

CLINICAL REVIEW

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Established Name Formoterol fumarate
(Proposed) Trade Name Foradil[®] Aerolizer[®]
Therapeutic Class bronchodilator
Applicant Novartis

Priority Designation N.A.

Formulation Inhalation powder
Dosing Regimen 12 mcg BID
Indication Asthma
Intended Population ≥ 12 years

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1 EXECUTIVE SUMMARY

Foradil[®] Aerolizer[®] from Novartis Pharmaceuticals is a racemate of the selective long-acting beta₂-adrenergic agonist, formoterol fumarate, in a dry powder inhalation formulation. It was approved for use in asthma in 2001. The Foradil NDA included three pivotal studies, two in adults and adolescents and one in children. In all three studies, two dosages of Foradil were evaluated (12 mcg BID and 24 mcg BID), but the approval was restricted to the lower dose because serious asthma exacerbations occurred with more frequency in patients, both adult and pediatric, who received the higher dose. The finding was significant enough to warrant a commitment to perform a Phase 4 clinical study to further investigate the relative safety of the difference doses.

The medical literature reflects concern about possible adverse effects of using long-acting beta-agonists on a long-term basis. Two large, simple surveillance studies using salmeterol found that asthma-related deaths or life-threatening asthma exacerbations occurred at low rates, but were increased in patients who received salmeterol as compared to placebo or albuterol.

The Phase 4 study with Foradil was relatively small compared to the salmeterol studies. It was also too small to be able to conclusively confirm the results obtained from the Foradil Phase 3 studies, but the Phase 4 results were generally consistent with the Phase 3 results, suggesting higher rates of clinically serious asthma exacerbations when the higher dose of Foradil was used.

1.1 Summary of Clinical Findings

The Foradil Phase 4 study was a multicenter, randomized, placebo-controlled, blinded, large simple study of 16 weeks duration. Patients 12 years of age and older with mild to moderate persistent asthma, $\geq 12\%$ reversibility, and no recent illnesses or exacerbations were eligible. The protocol was amended to allow more liberal use of anti-inflammatory medications. The amendments were intended by the Sponsor to reflect the changing standard of care which occurred during the course of the study with dissemination of the GINA guidelines.

Patients were randomized to receive Foradil 12 mcg BID, Foradil 24 mcg BID, Foradil 12 mcg BID with up to two additional on-demand 12 mcg doses per day, or placebo. The Foradil fixed-dose and placebo groups were treated in double-blind fashion. The Foradil on-demand group was open-label. The patients were seen in clinic every four weeks for study assessments including FEV₁ determinations and solicitation of adverse events. The primary outcome measure was the proportion of patients who had a serious asthma-related adverse event while receiving 24 mcg BID vs. the proportion while receiving 12 mcg BID.

At study completion, 2083 patients had been randomized in equal ratio among the four treatment groups. The groups did not differ in their demographic characteristics, in their pre-study pharmacologic management, or in the historical indicators of asthma severity. Importantly, these baseline factors also appeared to be similar to the patients in the Phase 3 studies, with one exception. More patients in the Phase 4 studies received inhaled corticosteroids during the study

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than those in the Phase 3 studies (58% vs. 47%). This most likely reflects the change in asthma management previously mentioned.

There were no deaths in the study. Nine patients had serious asthma-related adverse events. Of the nine, seven had events that could be specifically considered exacerbations, the endpoint of interest generated from the Phase 3 data: 3 (0.6%) in Foradil 12mcg BID; 2 (0.4%) in Foradil 24 mcg BID; 1 (0.2%) in placebo; and 1 (0.2%) in Foradil open-label. Two patients, one in Foradil 12 mcg BID and one in Foradil 24 mcg BID, had exacerbations that required intubation. There were additional patients who had asthma exacerbations that did not meet the regulatory criteria of seriousness, but that did lead to study dropout. There were more patients in the higher dose Foradil group than in the lower dose group who had either serious asthma exacerbations or study dropout because of non-serious exacerbations (13 vs. 8).

[Referential Notation: References to source material are provided in this review. Within text, the references are bracketed []. Source material was of two formats: paper hard copy and electronic. References to hard copy material (e.g., FDA reviews, correspondence, meeting minutes) are descriptive; for example, [NDA XX-XXX, Medical Officer's Review, December 12, 1998]. References to electronic material show the file name and letter date. Unless otherwise noted, references refer to the original submission. When referring to source material submitted after the date of the original submission, the stamp date is also noted.]

2 INTRODUCTION AND BACKGROUND

This is the Medical Officer review of a single clinical study conducted by Novartis Pharmaceuticals Corporation in compliance with a Phase 4 commitment made upon approval of its product, Foradil[®] Aerolizer[®]. Foradil is a racemate of formoterol fumarate in a dry powder inhaler formulation.

2.1 Product Information

Formoterol fumarate is a long-acting selective beta₂-adrenergic receptor agonist. As a class, the beta₂-adrenoreceptor agonist drugs act at least in part by stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Cyclic AMP in turn causes relaxation of bronchial smooth muscle and inhibition of cellular release of mediators of immediate hypersensitivity. Among the resultant effects is bronchodilation.

Foradil is indicated for “*long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting, beta₂-agonists.*” [Foradil Aerolizer package insert] It is also indicated for the acute prevention of exercise-induced bronchospasm and for the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease. The indication of interest for this review is asthma. The approved dose for asthma is one 12 mcg capsule every 12 hours via the Aerolizer inhaler.

The approved package insert for Foradil includes warnings and precautions about the following events and circumstances that are most relevant to this review:

- the dosage should not exceed one 12 mcg capsule twice daily (24 mcg total daily dose)
- deterioration of asthma, with consequent need for re-evaluation of the patient, increased dosage of Foradil, and/or other medications
- notable adverse events: tremors, insomnia, tachycardia, decreased serum potassium, increased plasma glucose
- beta-agonist-associated ECG changes including flattening of the T wave, QT interval prolongation, and ST segment depression

- tolerance to the bronchoprotective effect. Note, this is not so much true tachyphylaxis, with loss of bronchodilatory effect, as tolerance to bronchoprotective effect upon challenge
- paradoxical bronchospasm

There are additional warnings about not using Foradil for acute relief of symptoms, and not using it as substitute for corticosteroids or other anti-inflammatory agents.

