provider (HCP) reports, during the 3-year period. Asthma was reported 30 times, asthmatic crisis was reported twice, and bronchospasm was reported 10 times. For 16 of the case reports, the patient was hospitalized for the asthma-related event.

Of the 41 reports, six were reported in children (ages 6, 8, 10, 11 and 12 years; for one case age was not specified), three in adolescents (ages 13, 15 and 16 years), nine in adults (defined as age 19–69 years), and seven in elderly patients (defined as age 70 years and above); in 16 cases age was not specified.

One HCP report classified the case as being life-threatening: a child (age unspecified) experienced bronchospasm and required intubation after concomitant administration of Foradil and Pulmicort (budesonide). Additionally, one non-HCP classified a case as life-threatening (an adolescent patient hospitalized for asthmatic crisis).

Foraseq

For Foraseq, the search revealed 34 spontaneous reports, including 27 non-HCP reports, during the 3-year period. Three of these cases (one adult, one elderly, one age not specified) are also listed in the results of the Foradil search, described above. One duplicate Foraseq case retrieved in the search and classified as life-threatening is excluded from the counts. Asthma

was reported 25 times, status asthmaticus once, asthma crisis three times and bronchospasm six times. For 19 of the case reports the patient was hospitalized for the asthma-related event.

For the majority of cases, serious medical problems from other system organ classes were reported in addition to the asthma-related term(s).

Of the 34 reports, one was reported in a child (age 4 years), one in an adolescent (age 18 years), 22 in adults (defined as age 19–69 years) and six in elderly patients (defined as age 70 years and above); in four cases age was not reported.

Five cases were classified by the reporter as life-threatening (all reported by non-HCPs, and involving adult or elderly patients).

6.1.4 Asthma-related deaths during the 3-year period (spontaneous reports)

There were three spontaneously-reported cases with fatal outcome for which one or more preferred terms from the asthma/bronchospasm SMQ were reported for Foradil, and no cases for Foraseq, during the 3-year period. In none of the three cases was it stated that the death was due to asthma.

The first case involved an adult male patient who had been treated with Foradil and cromoglycate for allergy for an unspecified period. The patient received a hypo-sensitization injection, and died 1 hour later despite CPR. The physician found an empty Foradil capsule in the patient's shirt, and stated that he believed the patient experienced a bronchospasm leading to death following an accidental overdose of Foradil.

The second case involved an adult male patient with a history of pneumopathy and diabetes who had been treated with Foradil for bronchospasm. The patient experienced malaise, fever, cough, tachypnea and bronchospasm, and was diagnosed via lung biopsy as having metastatic adenocarcinoma and fibrosis. The following month, the patient developed a pulmonary streptococcal infection, and died after experiencing dyspnea, oxygen desaturation, and then cardiac arrest. The patient was taking multiple concomitant medications, including IV methylprednisolone and ipratropium-albuterol nebulizations.

The third case involved an elderly male patient who was treated with Foradil and ICS for asthma. He was hospitalized for an asthma exacerbation after 10 months, and then for pleurisy the following month. The patient died of an unspecified cause several months later.

6.1.5 Asthma-related deaths during the 3-year period (solicited reports)

One solicited case with a fatal outcome, which included one or more preferred terms from the asthma/bronchospasm SMQ, was reported for Foradil, and four cases were reported for Foraseq, during the 3-year review period.

Foradil

One adult male patient who received Foradil in a post-marketing surveillance (PMS) study died at home following a severe asthma attack. The patient's concomitant conditions included

cor pulmonale, respiratory failure, diabetes, obesity and sinus tachycardia. Concomitant medications included Berodual (fenoterol and ipratropium), inhaled fluticasone, albuterol, verapamil and methylprednisolone. The case was reported by a physician as not being suspected to be related to the use of Foradil. The death occurred 9 months prior to the 3-year review period, but was not reported until September 2005.

Foraseq

Four deaths were reported from a patient use program in Brazil (approximately 7,500 patients purchased Foradil and approximately 122,900 patients purchased Foraseq while enrolled in the Vale Mais Saúde Card patient use program during the 3-year period).

The first case involved an elderly female who took Foraseq for bronchitis and asthma. Concomitant medications included valsartan and amiodarone. The case was initially reported by a non-HCP, who stated that the patient was hospitalized for worsening of bronchitis and asthma, and died from bronchitis, chronic asthma, and cardiac arrest. When contacted in follow-up, the patient's physician, who had not been involved in treating the patient during the hospitalization during which she died, stated that the bronchitis, chronic asthma, and cardiac arrest were not due to valsartan (another Novartis product).

The second case involved an adult female with a history of hypertension. The case was initially reported by a non-HCP. It was reported that she was taking Foraseq for COPD, and was also taking multiple concomitant medications. The patient was hospitalized for a pulmonary embolus, and died 1 week later. According to the death certificate, she died of ventilatory failure, bronchopneumonia, pulmonary thromboembolism and encephalic vascular accident. The patient was reported to have been previously hospitalized twice during the year because of asthma. When contacted in follow-up, the patient's physician stated that the patient died of respiratory infection, not related to medication.

The third case was reported by a non-HCP. The adult female patient had a history of asthma, bronchitis, angina pectoris, diabetes and hypertension. Concomitant medications included fenoterol, ipratropium bromide, albuterol, captopril, and hydrochlorothiazide. The patient had been taking prednisone, but on an unspecified date earlier in the year she replaced this with Foraseq. The patient experienced an acute asthma attack and died of cardiac arrest on the way to the hospital.

The fourth case was reported by a non-HCP. The adult male patient had a history of asthma, hypertension, and chronic renal disorder. Concomitant medications included digoxin, captopril, nifedipine, aspirin and folic acid. The patient was reported to have felt bad, and to have died that day at home. The death certificate stated cardiac arrest, asthma and chronic renal disorder.

6.1.6 All-cause pediatric and adolescent deaths reported during the 3-year period

A search was conducted of the ARGUS safety database for cases with a fatal outcome involving a child or adolescent patient up to 18 years of age. One case was reported during the 3-year period.

A female child (age not specified in this non-HCP report) used Foraseq on unspecified dates for an unspecified indication. The patient died on an unspecified date of an unspecified cause.

6.1.7 Discussion

There were 41 serious spontaneous reports for Foradil, and 34 serious spontaneous reports for Foraseq, which included at least one asthma-related preferred term during the 3-year period (three of these cases are included in the searches for both Foradil and Foraseq). Of these, six Foradil and one Foraseq cases involved a child (up to age 12 years), and three Foradil and one Foraseq cases involved an adolescent patient (age 13–18 years). For many of these spontaneously reported cases, adverse events from other system organ classes were reported in addition to the asthma-related events. None of the spontaneous case reports was for a death reported as being due to asthma.

A further evaluation of asthma-related deaths was made by reviewing solicited cases received during the 3-year review period. There was one asthma-related death for a patient in a Foradil PMS study, which occurred 9 months prior to the review period. There were four deaths which included at least one asthma-related event reported for patients taking Foraseq via a marketing program. For one of these cases, the patient died of multiple medical problems, and asthma was not listed as a cause of death. None of these solicited case reports assessed the death as being due to Foradil/Foraseq.