2.2 Important Issues With Pharmacologically Related Products

Salmeterol xinafoate is also a long-acting beta₂-agonist (LABA). It was approved for asthma as Serevent[®] Inhalation Aerosol in 1994. In 1996, the Sponsor, GlaxoSmithKline (GSK), initiated the Salmeterol Multicenter Asthma Research Trial (“SMART”) to investigate possible detrimental effects of chronic beta₂-agonist use, a topic discussed more and more in the pulmonary literature of the time. Specifically, the 1993 Salmeterol Nationwide Surveillance (SNS) study in the United Kingdom compared Serevent to albuterol and reported a “small but non-significant excess mortality” in patients taking salmeterol, and a significant excess of asthma events including death in patients with severe asthma on entry¹.

The SMART study was a multi-center, double-blind, parallel group, placebo-controlled, 28-week study in asthmatics naïve to LABAs who had either salmeterol 42 mcg BID or placebo added to their usual asthma pharmacotherapy. The primary endpoint was combined respiratory-related deaths and respiratory life-threatening experiences (intubation plus mechanical ventilation). Secondary endpoints included asthma-related deaths, asthma-related deaths or life-threatening experiences, all cause deaths, SAEs, changes in medications, and several patient-reported outcomes. There was an initial clinic visit and then telephone contacts at 4, 8, 12, 16, 20, 24, and 28 weeks. The study was planned for 60,000 patients with a halfway interim analysis. Stopping criteria were pre-specified to be increased combined respiratory-related deaths and respiratory life-threatening experiences, or increased asthma-related deaths in the salmeterol group. Stopping was to be based on a risk ratio of 1.4 for the first criterion and 3 for the second. A significance level of 0.01 was to be used to determine confidence limits at the interim analysis.

The interim analysis was performed when 25,858 patients had been enrolled. The results, reviewed by the Data Safety Monitoring Board (DSMB) for the study, showed a relative risk of 1.26 (0.74, 2.13) for the primary endpoint and 3.25 (0.86, 12.27) for asthma-related deaths. These relative risk point estimates were close to those the study was designed to exclude. The DSMB determined that the study could not be completed in a reasonable time (2 more years) to provide conclusive findings, and recommended that the study be stopped and the results disseminated. The study was therefore stopped in January, 2003, with a total of 26,535 patients enrolled. The results for those patients, as initially reported by the Sponsor, are shown in the next Table.

Table 1: Initial Results of SMART Study at Termination

Outcome	Salmeterol	Placebo	Relative Risk (95% CI)
	N=13,174	N=13,179	
	N		
Combined respiratory-related deaths and life-threatening experiences	48	42	1.1433 (0.7562, 1.7286)
Respiratory-related deaths	23	17	1.3535 (0.7234, 2.5322)
Combined asthma-related deaths and life-threatening experiences	36	23	1.5658 (0.9285, 2.6407)
Asthma-related deaths	13	4	3.2512 (1.0604, 9.9685)
Combined all cause deaths and life-threatening experiences	69	68	1.0151 (0.7268, 1.4177)
All cause deaths	41	42	0.9766 (0.6355, 1.5007)
All cause hospitalizations	498	449	1.1096 (0.9789, 1.2576)

Source: NDA 20-236/S-030, Medical Officer's Review, DFS, September 20, 2004, p 38

Subgroup analyses further suggested that the observed overall differences were accentuated in African American patients.

With these results, several labeling changes were enacted in August, 2003, for products containing salmeterol:

- a boxed warning was added to the labels for Serevent products (Inhalation Aerosol and Diskus Inhaler) and for Advair, a combination of salmeterol and fluticasone. The boxed warning states

“Data from a large placebo-controlled US study that compared the safety of salmeterol (Serevent Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians...”

- a description of the SMART study and its results was added to the Clinical Trials sections of the Serevent products
- descriptions of the SMART study and the SNS study were added to the Warnings sections of the Serevent products’ and Advair labels

In February, 2004, GSK submitted a prior approval labeling supplement with an amended SMART study report. At issue was new information from the Sponsor captured from the National Death Index (NDI) about patients in the study who had been lost to follow up. In the course of reviewing this supplement, the Division became aware of discrepancies between the datasets specified by the SMART study protocol and those presented by the Sponsor in its initial study report. The latter included 6-month follow-up results, while the protocol specified only a 28-week study period. The Division considered the protocol-specified 28-week period to be the proper one. The Division also considered the NDI search to be justified.

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Table 2 below re-displays the results from Table 1, revised to include the NDI data, confining results to the 28-week study period, and using life table analyses to calculate relative risks to account for the Sponsor's method of censoring.

Table 2: Results of SMART Study at Termination – Revised

Outcome	Salmeterol	Placebo	Relative Risk (95% CI)
	N=13,176	N=13,179	
N			
Combined respiratory-related deaths and life-threatening experiences	50	36	1.40 (0.91, 2.14)
Respiratory-related deaths	24	11	2.16 (1.06, 4.41)
Combined asthma-related deaths and life-threatening experiences	37	22	1.71 (1.01, 2.89)
Asthma-related deaths	13	3	4.37 (1.25, 15.34)
Combined all cause deaths and life-threatening experiences	70	59	1.19 (0.84, 1.68)
All cause deaths	42	32	1.30 (0.82, 2.06)

Source: NDA 20-236/S-030, Medical Officer's Review, DFS, September 20, 2004, pp 18, 20

In September, 2004, in response to the supplement of February, 2004, the most recent labeling changes for Serevent were enacted to include the following language, which is the most current at the time of this review.

Salmeterol Multi-center Asthma Research Trial: *The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta₂-agonist-naïve patients with asthma (average age of 39 years, 71% Caucasian, 18% African American, 8% Hispanic) to assess the safety of salmeterol (SEREVENT Inhalation Aerosol, 42 mcg twice daily over 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355). Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. However, analyses of secondary endpoints suggested that patients receiving salmeterol may be at increased risk for some of these events compared to patients receiving placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.91, 2.14) for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176 vs. 36 out of 13,179, respectively). In the total population, a higher number of asthma-related deaths (13 vs. 3, RR 4.37, 95% CI 1.25, 15.34) and combined asthma-related deaths or life-threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with salmeterol than those treated with placebo. The analysis of the African American subgroup showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated with salmeterol relative to those treated with placebo (20 out of 2,366 vs. 5 out of 2,319, respectively). In African Americans, a higher number of asthma-related*

deaths (7 vs. 1, RR 7.26, 95% CI 0.89, 58.94) and combined asthma-related deaths or life-threatening experiences (19 vs. 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62, 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with placebo (29 out of 9,281 vs. 28 out of 9,361, respectively). In Caucasians, a higher number of asthma-related deaths (6 vs. 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with salmeterol than in patients treated with placebo. In Caucasians, the relative risk was 1.08 (17 vs. 16, 95% CI 0.55, 2.14) for combined asthma-related deaths or life-threatening experiences in patients treated with salmeterol relative to placebo. The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African American patients and difficulties in enrollment.

2.3 Presubmission Regulatory Activity

NDA 20-831 for the asthma indication for Foradil was submitted in June, 1997. An approvable action was issued in June, 1998. A complete response to the approvable action was received from the Applicant in August, 2000.

Two doses of Foradil were evaluated in pivotal studies; i.e., 12 mcg BID and 24 mcg BID, and the Applicant sought approval for both. The clinical review team, however, had concerns about the safety of the higher dose. Specifically, the rates of serious asthma exacerbations in the patients treated with the higher dose were higher than those in patients treated with the lower dose. At the same time, there was not consistent evidence across the studies that the higher dose held an efficacy advantage over the lower; and moreover, it was noted that protection from bronchoprovocation waned over time with prolonged use of the higher dose. Considering these factors together, when Foradil was approved for asthma in February, 2001, the higher dose was not approved.

The specific findings in the Phase 3 studies related to serious asthma exacerbations are reviewed in the next Section. Although the safety signal was clear, the number of affected patients was small. The Division believed further investigation was warranted, but was doubtful that routine post-marketing surveillance would be illuminating when the safety event of interest is also the underlying disease. A decision was made to require a commitment from the Applicant to further study the issue in Phase 4. The approval letter stated, “*You have committed to conduct a large, simple, placebo-controlled postmarketing study to further evaluate the safety and efficacy of regular, twice-daily administration of one or more dose levels of Foradil Aerolizer above that of the approved dose (12 mcg twice daily), in comparison to the safety and efficacy of the approved dose.*” Further details about the Phase 4 study were not negotiated before approval. That occurred later, as detailed in Section 6 REVIEW OF EFFICACY below.

Meanwhile, as noted above, at the same time the Foradil NDA was being reviewed, GSK was conducting the SMART Study. As described in the preceding section, SMART was stopped two years after the Foradil approval because of the incidence of severe asthma exacerbations

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SAE	Foradil 12 mcg BID	Foradil 24 mcg BID	Albuterol	Placebo
	Study 040 ^a N=541			
asthma				
Other	2/171 (1.2%)	1/171 (0.6%)	N.A.	1/176 (0.6%)

^aAdults and adolescents ≥12 yrs

^bChildren 5-12 yrs

Source: Drugs@FDA, NDA 20-831, Medical Officer's Review

Among the events represented in Table 3 are some of particularly notable severity:

- A 23 year-old male who received Foradil 24 mcg BID in 040 required intubation and mechanical ventilation for his asthma exacerbation
- A 66 year-old female who received Foradil 24 mcg BID in 041 had a cardiorespiratory arrest from her exacerbation and died 19 days after treatment
- A 49 year-old male who received Foradil 24 mcg BID in 041 had a respiratory arrest after 25 days of treatment

The reviewer of the Phase 3 studies also noted the rates of premature study discontinuation because of an AE. Those events are summarized in the next Table.

Table 4: Adverse Events Leading to Study Discontinuation: Foradil Phase 3 Studies

SAE Reason for Study Discontinuation	Foradil 12 mcg BID	Foradil 24 mcg BID	Albuterol	Placebo
	Study 040 ^a N=541			
Asthma	3/136 (2.2%)	6/135 (4.4%)	5/134 (3.7%)	3/136 (2.2%)
Respiratory, not asthma	0/136 (0)	0/135 (0)	0/134 (0)	3/136 (2.2%)
Other	4/136 (2.9%)	3/135 (2.2%)	5/134 (3.7%)	3/136 (2.2%)
Study 041 ^a N=554				
Asthma	4/139 (2.9%)	5/136 (3.7%)	0/138 (0)	6/141 (4.3%)
Respiratory, not asthma	0/139 (0)	1/136 (0.7%)	0/138 (0)	0/141 (0)
Other	3/139 (2.2%)	4/136 (3.0%)	4/138 (2.8%)	3/141 (2.1%)
Study 049 ^b N=518				
Asthma	1/171 (0.6%)	3/171 (1.8%)	N.A.	7/176 (4.0%)
Respiratory, not asthma	0/171 (0)	0/171 (0%)	N.A.	1/176 (0.6%)
Other	9/171 (5.3%)	2/171 (1.2%)	N.A.	4/176 (2.3%)

^aAdults and adolescents ≥12 yrs

^bChildren 5-12 yrs

Source: Drugs@FDA, NDA 20-831, Medical Officer's Review

These findings of concern regarding serious asthma exacerbations were discussed with the Applicant, who rebutted with two arguments. First, two other, non-pivotal clinical studies included in the NDA did not contain similar findings; and second, the differences in the rates of asthma exacerbation SAEs were due primarily to unusually low rates in the placebo groups, rather than high rates in the treated groups. The Applicant argued that patients in the placebo groups with more severe asthma (FEV₁ ≤75% predicted) discontinued the study early and were therefore not available to develop asthma exacerbations at the same rate as Foradil-treated patients. The FDA reviewers affirmed the first point, but rejected the second. The reviewers

noted that the Applicant's observation about placebo patients was only true when all studies were combined; the rates of premature discontinuations were not different among treatment groups in the three pivotal studies, individually considered.

Although the numbers of patients with serious asthma exacerbations were small, the consistency of the findings through all three studies strengthened the reviewers' concern that a true signal was being observed. At the same time, the reviewers were skeptical that post-marketing surveillance would be helpful in a case where the event of interest is also the underlying disease. The final decision was that the 24 mcg dose of Foradil would not be approved and a Phase 4 study would be used to "evaluate more definitively the occurrence of serious asthma exacerbations in patients treated with Foradil 24 mcg bid." [NDA 20-831, *Clinical Team Leader Review, DFS, February 14, 2001*]

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

This Section is not applicable for this Phase 4 clinical study report.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

The sole source of data for this review was the final study report, submitted electronically by the Sponsor, and the relevant previous submissions cited throughout the review. Auditing of the study was not indicated and was not undertaken.

5 CLINICAL PHARMACOLOGY

This Section is not applicable for this Phase 4 clinical study report.

6 REVIEW OF EFFICACY

As noted, the primary objective of the study was not efficacy, but was to further investigate certain safety outcomes noted in the Phase 3 studies. The Sponsor did include some efficacy assessments in the Phase 4 study, however, and those are briefly reviewed in this Section. The review of the efficacy findings is preceded by a description of the study protocol and the study implementation. The safety outcomes are reviewed in depth in Section 7 REview of Safetybelow.