There were no asthma-related deaths reported during the 3-year period for a child or an adolescent patient.

Overall, with respect to asthma-related SAEs and deaths, the results of this review of post-marketing safety data do not show new findings that heighten concern regarding the safety of Foradil.

6.2 Post-marketing experience, spontaneous reports (US FDA AERS 2001–Q1 2008)

The Spontaneous Reporting System and Adverse Event Reporting System (SRS/AERS) is an FDA-sponsored US database collecting spontaneously reported drug-related AEs. The AERS database annually receives more than 250,000 AE reports covering all marketed drug products in the USA. The following analyses focused on US spontaneous cases only.

6.2.1 Number of all AEs by ages and calendar years

The database showed a total of 1,057 AEs of any kind for the reporting period from January 1, 2001 (the year Foradil was approved to be marketed in the USA) to March 31, (Q1) 2008 among patients who reported Foradil use, irrespective of other concomitant medications (Table 6-1). Of the 1,057 AEs, the majority were reported in adults, and 44 were reported among patients 5-18 years of age.

Table 6-1 **Number of AEs of any kind by age group among patients reported using Foradil from US FDA AERS database, 2001 to Q1 2008**

Period	Age (years)					
	<5	5–12	13–18	>18	Unknown	All
	No. of AEs	No. of AEs	No. of AEs	No. of AEs	No. of AEs	No. of AEs
2001	0	1	1	5	4	11
2002	0	2	2	85	12	101
2003	1	2	2	52	10	66
2004	1	8	5	130	33	177
2005	1	6	5	128	52	192
2006	0	5	4	132	60	201
2007	0	1	0	143	113	257
Q1 2008	0	0	0	30	22	52
2001–Q1 2008	3	25	19	705	306	1,057

6.2.2 Number of asthma-related SAEs by ages and calendar years

The database was also queried for asthma-related SAEs. Severe adverse events of interests were defined using the following preferred terms (the narrow SMQ [Standardized MedDRA Query] for asthma / bronchospasm): Analgesic asthma syndrome, Asthma, Asthma exercise induced, Asthma late onset, Asthmatic crisis, Bronchial hyperreactivity, Bronchospasm, Infantile asthma, Status asthmaticus. The definition of asthma-related deaths was deaths as outcomes reported with the predefined asthma-related SAEs described above in their spontaneous reports.

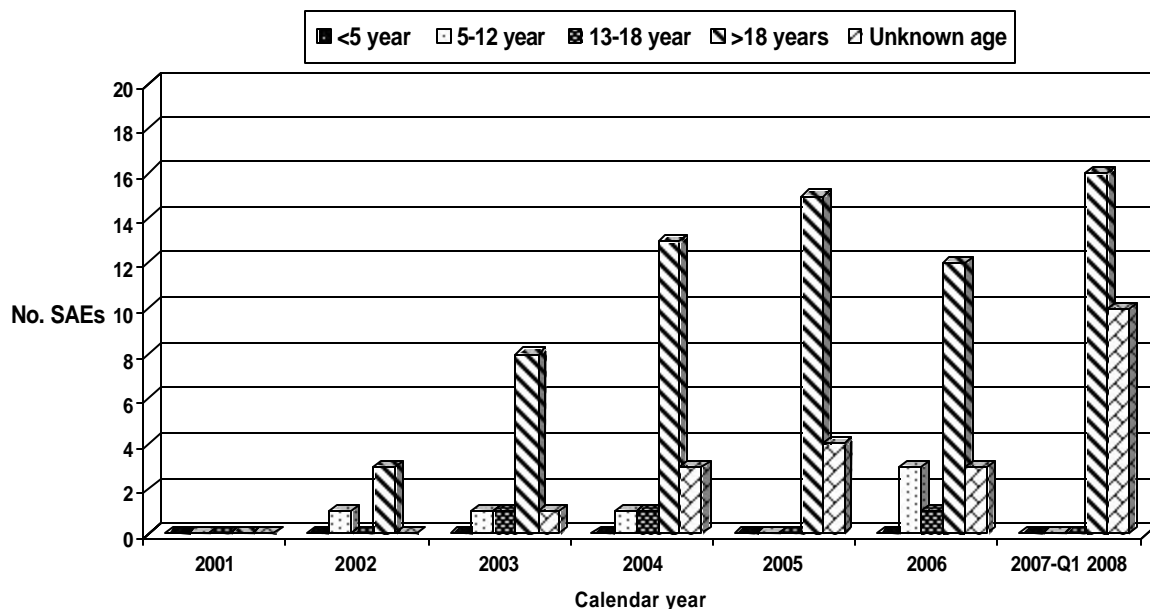
For the 7.25 year reporting period (2001 to Q1 2008), there were a total of 97 asthma-related SAEs for patients using Foradil (Table 6-2). The total number of SAEs reported by patients aged 5–12 years (N=6), 13–18 years (N=3) is low relative to the number in patients >18 years (N=67). An additional 21 SAEs were reported among Foradil patients with unknown age (Table 6-2).

Table 6-2 **Number of asthma-related SAEs by age group among patients reported using Foradil from US FDA AERS database, 2001 to Q1 2008**

Period	Age (years)					
	<5	5-12	13-18	>18	Unknown	All
	No. of SAEs	No. of SAEs	No. of SAEs	No. of SAEs	No. of SAEs	No. of SAEs
2001	0	0	0	0	0	0
2002	0	1	0	3	0	4
2003	0	1	1	8	1	11
2004	0	1	1	13	3	18
2005	0	0	0	15	4	19
2006	0	3	1	12	3	19
2007	0	0	0	16	9	25
Q1 2008	0	0	0	0	1	1
2001-Q1 2008	0	6	3	67	21	97

The number of SAEs by age and by calendar year is shown below in Figure 6-1. The total number of SAEs in adults has increased through the years, whereas among patients younger than 18 years, the number remains low from year to year.