6.1 Study Protocol: FOR258D 2307: “A Randomized, Multicenter, Placebo-controlled Parallel Group Study of Four Months Duration Per Patient To Evaluate the Safety and Efficacy of Treatment with 24 µg b.i.d. and 12 µg b.i.d. Formoterol, Double-blind, and 12 µg b.i.d. Formoterol with Additional On-demand Formoterol Doses, Open-label, in Adolescent and Adult Patients with Persistent Stable Asthma”

6.1.1 Study Administrative Information

Protocol Release Date: October 15, 2001
Protocol Amendment Dates: April 22, 2002; March 7, 2003; April 28, 2003
Study Dates: February 27, 2002 – March 19, 2004
Study Sites: 194 centers in the United States
Study Report Date: July 22, 2004
Source: 2307.pdf, August 12, 2004

6.1.2 Study Design

6.1.2.1 Overview

As noted in Section 2.3 Presubmission Regulatory Activity above, the determination that a Phase 4 study was needed was not made until late in the review cycle, so negotiating the design of the study occurred after approval. In May, 2001, Novartis submitted a proposed protocol for the study, which was designated “2307.” It was to be a large simple study in adolescents and adults that would essentially follow the design of the pivotal studies 040 and 041. However, there was a critical difference in that the protocol for 2307 proposed entry criteria which would result in a study population with milder asthma than in studies 040 and 041, rendering the frequencies of SAEs and asthma exacerbations among the studies incomparable. The Division believed that even though the Phase 4 commitment did not specify study design issues, the commitment implicitly meant to make the results comparable to those obtained in the pivotal Phase 3 studies (“...in comparison to the safety and efficacy of the approved dose.”) A revised, acceptable protocol was submitted in November, 2001, and the study began.

Study 2307 was a 16-week, multicenter, randomized, parallel group, double-blind, placebo-controlled study designed to demonstrate the safety and efficacy of regular BID use of formoterol 24 mcg compared to the approved dose of 12 mcg BID and to placebo in adults and adolescents ≥12 years with mild to moderate persistent asthma. An additional open-label treatment group received formoterol 12 mcg BID with up to two additional rescue doses per day of 12 mcg. The study had a run-in period and treatment period of 16 weeks comprising five total clinic visits. There was not a follow-up period.

Reviewer’s Comment: *The addition of the open-label treatment group with the extra rescue doses of formoterol is not explained by the Sponsor, nor does it receive any comments in Division documents except to note its presence. The purpose of that treatment group is not clear.*

Three amendments were made to the protocol after its start, which were intended, according to the study report, to accelerate enrollment and bring the protocol in line with modern standards of treatment which had changed since studies 040 and 041 were conducted. Those amendments are detailed in Section 6.1.2.8 Changes to the study protocol or plan below. This review reflects the amended protocol.

6.1.2.2 Study objectives

The study's primary objective was to evaluate the safety of regular twice-daily use of 24 mcg of formoterol in comparison with the approved twice-daily 12 mcg dose and placebo.

Secondary objectives were to further evaluate the efficacy of the higher dose compared with the lower dose and placebo; and to investigate the safety and efficacy of up to two "on-demand" doses of 12 mcg additional to maintenance twice-daily 12 mcg doses.

6.1.2.3 Study population

The study inclusion and exclusion criteria, as amended, were as follows.

6.1.2.3.1 Inclusion criteria

Male and female outpatients 12 years of age or older with a diagnosis of mild to moderate persistent asthma as defined by:

- Prescribed asthma treatment with an inhaled β_2 -selective adrenergic agent for two or more months before study participation (Amendment 1), and appropriately treated for their asthma; i.e., the GINA stepwise approach (Amendment 2)
- $FEV_1 \geq 40\%$ predicted after the following washout periods (Amendments 1 and 3):
 - short-acting β_2 -agonist for at least 6 hours
 - long-acting β_2 -agonist for at least 24 hours
 - short-acting anticholinergic for at least 8 hours
 - long-acting anticholinergic for at least 48 hours
- Predicted FEV_1 standards according to Crapo for patients 18 years and older, and according to Polgar for patients 12-17 years (Amendment 3)
- FEV_1 reversibility of $\geq 12\%$ over baseline after 360 mcg albuterol at screening or a documented history of same within past 12 months (Amendments 1 and 3)
- Normal chest x-ray or findings consistent with asthma within the 18 months before study participation (Amendment 3), or during the study run-in period

6.1.2.3.2 Exclusion criteria

Patients were excluded who had evidence or history of a large array of other systemic diseases; abnormal laboratory profile; or who were pregnant, nursing, or of child-bearing potential and not using reliable contraception. In addition, patients were excluded for the following asthma-specific conditions or events.

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- Hospitalization or emergency room treatment for an acute asthmatic attack in the month before Visit 1 or during the run-in period
- Recent treatment with:
 - parenteral, oral, or nebulized β_2 -agonists in the two weeks before Visit 1 or during the run-in period (Amendment 1)
 - parenteral or oral corticosteroids in the one month before Visit 1. Patients who required new therapy with these medications during the run-in period were not randomized
 - inhaled or nasal corticosteroids starting, discontinuing, or changing in the 3 weeks before Visit 2. Patients who required new therapy with these medications during the run-in period had to have received a stable dosage of the medications for at least 3 weeks during the period (Amendment 3)
 - fixed combination products of a LABA and inhaled corticosteroid (ICS) must be washed out for at least 24 hours before Visit 1. The combination product must be discontinued and monotherapy begun with the ICS (Amendments 1 and 3)
 - non-sustained-release theophylline in the 1 month before Visit 1 (Amendment 3)
 - sustained-release theophylline newly initiated or changed in the 1 month before Visit 1. Patients on theophylline should have had a blood level within the therapeutic range in the month before Visit 1 (Amendments 1 and 3)
 - nedocromil or ketotifen in the month before Visit 1.
 - leukotriene antagonists or inhaled disodium cromoglycate at stable doses for at least 3 weeks before Visit 1 are allowed, but the dose must not be changed during the study. Newly initiated therapy with these medications must have been at a stable dose for at least 3 weeks during the run-in period (Amendments 1 and 3)
 - Other treatments for asthma (desensitization, astemizole, anti-histamines labeled for QT prolongation) in the 3 months before Visit 1
 - Other treatments including non-potassium sparing diuretics, β -blockers, anti-arrhythmics, tricyclic anti-depressants, altered-dose SSRIs, live attenuated virus, other investigational drugs

6.1.2.4 Study procedures

6.1.2.4.1 Study treatments

Patients were randomized without stratification into four treatment groups. Three of the treatments were administered in a double-blind manner and the fourth in open-label, as follows.