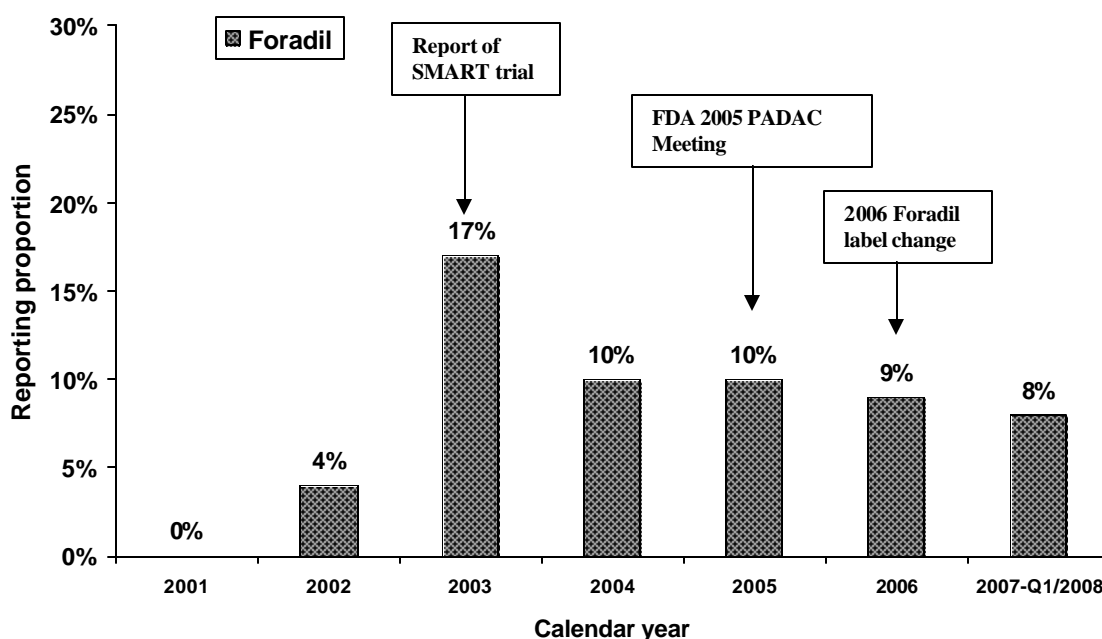
Figure 6-1 **Number of reported asthma-related SAEs by ages and by calendar years from 2001 to Q1 2008 among spontaneous reports for Foradil use using US FDA AERS database**



6.2.3 Reporting proportion of asthma-related SAEs

To identify changes in reporting frequency before and after the 2005 FDA PADAC meeting on long-acting beta₂-agonist safety and the Foradil labeling change in 2006, the results are also presented by reporting proportion (number of SAEs per 100 of all AEs). The results are shown in Figure 6-2.

Figure 6-2 Reporting proportions (No. SAEs per 100 AEs) of asthma-related SAEs among patients of all ages who reported Foradil uses in spontaneous reports by calendar years using US FDA AERS database



The reporting proportion of asthma-related SAEs among patients reported using Foradil decreased by 1%, from 10% (52 SAEs per 547 AEs) to 9% (45 SAEs per 510 AEs), after the 2005 FDA PADAC meeting on long-acting beta₂-agonist safety. A further 1% decrease, from 9% (71 SAEs per 748 AEs) to 8% (26 SAEs per 309 AEs), in the reporting proportion of asthma-related SAEs was observed after the labeling change in 2006.

6.2.4 Asthma-related deaths

Overall, asthma-related deaths were rare among spontaneous AE reports in the FDA AERS database of patients using Foradil from 2001 to Q1 2008. Of the 1,057 AEs, eight were considered asthma-related deaths. None was reported in patients <18 years of age, and six deaths were reported in patients aged >18 years; two deaths were reported with age unknown.

6.2.5 Discussion

It is estimated that 4.6 million Foradil Aerolizer prescriptions were written in the USA from 2001 (US marketing approval) to August 2008 for all indications (based on the IMS database). Taken in association with the reports of asthma-related SAEs from the AERS database, it can be estimated that the rate of asthma-related SAEs and death is low, at 2.1/100,000 prescriptions and 0.17/100,000 prescriptions, respectively.

Concordant with the increased awareness of long-acting beta₂-agonist safety after the 2005 FDA PADAC meeting and the 2006 Foradil labeling change, there were slight decreases in the reporting proportions of asthma-related SAEs among spontaneous AE reports in patients using Foradil.

7 Efficacy

The efficacy of Foradil has been demonstrated consistently in asthma clinical trials. The following section describes results from three key studies describing the benefits of Foradil in the treatment of patients older than 5 years.

7.1 Adult clinical trials

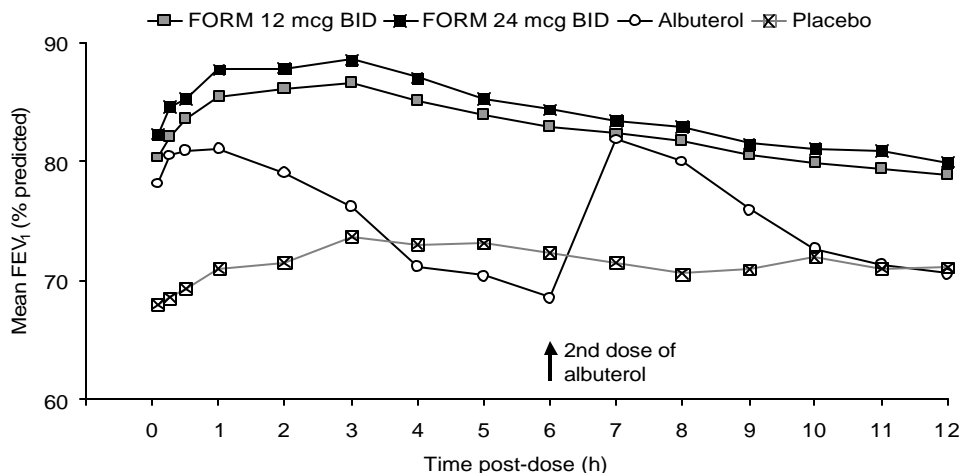
7.1.1 Studies 40 and 41 (pivotal studies)

The initial Foradil asthma submission included two 12-week studies of identical design in which patients received either formoterol 12 mcg BID, formoterol 24 mcg BID, albuterol 180 mcg QID or placebo. In Study 40 (Bensch et al. 2002), 541 subjects aged 12–75 years were randomized to the study therapies in a 1:1:1:1 ratio. Subjects were permitted, but not required, to use ICS. At baseline 51% of subjects reported using ICS with usage evenly distributed across treatment arms. Baseline FEV₁ was 66–67% predicted across the treatment groups. Patients were symptomatic as measured by a 0–4 scale, reporting average baseline daytime symptoms of 1.0 and nocturnal symptoms of 0.3. Average rescue medication use was 2 puffs taken during the day and 1.3 puffs used at night.

Lung function

After 12 weeks of treatment, subjects randomized to formoterol 12 mcg BID demonstrated highly significant differences in lung function as measured by the average FEV₁ over the 12 hours after dosing (FEV₁AUC_{0–12h}) compared with placebo and albuterol. The improvement represented an average increase of 21% compared with baseline.