- Double-blind treatments
 - Formoterol 24 mcg BID
 - Formoterol 12 mcg BID
 - Placebo
- Open-label treatment
 - Formoterol 12 mcg BID with up to two additional on-demand doses per day

Study medications were administered with the Aerolizer device between 6 and 9 a.m. and 6 and 9 p.m. every day. Dosing on a Visit day was done at the study site.

Rescue medication was also administered during the study. It was albuterol 90 mcg per actuation. Patients were instructed to take rescue medication for actual worsening of symptoms. Patients in the double-blind treatment groups were instructed to take up to eight puffs per day, while patients in the open-label formoterol group were instructed to take up to four puffs after taking the two extra formoterol doses.

6.1.2.4.1.1 Concomitant medications

In the original protocol, β_2 -agonists other than those required for the study were not allowed. Oral and parenteral corticosteroids, oral and inhaled anticholinergics, inhaled chromones, leukotriene antagonists, or 5-lipoxygenase inhibitors were not allowed except as needed for exacerbations and as prescribed by the patients' physicians. The protocol amendments, however, changed the use of concomitant medications to bring the treatments more in line with GINA standards. The changes made are reflected in the revised exclusion criteria listed in Section 6.1.2.3.2 Exclusion criteria above.

6.1.2.4.2 Study assessments

Consistent with a large simple study, 2307 had relatively few procedures or assessments. The main data collection focused on adverse events. The schedule of study Visits and assessments is shown in the next Table.

Table 5: Schedule of Study Visits and Assessments

	Run-in		Treatment				
	Visit	1	2	3	4	5	6
	Day	-14 to -3	1	29±7	57±7	85±7	113±3
Baseline evaluations	X						
Spirometry	X	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Vital signs, physical exam	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X
Medications taken	X	X	X	X	X	X	X
ER visits		X	X	X	X	X	X
Dispense study med		X	X	X	X		
Administer study med			X	X	X	X	X
Dispense rescue albuterol	X	X	X	X	X	X	X

^aFEV₁ pre-dose and 2 hours post-dose
 Source: 2307.pdf, August 12, 2004, p 28

6.1.2.4.3 Study discontinuation

Reasons stated in the protocol for study discontinuation were as follows. No further definition or qualification of the events is given, except that discontinuation could occur "whenever the patient or investigator felt that it was in the patient's best interest."

- adverse event(s)
- abnormal laboratory value(s)
- abnormal test procedure result(s)

- **unsatisfactory therapeutic effect**
- **patient's condition no longer requires study treatment**
- protocol violation
- patient withdrew consent
- lost to follow-up
- **administrative problems**
- death

Reviewer's Comment: *There is a bothersome degree of subjectivity to several of the listed reasons. Those highlighted in bold font are particularly so.*

6.1.2.5 Efficacy assessments

The sole measures of efficacy in this study were the FEV₁ at pre-dose at Visits 3-6 and at 2 hours post-dose at Visits 2-6. The spirometric measurements were to be done at approximately the same time each visit and performed by qualified personnel, preferably the same person. The largest FEV₁ out of three maneuvers was recorded.

6.1.2.6 Safety evaluations

Safety in this study is considered separately in Section 7 REview of Safetybelow.

6.1.2.7 Statistical plan

The study was designed to detect whether the proportion of patients having a serious asthma-related adverse event while receiving 24 mcg formoterol BID differed from the proportion of patients with events while receiving 12 mcg formoterol BID over the duration of the study.

Three populations were defined by the protocol for analysis purposes. The protocol indicated that the ITT population would be used for the primary efficacy analyses.

- *Randomized* population: all patients randomized to treatment
- *Intent-To-Treat (ITT)* population: all patients who received at least one dose of study medication
- *Safety population*: same as ITT population

Efficacy analyses were performed on the ITT population. For patients who discontinued prematurely, the End of Study visit was considered the next visit that would have occurred if not for discontinuation. The efficacy comparisons were the following. Adjustments were not made for multiple comparisons because efficacy was not the primary objective of the study.

- | | | |
|--|-----|-----------------------|
| ▪ formoterol 24 mcg BID | vs. | formoterol 12 mcg BID |
| ▪ formoterol 24 mcg BID | vs. | placebo |
| ▪ formoterol 12 mcg BID | vs. | placebo |
| ▪ formoterol 12 mcg BID + 2 additional doses | vs. | placebo |
| ▪ formoterol 12 mcg BID + 2 additional doses | vs. | formoterol 24 mcg BID |
| ▪ formoterol 12 mcg BID + 2 additional doses | vs. | formoterol 12 mcg BID |

Baseline FEV₁ was considered the value obtained at Visit 2. Centers that did not achieve a minimum number of patients were pooled. Each comparison was tested using a two-sided test at the 5% level.

No interim analyses were planned or conducted.

The sample size for the study was based on being able to detect a rate of serious asthma-related adverse events of 1.5% in the 12 mcg BID group vs. a 4.5% rate in the 24 mcg BID group. With a two-sided test at 5% level of significance, approximately 500 patients per group would be needed to detect this difference with 80% power.

Reviewer's Comment: *There is nothing in the study protocol or study report, or in the Division documents, to indicate how the difference to be detected was determined. It is more or less within the order of magnitude of the event rates in the Phase 3 studies, but justification for the sample size cannot be judged beyond that.*

6.1.2.8 Changes to the study protocol or plan

As previously noted, the protocol was amended three times. All three amendments were issued during the course of the studies, thereby altering the study during its actual conduct.

The first two amendments, issued April 22, 2002, and March 7, 2003, primarily modified the use of concomitant medications. The Sponsor and investigators felt that the approach to the use of anti-inflammatory medications in asthma had been substantially changed by the 2002 GINA guidelines in ways that outdated the study's original protocol. The first two amendments were intended to bring the study in line with the guidelines. The specific changes made by these amendments are reflected in the study eligibility criteria listed in Section 6.1.2.3 Study population above.

The third amendment was issued April 28, 2003, in response to feedback from the investigators regarding slow enrollment in the study. Indeed, previously in August, 2002, the Sponsor had requested the Division to extend its deadline for reporting the study because of slow enrollment. The Sponsor reported to the Division in a submission of February, 2003, that the reason for the slow enrollment was a high screening failure rate of 45%. The most common reasons for failure reported by the Sponsor were patients failing baseline FEV₁ criteria, FEV₁ reversibility criteria, long washouts required of other drugs, exclusion of antidepressants, patients refusing to discontinue Advair, and other concomitant medication exclusions. In response, Amendment #3 modified the applicable entry criteria in an effort to accelerate enrollment. Specific changes included removing the upper age limit for enrollment; reducing the reversibility criterion from 15 to 12% over baseline; changing the FEV₁ from 40-80% predicted to $\geq 40\%$; shortening certain medications' washout periods; shortening the stabilization periods on medications started during run-in, as well as extending the run-in period for stabilization if needed; and allowing patients who were stable on approved doses of SSRIs.

The clinical study report states that the second amendment was "issued after a review of blinded data indicated a proportion of patients had risk factors for serious/life threatening asthma

exacerbations but were not receiving anti-inflammatory therapy.” [2307.pdf, August 12, 2004, p 30]

Reviewer’s Comment: *Because no interim data analyses were planned for the study, the statement that a “review” had been done prompted a request to the Sponsor to clarify and explain the statement. The Sponsor replied that the review was done on February 20, 2003; i.e., about halfway through the study. The Sponsor stated that the review was prompted by results of the SMART study which showed SAEs occurring when patients were not being adequately treated with anti-inflammatory medications. Novartis stated that it performed a blinded enrollment surveillance to determine the status of its study patients. The survey found that 43% of the patients enrolled at that time with moderate to severe asthma were not receiving any anti-inflammatory medications. This information was shared with investigators by letter, with encouragement to review their patients’ treatment regimen.*

In addition to the protocol amendments, other changes to the study plan included discontinuation of some study centers. There were 23 such centers. Most were closed because they were enrolling too few patients and failed to maintain their commitment to the Sponsor. One center was closed, however, when the Sponsor became aware of a warning letter from the FDA. The site had been audited for a prior study and the response to the audit was unsatisfactory, prompting the warning letter. Another center was discontinued by the Sponsor when GCP violations were found. According to the study report, Novartis reported the violations to FDA. No other information about these events is given in the study report.

6.1.3 Efficacy Findings

6.1.3.1 Disposition of Patients

A total of 3820 patients were screened for the study at 194 centers. Of those, 2083 were randomized. Two other patients who were not randomized were treated. It is not clear from the study report how this occurred or how it was uncovered, but apparently it was impossible to determine what treatment the patients received, so they were included in the highest dose group (24 mcg formoterol BID) for analysis.

Table 6 summarizes the dispositions of the study patients. Overall, withdrawn consent was the most frequent reason for discontinuing the study, and this was true also in the placebo group. The group with most discontinuations because of adverse events was the formoterol 24 mcg group. The most common protocol violations were use of prohibited concurrent medications and participation in other clinical studies. Patients were not excluded from analysis because of protocol violations. Notably, the rate of premature discontinuation in this study was quite comparable to the rates in the two adult/adolescent Phase 3 studies: 15.3% and 12.6%, respectively.

Table 6: Disposition of Study Patients

	Formoterol 12 mcg BID N (%)	Formoterol 24 mcg BID N (%)	Placebo N (%)	Formoterol Open-Label N (%)	Total N (%)
Disposition Screened					3820

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	Formoterol 12 mcg BID N (%)	Formoterol 24 mcg BID N (%)	Placebo N (%)	Formoterol Open-Label N (%)	Total N (%)
Randomized	527 (100.0)	525 (99.6)	514 (100.0)	517 (100.0)	2083 (99.9)
Treated^a	527 (100.0)	527 (100.0)	514 (100.0)	517 (100.0)	2085 (100.0)
Completed	455 (86.3)	453 (86.0)	434 (84.4)	449 (86.6)	1791 (85.9)
Discontinuations	72 (13.7)	74 (14.0)	80 (15.6)	68 (13.2)	294 (14.1)
Reasons for Discontinuation					
Adverse event	22 (4.2)	39 (7.4)	21 (4.1)	21 (4.1)	103 (4.9)
Abn. lab value	0	1 (0.2)	0	0	1 (0.0)
Abn.test result	3 (0.6)	1 (0.2)	1 (0.2)	2 (0.4)	7 (0.3)
Unsatisfactory therapeutic effect	11 (2.1)	12 (2.3)	22 (4.3)	7 (1.4)	52 (2.5)
Protocol violation	15 (2.8)	11 (2.1)	7 (1.4)	10 (1.9)	43 (2.1)
Withdrawn consent	22 (4.2)	27 (5.1)	40 (7.8)	25 (4.8)	114 (5.5)
Lost to follow-up	10 (1.9)	5 (0.9)	12 (2.3)	16 (3.1)	43 (2.1)
Admin problem	5 (0.9)	5 (0.9)	2 (0.4)	5 (1.0)	17 (0.8)
Withdrawal by Time					
Day 1-28	29 (5.5)	36 (6.8)	25 (4.9)	23 (4.4)	113 (5.4)
Day 29-56	20 (3.8)	18 (3.4)	27 (5.3)	20 (3.9)	85 (4.1)
Day 57-84	12 (2.3)	8 (1.5)	12 (2.3)	11 (2.1)	43 (2.1)
> Day 84	10 (1.9)	12 (2.3)	16 (3.1)	13 (2.5)	51 (2.4)
Missing	1 (0.2)	0	0	1 (0.2)	2 (0.1)

^aNumber treated was used as denominator for percentages

Source: 2307.pdf, August 12, 2004, p 41

The same randomization number was assigned to two patients. Both patients were assumed to have received the treatment appropriate to the randomization number. After the original database lock (April 21, 2004), it was discovered that two patients had missing randomization numbers in the dataset and that values for the systolic and diastolic blood pressures and pulse were transposed. The database was unlocked, corrected, and relocked on April 30, 2004.

6.1.3.2 Baseline and Demographic Characteristics

Demographic characteristics and indicators of baseline disease severity of the ITT study population are shown in the next Table.

Table 7: Baseline Summary of Study ITT Population

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Age (yrs)				
Mean (SD)	39.2 (17.24)	38.5 (15.96)	37.8 (15.76)	36.9 (15.93)
Median	39.0	38.0	38.0	37.0
Range	12-82	12-78	12-81	12-76
Age Group – N (%)				
12-18	81 (15.4)	72 (13.7)	76 (14.8)	85 (16.4)
19-64	403 (76.5)	426 (80.8)	410 (79.8)	410 (79.3)
65-74	32 (6.1)	26 (4.9)	25 (4.9)	20 (3.9)
>74	11 (2.1)	3 (0.6)	3 (0.6)	2 (0.4)
Gender N(%)				
Male	251 (47.6)	234 (44.4)	211 (41.1)	240 (46.4)