Figure 7-1 **FEV₁ after 12 weeks of treatment (Study 40; adult patients with asthma)**

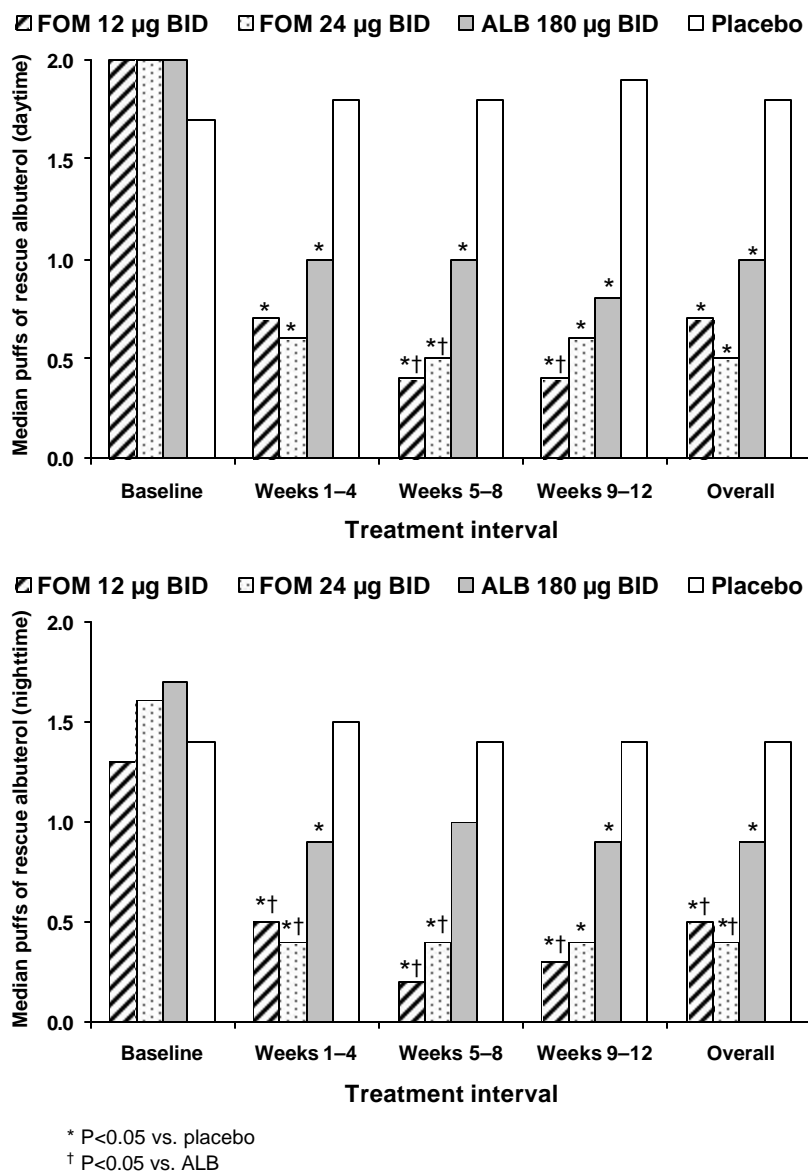


Asthma symptoms

Formoterol 24 mcg TDD improved symptoms and decreased rescue medication use compared with albuterol and placebo. The percentage of symptom-free days during the double-blind period was 53.2% for formoterol 24 mcg TDD, 52% for formoterol 24 mcg BID, 42.3% for albuterol and 32.7% for placebo. Patients randomized to formoterol 24 mcg TDD used significantly less rescue medication use than those randomized to placebo or albuterol.

Patients randomized to formoterol 12 mcg BID had a 38% reduction in night-time rescue medication use throughout the treatment period, while use in the placebo group remained unchanged. The percentages of nights with awakenings during the treatment period were 27.6%, 27.6%, 41.4% and 47.5% for formoterol 12 mcg BID, 24 mcg BID, albuterol and placebo, respectively. A similar pattern was seen for day-time rescue medication use.

Figure 7-2 Daytime and nocturnal rescue medication use (Study 40, adult patients with asthma)



Asthma worsening

Asthma worsening was defined as an increase in symptoms necessitating a change in asthma therapy. The percentages of patients with at least one episode of asthma worsening during the study were 10.4%, 12.7%, 16.5% and 15.8% for the formoterol 12 mcg BID, formoterol 24

mcg BID, albuterol and placebo treatment groups. This result was supported by an analysis of days in which subjects reported the use of more than eight puffs of rescue albuterol: 1.6% for formoterol 12 mcg BID, 2.2% for patients taking formoterol 24 mcg BID, 3.3% for patients taking albuterol and 6.3% for those on placebo.

Study 41 (Pleskow et al. 2003) demonstrated similar results.

7.1.2 Study FO/OD1 (ICS background)

The benefit of formoterol in patients receiving ICS controller medications was evaluated in a 6-month study in which bronchial hyper-responsiveness (BHR), lung function, symptoms and other measures of asthma control were measured in patients on background ICS therapy (Fitzgerald et al. 1999).

A total of 271 patients were randomized to receive formoterol, regularly dosed albuterol 180 mcg QID, or albuterol as needed. At baseline, subjects had a mean FEV₁ of 2.73 L (79.7% predicted normal).

Lung function and BHR

Formoterol was associated with significant improvement in FEV₁ and AM and PM peak expiratory flow (PEF) compared with as-needed albuterol at each post-baseline study visit. Formoterol was also associated with a reduction in BHR, as demonstrated by a significantly higher PC₂₀ after methacholine challenge (the provocation concentration required to cause a 20% fall in FEV₁) at the end of the treatment period.

Asthma symptoms

Patients receiving formoterol demonstrated an improvement in day-time and evening symptoms, leading to significantly less rescue medication use throughout the day and night (Table 7-1).

Table 7-1 Symptom and rescue medication use (Study FO/OD1, adults with asthma)

	Regular formoterol (n=89)	Regular albuterol (n=91)	On-demand albuterol (n=79)
Mean morning pre-medication PEF, L/min			
Last week of run in	442	447	438
Entire double-blind period	470* [†]	455	443
Last week of double-blind period	473* [†]	471	446
Mean night-time asthma symptom score (0–4)			
Last week of run in	0.13	0.10	0.12
Entire double-blind period	0.16* [†]	0.24	0.22
Last week of double-blind period	0.11* [†]	0.22	0.22
Mean night-time number of rescue puffs			
Last week of run in	0.70	0.72	0.86
Entire double-blind period	0.29* [†]	0.60	0.70
Last week of double-blind period	0.18* [†]	0.51	0.69
Mean day-time asthma symptom score (0–4)			
Last week of run in	1.01	0.86	0.93
Entire double-blind period	0.50*	0.60*	0.74
Last week of double-blind period	0.39*	0.50*	0.76
Mean day-time number of rescue puffs			
Last week of run in	1.69	1.51	1.68
Entire double-blind period	0.68*	0.91*	1.22
Last week of double-blind period	0.53*	0.80*	1.15

* p<0.05 vs. on-demand albuterol

[†] p<0.05 vs. regular albuterol

7.2 Pediatric studies

7.2.1 Studies Supporting Pediatric Dose Selection (DP/PD1, DP/PD2, DP/PD6)

The pediatric dose of formoterol was evaluated in 3 studies in which formoterol 24 mcg TDD was compared to formoterol 12 mcg TDD (6 mcg BID) and 48 mcg TDD (24 mcg BID). In two single-dose cross-over studies, 12 mcg TDD was less effective than 24 mcg TDD with a shorter duration of action. These findings were confirmed in a 12-week parallel-group study in which 219 patients were randomized to formoterol 12 mcg TDD, formoterol 24 mcg TDD or albuterol 180 mcg QID. Morning pre-dose peak expiratory flow (PEF), the primary

endpoint, was significantly higher in the formoterol 24 mcg TDD compared to albuterol and formoterol 12 mcg TDD. There was no statistically significant difference between the lower dose of formoterol and albuterol.

The results for the primary variable are supported by analyses of symptomatic endpoints, including daytime and nocturnal symptoms, rescue medication use and sleep disturbances in which formoterol 24 mcg TDD demonstrated a numeric, though not statistical, improvement over formoterol 12 mcg TDD.

Serious asthma exacerbations were reported for a total of 8 patients. Five patients in each of the formoterol treatment arms and 3 patients in the albuterol treatment arms were hospitalized, none of the patients required intubation.

7.2.2 Study 49 (12-month pediatric pivotal study)

The long-term safety and efficacy of Foradil Aerolizer was evaluated in a 1-year clinical study (Bensch et al. 2002), which is described in the US prescribing information. In this double-blind, parallel-group study, 518 children (aged 5–12 years) with persistent asthma were randomized to receive formoterol 12 mcg twice daily, formoterol 24 mcg twice daily or placebo. Patient demographic and baseline characteristics are shown in Table 7-2.

Table 7-2 Demographics and baseline characteristics (Study 49, children 5–12 years of age with asthma)

Characteristic	Formoterol 24 mcg (TDD) (N=171)	Formoterol 48 mcg (TDD) (N=171)	Placebo (N=176)
Mean (SD) age, years	9 (2)	9 (2)	9 (2)
Female, n (%)	64 (37)	74 (43)	56 (32)
Mean (SD) duration of asthma, y	5.3 (2.9)	5.1 (3.2)	5.3 (3.0)
≥1 concomitant disease, n (%)	100 (58)	108 (63)	114 (65)
Mean (SD) baseline FEV ₁ , L	1.63 (0.48)	1.71 (0.51)	1.65 (0.49)
Mean (SD) FEV ₁ before inhalation, % of predicted	70.7 (10.0)	71.2 (9.1)	71.2 (9.8)
Mean (SD) FEV ₁ after inhalation, % of before inhalation	130.2 (16.7)	129.2 (14.0)	129.9 (16.3)
Mean (SD) morning pre-medication PEF, L/min	234 (71)	246 (68)	243 (72)
Concomitant medication, % of patients			
Corticosteroids	75	74	74
Cromone/ketotifen	30	35	32
Others	12	15	13

Concomitant anti-inflammatory treatment was required. The children included in the trial were symptomatic despite anti-inflammatory treatment with ICS or cromones, the latter used by approximately 30% of patients.

Lung function

The primary efficacy variable was the 12-hour bronchodilator effect ($FEV_{1AUC_{0-12h}}$) at 12 weeks, which significantly favored both formoterol doses compared with placebo ($p < 0.0001$), with treatment differences of 0.15 L (24 mcg TDD) and 0.18 L (48 mcg TDD).

Patients in the formoterol-treated arms also improved in other lung function variables. Patients randomized to formoterol 24 mcg TDD demonstrated a 14.5% increase in AM PEF (+34 L/min). Treatment with formoterol 48 mcg TDD resulted in a 16.3% increase (+40 L/min) while placebo use was associated with an 8.6% improvement (21 L/min). A similar effect was seen in PM PEF.

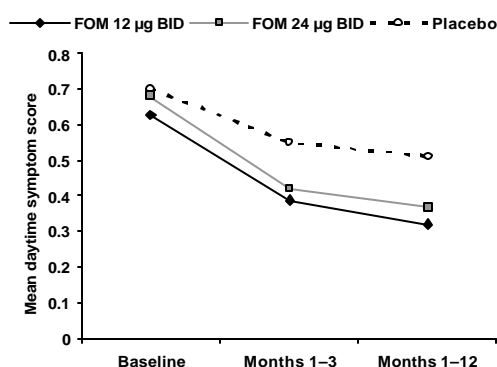
Symptom control

The formoterol-treated groups reported a reduction in day-time symptom scores greater than placebo. The decrease in symptom scores was accompanied by a decrease in rescue medication use. Deterioration days were defined as days in which more than four puffs of rescue medication were used, patients had a symptom score greater than 1 or an additional controller medication was used. On average, patients treated with formoterol experienced 11 deterioration days during the course of the study compared with an average of 20 deterioration days among patients in the placebo group.

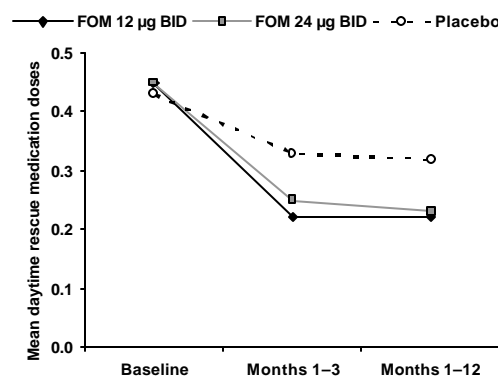
As this is a large and relatively long-term study which generated most of the serious asthma exacerbations for the current database, it is worth considering efficacy over time. Asthma control in terms of day- or night-time symptom scores or increased use of rescue medication was maintained throughout the study period when scores averaged over 12 months are compared with scores averaged over the first 3 months.

Figure 7-3 Asthma control over time (Study 49, children 5–12 years of age with asthma): symptom scores and rescue medication use

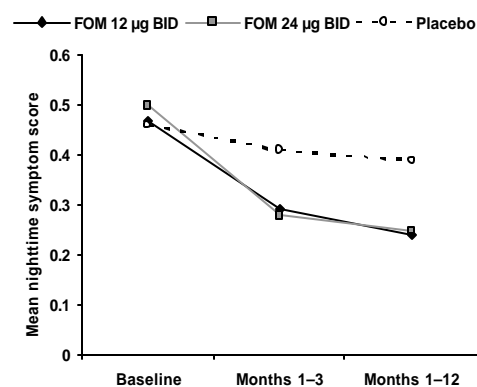
Daytime symptom scores



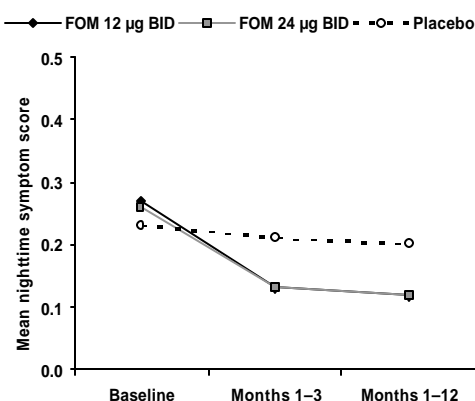
Daytime rescue use



Nighttime symptom scores



Nighttime rescue use



7.3 Efficacy conclusions

The data from the representative trials described demonstrate that formoterol improved lung function and decreased BHR, asthma symptoms and rescue medication use in adults and children with asthma. When used as a free combination with ICS, formoterol demonstrated a significant improvement in these variables compared with ICS and as-needed albuterol. In children, formoterol improved lung function throughout the day and evening. The improved lung function was associated with fewer symptoms and less rescue medication use and a halving in the number of deterioration days over the course of a 1-year study. The Foradil data are similar to studies performed with other formulations of formoterol, which also

demonstrate the efficacy of formoterol compared with ICS monotherapy (Pauwels et al. 1997, Noonan et al. 2006).