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	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Female	276 (52.4)	293 (55.6)	303 (58.9)	277 (53.6)
Race N(%)				
Caucasian	430 (81.6)	411 (78.0)	402 (78.2)	401 (77.6)
Black	59 (11.2)	75 (14.2)	61 (11.9)	73 (14.1)
Asian	10 (1.9)	11 (2.1)	14 (2.7)	11 (2.1)
Other	28 (5.3)	37 (7.2)	37 (7.2)	32 (6.2)
Duration of Asthma (yr)				
Mean (SD)	21.1 (14.52)	21.1 (14.09)	20.1 (14.08)	19.8 (14.11)
Median	18.0	18.0	17.0	16.0
Range	0-80	0-72	0-71	0-66
Prior asthma medications N (%)				
Any	507 (96.2)	505 (95.8)	499 (97.1)	501 (96.9)
Anti-cholinergic	5 (0.9)	3 (0.6)	2 (0.4)	2 (0.4)
Antihistamine	202 (38.3)	218 (41.4)	200 (38.9)	203 (39.3)
β-agonist	458 (86.9)	447 (84.4)	439 (85.4)	443 (85.7)
Advair	69 (13.1)	72 (13.7)	64 (12.5)	72 (13.9)
Combivent	4 (0.8)	4 (0.8)	8 (1.6)	3 (0.6)
Corticosteroid	338 (64.1)	343 (65.1)	343 (66.7)	322 (62.3)
Cromoglycate/nedocromil	1 (0.2)	2 (0.4)	1 (0.2)	2 (0.4)
Leukotriene modifier	72 (13.7)	65 (12.3)	59 (11.5)	74 (14.3)
FEV₁ at Visit 1 Before albuterol (% predicted)				
Mean (SD)	68.2 (13.20)	68.5 (14.85)	69.0 (13.24)	69.5 (13.78)
Range	38.7-105.5	35.2-123.6	39.9-107.8	36.6-119.7
FEV₁ Reversibility (%) Visit 1				
N	517	513	501	505
Mean (SD)	23.2 (14.88)	23.1 (16.69)	22.6 (13.01)	21.4 (12.33)
Range	-8.1-121.8	-15.4-196.4	-7.4-119.2	-4.4-121.9
FEV₁ Reversibility (%) Qualifying				
N	526	526	512	517
Mean (SD)	24.2 (14.4)	24.1 (16.00)	23.3 (12.58)	22.4 (12.39)
Range	10.1-121.8	-15.4-196.4	7.2-119.2	2.8-121.9

Source: 2307.pdf, August 12, 2004, pp 45, 46, 283ff

In order for the Phase 4 study to provide meaningful information, it was important for it to be as similar as possible to the Phase 3 studies from which the original concern arose. The next Table displays some of the same baseline factors as shown in Table 7, but also includes the results from the pooled Phase 3 studies 040 and 041 for comparison. The two apparent differences are in the use of corticosteroids and in the degree of reversibility. The former probably represents different prescribing patterns over time with less use of corticosteroids in the older studies. The smaller average reversibility in the Phase 4 study probably represents the loosening of the reversibility entry criterion from 15% to 12%, which was made to accelerate enrollment.

Table 8: Baseline Factors in Phase 3 and Phase 4 Studies

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517	Phase 3 Studies N=1095
Age (yrs)					
Mean (SD)	39.2 (17.24)	38.5 (15.96)	37.8 (15.76)	36.9 (15.93)	34.3

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	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517	Phase 3 Studies N=1095
Median	39.0	38.0	38.0	37.0	
Range	12-82	12-78	12-81	12-76	
Age Group – N (%)					
12-18	81 (15.4)	72 (13.7)	76 (14.8)	85 (16.4)	159 (14.5)
19-64	403 (76.5)	426 (80.8)	410 (79.8)	410 (79.3)	896 (81.8)
65-74	32 (6.1)	26 (4.9)	25 (4.9)	20 (3.9)	40 (3.7)
>74	11 (2.1)	3 (0.6)	3 (0.6)	2 (0.4)	
Gender N(%)					
Male	251 (47.6)	234 (44.4)	211 (41.1)	240 (46.4)	497 (45.4)
Female	276 (52.4)	293 (55.6)	303 (58.9)	277 (53.6)	598 (54.6)
Race N(%)					
Caucasian	430 (81.6)	411 (78.0)	402 (78.2)	401 (77.6)	947 (86.5)
Black	59 (11.2)	75 (14.2)	61 (11.9)	73 (14.1)	73 (6.7)
Asian	10 (1.9)	11 (2.1)	14 (2.7)	11 (2.1)	0
Other	28 (5.3)	37 (7.2)	37 (7.2)	32 (6.2)	75 (6.8)
FEV₁ at Visit 1 Before albuterol (% predicted)					
Mean (SD)	68.2 (13.20)	68.5 (14.85)	69.0 (13.24)	69.5 (13.78)	64.3
Range	38.7-105.5	35.2-123.6	39.9-107.8	36.6-119.7	
FEV₁ Reversibility (% Qualifying					
N	526	526	512	517	1094
Mean (SD)	24.2 (14.4)	24.1 (16.00)	23.3 (12.58)	22.4 (12.39)	34.8 (18.33)
Range	10.1-121.8	-15.4-196.4	7.2-119.2	2.8-121.9	6-172
Corticosteroids Throughout Study N(%)					
			1205 (57.8)		518 (47.3)

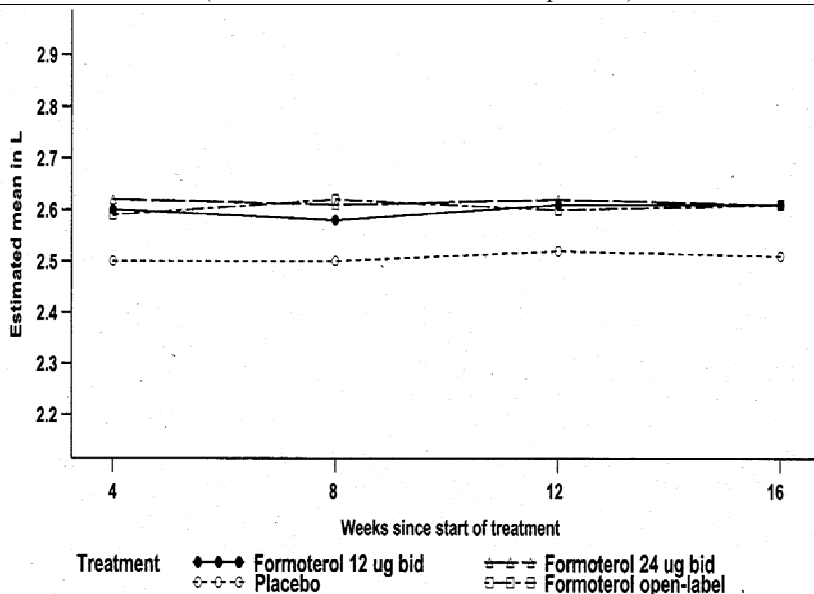
Source: 2307.pdf, August 12, 2004, p 48

6.1.3.3 Efficacy endpoint outcomes

Efficacy analyses were performed on the ITT data set. No imputation was used for missing data. Because efficacy was not the primary objective of this study, endpoints were not designated as either primary or secondary.