8 Benefit:risk assessment and conclusions

8.1 Burden of disease and the role of long-acting beta₂-agonists in treatment

In the USA, 20 million people are reported to have a current diagnosis of asthma. Of these, 6.2 million are children (prevalence of 8.5%). The burden of asthma includes missed days of school and work, decreased productivity, emergency department visits and hospitalizations (CDC/NIH, Healthy People 2010). The number of asthma-related hospitalizations among children has remained essentially the same over the past 10 years (27 per 10,000 in 2004). Asthma-related deaths remain a rare but devastating consequence of the disease, with the number of deaths due to asthma decreasing since 1999 (Akinbami et al. 2006, Moorman et al. 2007). In 2004, the most recent year for which data are available, the rate of death was 1.9 per 10,000 patients with asthma.

Evidence-based guidelines from the NHLBI Expert Panel Report 3 (NHLBI Expert Panel 3 2007) recommend ICS as first-line therapy for asthma patients of all ages and long-acting beta₂-agonists as add-on therapy for those patients not controlled by ICS alone. In children aged 5–11 years, long-acting beta₂-agonists, moderate-strength ICS, leukotriene antagonists and theophylline are recommended as adjuvant therapy for children whose symptoms are not controlled with low-dose ICS alone. Particularly in children who complain of asthma-related symptoms or increased impairment, the guidelines state that there is evidence to suggest that a long-acting beta₂-agonists is an appropriate add-on therapy.

In adolescents 12–18 years of age and adults, the EPR-3 recommends medium-strength ICS or the addition of long-acting beta₂-agonists to low-dose ICS for those patients not controlled on low-dose ICS. For patients inadequately controlled on medium- or high-strength ICS, long-acting beta₂-agonists are the preferred treatment option based on evidence that the concomitant use of long-acting beta₂-agonists and ICS provides greater improvement in lung function and other measures of asthma control compared with doubling the dose of ICS or adding theophylline or leukotriene antagonists (Pauwels et al. 1997, Bateman et al. 2004).

For patients of all ages, the EPR-3 advises physicians to step up therapy until patients are well controlled, with near-normal lung function, minimal symptoms and rescue medication use and no activity limitations. Once the patient has been well controlled for a period of time, guidelines recommend stepping down treatment or decreasing additional medications then decreasing the dose of ICS (NHLBI Expert Panel 3 2007).

8.2 Summary of benefit

In children and adults, Foradil Aerolizer has been demonstrated to improve various aspects of asthma control including measures of lung function, symptoms, the need for rescue medication use and mild exacerbations, including asthma worsening requiring treatment with systemic corticosteroids. The efficacy of Foradil Aerolizer was demonstrated in two 12-week

studies including approximately 1,100 adults and adolescents with asthma. Bronchodilation was rapid in onset and lasted for 12 hours post-dose. The magnitude and duration of bronchodilation were maintained throughout the studies. In addition, formoterol improved asthma symptoms, reduced the use of rescue medication, and increased PEF (Bensch et al. 2001, Pleskow et al. 2003).

In a 6-month study of 271 patients using concomitant ICS, aged between 18 and 65 years, formoterol was superior for bronchodilation (FEV₁), bronchoprotection (BHR, assessed as methacholine PD₂₀), and measures of clinical control (PEF, symptoms and use of rescue medication) compared with as-needed albuterol. Importantly, the study found no evidence of progressive tolerance to bronchodilator effects, or any rebound increase in BHR following discontinuation of treatment (Fitzgerald et al. 1999).

Foradil Aerolizer provided similar improvements in pediatric populations. When given for 12 months to 518 children with asthma receiving anti-inflammatory treatment (cromones or ICS) (Study 49), patients demonstrated an improvement in FEV₁ and a decrease in day-time and night-time symptoms, with trends favoring formoterol with regard to asthma exacerbations (Bensch et al. 2002).

Several non-Novartis studies suggest that the addition of a long-acting beta₂-agonist to an ICS provides greater improvement in lung function and other measures of asthma control compared with doubling the dose of ICS or adding one of the currently available alternatives, including leukotriene antagonists, leukotriene synthesis inhibitors or theophyllines. Two large studies, one comparing formoterol/budesonide to budesonide alone and the other comparing salmeterol/fluticasone to fluticasone monotherapy, demonstrated that adding a long-acting beta₂-agonist is more effective than increasing the ICS dose (Pauwels et al. 1997, Bateman et al. 2004). In the landmark FACET study (Pauwels et al. 1997), adding formoterol 12 mcg BID to budesonide 100 mcg BID was more effective than budesonide 400 mcg BID alone in improving lung function and decreasing asthma exacerbations requiring oral corticosteroids. A meta-analysis comparing leukotriene antagonists to long-acting beta₂-agonists as adjuvant therapy to ICS revealed that the addition of a long-acting beta₂-agonist provided greater efficacy in FEV₁ and asthma control than leukotriene receptor antagonists (Ducharme et al. 2006). There are few head-to-head studies comparing long-acting beta₂-agonists to leukotriene synthesis inhibitors and theophylline; however, both of these treatment options have significant systemic adverse events and require frequent monitoring.

8.3 Summary of risk

The current pooled analysis was performed with data from randomized, double-blind asthma studies of Foradil Aerolizer and Foradil Certihaler. As ICS are the foundation of asthma therapy, an assessment of the risk of long-acting beta₂-agonist use should focus on sub-populations in which formoterol is used in combination with an ICS. In this sub-population, Foradil does not appear to increase the risk of asthma-related hospitalizations in patients older than 12 years. In patients older than 18 years, the rate of asthma-related serious events was 1.2 per 100 patient years for patients randomized to formoterol, 1.9 per 100 patient years for placebo, and 4.1 per 100 patient years for albuterol QID. There was a single death in the pooled analysis of a patient treated with formoterol, with no record of concomitant ICS use.

In patients 5–12 years of age, there was a higher incidence of serious asthma exacerbations among patients randomized to formoterol compared with placebo. The rate of asthma-related hospitalizations in subjects treated with the approved dose of Foradil was 5.4 per 100 patient years (3.2%) overall compared with 16.2 per 100 patient years (3.1%) in patients receiving albuterol and 0.6 per 100 patient years among patients receiving placebo. The increased rate of serious asthma exacerbations in the albuterol-treated group may be due to a shorter duration of the trials in which this treatment was used. There were no asthma-related deaths among children in this pooled data set. Most of the patients in the pediatric pooled analysis were enrolled in Study 49, a 1-year placebo-controlled trial, which was the basis for approval in this age group and is described in the current prescribing information.

In all age groups, the risk of serious asthma exacerbations for patients treated with formoterol was similar to the risk for patients treated with albuterol dosed QID. Although regularly dosed albuterol is not a recommended regimen, if long-acting beta₂-agonists were removed from the market, QID dosing may become more common, either as a prescribed regimen, or more likely, as patients experience deteriorating asthma control, as more frequent rescue use. The current analyses suggest that this option would not decrease the risk of serious asthma exacerbations for patients of any age.

Although post-marketing data from the FDA AERS database are limited, analysis of the available information appears to indicate that the numbers of SAEs and deaths per 100,000 Foradil prescriptions are low. Among 4.6 million prescriptions, no deaths were reported among patients less than 18 years of age for the entire 7.25 year reporting period.

8.4 The role of monotherapy long-acting beta₂ agonists – importance of free combination

Foradil and other long-acting beta₂-agonists remain important therapeutic options for several reasons. Foradil allows physicians and patients the flexibility to add formoterol to any of the approved ICS monotherapies. Currently, Symbicort® (formoterol and budesonide 9 mcg/90 mg and 9 mcg/180 mg) is the only available fixed-dose combination of formoterol and ICS available in the USA. The availability of Foradil allows physicians to pair formoterol with other approved ICS, including fluticasone propionate, mometasone furoate and ciclesonide.

In accordance with current guidelines, the availability of long-acting beta₂-agonists as monotherapy allows physicians and patients to step up therapy in patients not controlled on ICS and to step it down once control is achieved. The formoterol/budesonide fixed-dose combination provides a maximum daily dose of 640 mcg budesonide while budesonide monotherapy is approved at a daily dose up to 1440 mcg. For difficult-to-control patients, a fixed-dose combination cannot be used to provide high-dose ICS without exceeding the recommended dose of formoterol.

Patients vary in their ability to use inhalation devices. Some patients lack the hand–breath coordination needed to use MDIs and prefer dry powder inhalers. The currently approved formoterol fixed-dose combinations are only available as an MDI.

Finally, formoterol monotherapy is used to prevent exercise-induced bronchospasm. Foradil has been demonstrated to prevent exercise-induced bronchospasm for up to 12 hours. The

monotherapy option allows patients who may not require chronic regular treatment with a long-acting beta₂-agonist/ICS combination to use formoterol in advance of activity.

8.5 Activities conducted to evaluate and minimize the risk of serious asthma exacerbations

To help ensure safe and effective use of Foradil Aerolizer, the following efforts have been made.

Post-marketing commitment study

A Phase IV post-marketing commitment 16-week study (2307) was performed in 2085 adult and adolescent (12 years and older) patients to specifically investigate the occurrence of serious asthma-related events observed in the pivotal studies (Studies 40 and 41). Inclusion criteria for this study were matched to the pivotal studies; the main observed difference was an increased use of steroids in Study 2307, which reflects the difference in asthma treatment when this study was performed (2002–2004) compared to Studies 40 and 41 (1995–1996). This study did not reveal a dose-response in terms of asthma-related exacerbations. The label was updated to include the rates of asthma-related exacerbations from this study (0.6% with formoterol 12 mcg BID, 0.4% with formoterol 24 mcg BID and 0.2% with placebo).

Pharmacogenetic analysis

Following the 2005 PADAC meeting, Novartis conducted a retrospective pharmacogenetic analysis of polymorphisms in the beta₂ adrenergic receptor gene (ADRB2) from two Phase 3 formoterol trials. The results of this exploratory analysis were submitted to and discussed with FDA as a Voluntary Genomic Data Submission (VGDS). No association between ADRB2 genotypes and clinical parameters (baseline FEV₁, FEV₁AUC and AM PEF) were found; however, it should be noted that due to the small sample size and large variation in the clinical responses, it would be difficult to detect small genetic effects.

Epidemiological studies

Novartis conducted an epidemiology study using the Ingenix Research Data Mart, a claims database from US health plan between 2000 and 2004 that aimed to estimate incidence rates of death, intubation, and asthma exacerbations leading to emergency room visit or hospitalization among long-acting beta₂-agonist initiators, as compared with rates of these outcome events among non-long-acting beta₂-agonist users in a cohort of inhaled corticosteroid users (N=49,116). We conducted a retrospective cohort study of inhaled corticosteroid users, some of whom initiated treatment with a long-acting beta₂-agonist, and followed the cohort over time for the following outcomes: all-cause mortality, intubations, and asthma exacerbations leading to emergency room visits or hospitalizations. The results indicate no increased risk of all-cause mortality or intubation associated with use of long-acting beta₂-agonists, but an increased risk of emergency room visits (HR=1.2; 95%CI:1.1–1.4) and hospitalizations (HR=1.8; 95%CI:1.4–2.3).

To further confirm these findings, and in acknowledgement of the potential study limitations associated with correctly interpreting these findings, another epidemiological study is planned to investigate the incidence of serious asthma exacerbation, asthma-related emergency room

visits, asthma-related hospitalizations, and intubations by different combinations of all available asthma medications used among asthmatic patients both in baseline and in time-dependant manner (re-access the asthma medication use every 6 month during the follow-up) using Multi-state Medicaid database from 2000 to 2007, which includes approximately 870,000 asthma patients.

Global Pharmacovigilance

Novartis pharmacovigilance procedures include routine review and assessment of each reported case by a physician. In addition, there is an annual signal detection review, which includes a focus on asthma-related SAEs and deaths for formoterol.

Labeling and Medication Guide

The US and global labeling were updated in 2006 to reflect the potential risks and to describe appropriate use of formoterol. As part of this update, a Medication Guide was also made available to patients.

Educate and communicate risk

Schering-Plough, the licensee of the product in the US, maintains a website (www.foradil.us) to educate prescribers and consumers on the appropriate use of formoterol. In addition, it contains a direct link to FDA MedWatch to report adverse events. The statement in the website reads “*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.*”

8.6 Conclusions

The findings of this safety review indicate that the benefit:risk ratio of formoterol remains positive. Among the 45 clinical trials included in this review, there were no deaths or intubations among subjects 5–12 and 13–18 years of age, and one asthma-related death occurred in a patient older than 18 years. The overall analysis, including patients of all ages demonstrates an increase in serious asthma exacerbations among patients treated with formoterol compared to placebo.

In adults and children 13–18 years of age, the risk of serious non-fatal asthma exacerbations is similar between patients using formoterol 24 mcg TDD and those on placebo. The analyses suggest that the risk of serious asthma exacerbations may be decreased by concomitant use of inhaled corticosteroids.

There is evidence of an increased risk of non-fatal serious asthma exacerbations in subjects taking formoterol when compared with placebo among children ages 5–12. These results should be considered in the context that the majority of the placebo-controlled data are from a single study conducted from 1996 to 1998 when the standard of care for the treatment of asthma differed from current treatment standards. In addition, this increased risk has not been observed in more recent studies in the literature nor in post-marketing experience.

Long-acting beta₂-agonists remain an important therapeutic option for those patients who remain uncontrolled on inhaled corticosteroids. When used according to labeling and treatment guidelines, Foradil enables patients and physicians to step-up treatment in patients

who are not controlled, then step down once control has been achieved. Foradil has been shown to improve lung function and symptoms in the great majority of uncontrolled patients. Other potential add-on therapies to inhaled corticosteroids are not without risk, including short-acting beta₂-agonists, which these analyses suggest are associated with increased risk of serious asthma exacerbations.

Novartis acknowledges the increased risk for serious asthma exacerbations in our database, which is reflected in the current labeling. In view of all of the evidence, however, the favorable benefit:risk ratio supports the continued use of formoterol in the treatment of patients with asthma.

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10 Appendix 1 - Trials included in the pooled analysis

Pediatric studies			
Study/ study number	Total randomized patients	Duration of double-blind therapy	Treatment arms
Study 49	518	365 days	Formoterol 12 & 24 mcg BID Placebo
DP/PD2	219	85 days	Formoterol 6 & 12 mcg BID albuterol 600 mcg BID
F0604	249	85 days	Formoterol 10 mcg BID Placebo
DP/PD5	39	28 days	Formoterol 12 mcg BID albuterol 400 mcg BID
F0602	77	7 days (4 period cross over)	Formoterol 5, 10, 15 & 30 mcg BID via MDDPI Formoterol 12 mcg BID via Aerolizer Placebo
I2202	34	1 day (6 period cross over)	Formoterol 3, 6 & 12 mcg BID via HFA MDI Formoterol 6 & 12 mcg BID via Aerolizer Placebo
DP/PD6	15	1 day (5 period cross over)	Formoterol 3, 6 & 12 mcg BID albuterol 200 mcg BID Placebo
DP/PD1	14	1 day (5 period cross over)	Formoterol 3, 6 & 12 mcg BID albuterol 200 mcg BID Placebo
Adolescent and adult studies			
Study/ study number	Total randomized patients	Duration of double-blind therapy	Treatment arms
FO/OD1	271	169 days	Formoterol 12 mcg BID albuterol 400 mcg BID Placebo + on-demand albuterol 100 mcg/puff up to 8 puffs/day
2307	2085	113 days	Formoterol 12 & 24 mcg BID Placebo Open-label Formoterol 12 mcg BID + <2 rescue doses of Formoterol 12 mcg/day
Study 40	541	85 days	Formoterol 12 & 24 mcg BID albuterol 360 mcg BID Placebo
Study 41	554	85 days	Formoterol 12 & 24 mcg BID albuterol 360 mcg BID Placebo
DP/RD1	304	85 days	Formoterol 12 mcg BID albuterol 800 mcg BID Placebo
DP/RD3	262	85 days	Formoterol 12 & 24 mcg BID albuterol 800 mcg BID
DP/RD2	318	85 days	Formoterol 12 & 24 mcg BID albuterol 800 mcg BID
Study 62	203	85 days	4 puffs BEC 250 mcg BID via MDI + 1 puff placebo Formoterol BID via dry powder capsule 2 puffs beclamethasone 250 mcg BID via MDI + 2 puffs placebo beclamethasone BID via MDI + Formoterol 12 mcg BID via dry powder capsule
F2302	265	85 days	Formoterol 10 mcg BID via MDDPI albuterol 360 mcg BID via MDI Placebo

Adolescent and adult studies			
Study/ study number	Total randomized patients	Duration of double-blind therapy	Treatment arms
F2303	239	85 days	Formoterol 10 mcg BID via MDDPI albuterol 360 mcg BID via MDI Placebo
F0605	365	85 days	Formoterol 10 mcg BID via MDDPI Formoterol 12 mcg BID via Aerolizer Placebo
MT/AO3	1033	85 days	Formoterol 6, 12 & 24 mcg BID via MT&A + placebo ISF Formoterol 6, 12 & 24 mcg BID via ISF + placebo MT&A Placebo ISF + placebo MT&A
FO/SO2	64	64 days	Formoterol 24 mcg BID budesonide 400 mcg BID Placebo
FO/UK2	18	28 days (2-period cross-over)	Formoterol 24 mcg BID Placebo
DP/SP2	19	15 days	Formoterol 24 mcg BID Placebo
DP/NA1	80	14 day (2 period cross over)	Formoterol 6 mcg BID albuterol 200 mcg BID
F0601	67	7 day (4 period cross over)	Formoterol 5, 10, 15 & 30 mcg BID via MDDPI Formoterol 12 mcg BID via Aerolizer Placebo
DP/NA2	18	2 day (2 period cross over)	Formoterol 6 mcg BID Placebo
DP/CU1	12	2 days	Formoterol 48 mcg BID via DPI Formoterol 48 mcg BID via aerosol
DP/SP4	22	1 day (5 period cross over)	Formoterol 6, 12, 24 & 48 mcg BID Placebo
FO/IT2	24	1 day (4 period cross over)	Real allergen + Formoterol 12 mcg BID Dummy allergen + Formoterol 12 mcg BID Real allergen + placebo Dummy allergen + placebo
DP/DF1	16	1 day (5 period cross over)	Formoterol 6, 12 & 24 mcg BID Formoterol solution 6 mcg BID Placebo
DP/DF2	15	1 day (5 period cross over)	Formoterol 3, 6 & 12 mcg BID albuterol 200 mcg BID Placebo
DP/DF3	30	1 day (3 period cross over)	Formoterol 6, 12 & 24 mcg BID Formoterol 6 mcg BID via MDI Placebo
DP/DF4	18	1 day (3 period cross over)	Formoterol 3, 6 & 12 mcg BID Formoterol suspension 12 mcg BID Placebo
DP/ME1	17	1 day (4 period cross over)	Formoterol 6 & 12 mcg BID albuterol 200 mcg BID Placebo
DP/ME2	6	1 day (4 period cross over)	Formoterol 6 & 12 mcg BID albuterol 200 mcg BID Placebo
DP/ON1	18	1 day (3 period cross over)	Formoterol 6 & 12 mcg BID Placebo
DP/ON2	16	1 day (4 period cross over)	Formoterol 6 & 12 mcg BID albuterol 200 mcg BID Placebo
DP/DA2	23	1 day (3 period cross over)	Formoterol 6 mcg BID albuterol 200 mcg BID Placebo

Adolescent and adult studies			
Study/ study number	Total randomized patients	Duration of double-blind therapy	Treatment arms
F2308	51	1 day (4 period cross over)	Formoterol 5 mcg BID via MDDPI-Z Formoterol 5 mcg BID via MDDPI-X Formoterol 6 mcg BID via Aerolizer
MT/A02	161	1 day (5 period cross over)	Formoterol 3, 6 & 12 mcg BID via MT&A + placebo ISF Formoterol 3, 6 & 12 mcg BID via ISF + placebo MT&A Placebo ISF + placebo MT&A
I2201	26	1 day (6 period cross over)	Formoterol 3, 6 & 12 mcg BID via HFA MDI Formoterol 6 & 12 mcg BID via Aerolizer Placebo
A2228	45	1 day (5 period cross over)	indacaterol 150, 300 & 600 mcg QD Formoterol 12 mcg BID Placebo
H2201	25	1 day (5 period crossover)	Mometasone/ Formoterol 50/5 & 100/10 mcg BID Formoterol 5 mcg BID via MDI Formoterol 6 mcg BID via Aerolizer
FORS02	19	1	Formoterol 12 mcg BID Formoterol fumarate (Oxis) 12 mcg BID
FORS01	19	1	Limited information available