All three groups receiving formoterol were significantly superior to placebo in pre-dose FEV₁ at all time points in the study, but there were no significant differences between the three formoterol groups. The Figure below from the study report indicates that there was no waning effect of the formoterol treatments over the course of the study.

Figure 1: Average Pre-dose FEV₁ Throughout Study



The results for the FEV₁ 2-hours post-dose are summarized below in Table 9.

Table 9: Treatment Differences in FEV₁ at 2 Hours Post-dose

Treatment Comparison	Time Point	Difference		
		LS Means (SE)	95% CI	p-value
Formoterol 24 mcg BID vs placebo	First dose	0.32 (0.019)	0.29-0.36	<0.0001
	Week 16	0.29 (0.028)	0.24-0.35	<0.0001
Formoterol 12 mcg BID vs placebo	First dose	0.27 (0.019)	0.23-0.31	<0.0001
	Week 16	0.30 (0.028)	0.24-0.35	<0.0001
Formoterol open-label vs placebo	First dose	0.27 (0.019)	0.24-0.31	<0.0001
	Week 16	0.27 (0.028)	0.22-0.33	<0.0001
Formoterol open-label vs formoterol 24 mcg BID	First dose	-0.05 (0.019)	-0.09- -0.01	0.0090
	Week 16	-0.02 (0.028)	-0.07- 0.03	0.4551
Formoterol open-label vs formoterol 12 mcg BID	First dose	0.00 (0.019)	-0.04-0.04	0.9167
	Week 16	-0.03 (0.028)	-0.08-0.03	0.3555
Formoterol 24 mcg BID vs formoterol 12 mcg BID	First dose	0.05 (0.019)	0.01-0.09	0.0065
	Week 16	-0.00 (0.028)	-0.06-0.05	0.8597

Source: 2307.pdf, August 12, 2004, p 52

7 REVIEW OF SAFETY

7.1 Methods

Reviewer's Comment: *The specific events in the Phase 3 studies that prompted the Phase 4 commitment were serious asthma exacerbations; however, as described in this Section, the Sponsor did not present that specific group of events. In fact, asthma exacerbations per se were not presented at all, except for "significant" exacerbations, a categorization of the*

Sponsor's invention. Information of interest to the Division about asthma exacerbations was available in the study report, but had to be extracted for analysis for this review. Those results are included in the discussion of the safety results in Section 7.2 Findings below. This Section describes the Sponsor's approach.

The sponsor evaluated safety in this study using five categories of variables:

- Serious asthma-related adverse events
- Asthma-related adverse events/"significant" asthma exacerbations
- All adverse events
- Premature discontinuations
- Vital signs

The incidence of serious asthma-related adverse events was the primary outcome of interest. Asthma-related events were considered to be those that fit the following MedDRA preferred terms: *chest discomfort, asthma, cough, wheezing, dyspnea, dyspnea exacerbated, status asthmaticus respiratory distress, bronchospasm, acute respiratory failure, and hypoxia*. Originally, these events were to be compared between treatments using the Fisher's Exact Test, but when the completed study showed so few events, this plan was cancelled and the events were reported descriptively. No imputation of events was used for patients who discontinued early.

Asthma exacerbations were categorized as *significant* if they required oral or parenteral corticosteroid use.

The incidence of all adverse events was summarized by MedDRA system organ class, preferred term, severity, and relationship to study drug. If a patient reported the same AE more than once, the event was counted with its worst severity and closest relationship to study drug. AEs occurring during the run-in period were not tabulated.

In addition to the three pre-specified study populations identified in Section 6.1.2.7 Statistical plan above, a "Safety sub-population" is identified in the study report which was not mentioned in the protocol. It consisted of all treated patients excluding those who had a regular anti-inflammatory medication added after randomization. Further, six other sub-populations were defined based on the use of ICS and other anti-inflammatory medications:

- Sub-population 1: regular ICS throughout the study
- Sub-population 2: regular ICS added after baseline
- Sub-population 3: no regular ICS during the study
- Sub-population 4: regular anti-inflammatory medication throughout the study
- Sub-population 5: regular anti-inflammatory medication added after the study
- Sub-population 6: no regular anti-inflammatory medication during the study

7.2 Findings

7.2.1 Populations for Analyses

As noted in the previous section, the Sponsor divided the study population into various sub-groupings for safety analyses. Those sub-populations essentially depended on the anti-inflammatory concomitant medications the patients received. Table 10 below shows the compositions of the various sub-populations defined by the Sponsor. The medications that defined each population are also shown for ease of reference.

Reviewer's Comment: *Note that the smaller number of patients in sub-population 5 than in sub-population 2 appears to be inconsistent with the definitions of the populations, but it is explained by patients who received anti-inflammatory medications throughout the study who had ICS added after baseline. Hence, they are not counted in sub-population 5 but are in sub-population 2.*

Table 10: Populations for Analysis and Concomitant Anti-inflammatory Medications

	Formoterol 12 mcg BID	Formoterol 24 mcg BID	Placebo	Formoterol Open-label	Total
	N (%)				
Safety Population^a	527 (100.0)	527 (100.0)	514 (100.0)	517 (100.0)	2085 (100.0)
Safety sub-population^b	518 (98.3)	520 (98.7)	498 (96.9)	504 (97.5)	2040 (97.8)
Sub-population 1: ICS throughout study	299 (56.7)	318 (60.3)	301 (58.6)	287 (55.5)	1205 (57.8)
Sub-population 2: ICS added after baseline	10 (1.9)	9 (1.7)	17 (3.3)	14 (2.7)	50 (2.4)
Sub-population 3: No regular ICS	218 (41.4)	200 (38.0)	196 (38.1)	216 (41.8)	830 (39.8)
Sub-population 4: AIM throughout the study	322 (61.1)	338 (64.1)	324 (63.0)	318 (61.5)	1302 (62.4)
Sub-population 5: AIM added after baseline	9 (1.7)	7 (1.3)	16 (3.1)	13 (2.5)	45 (2.2)
Sub-population 6: No regular AIM	196 (37.2)	182 (34.5)	174 (33.9)	186 (36.0)	738 (35.4)

AIM=anti-inflammatory medications. Includes ICS

^aSame as ITT population

^bExcludes patients who had regular anti-inflammatory medications throughout the study

Source: 2307.pdf, August 12, 2004, p 44

Reviewer's Comment: *The study report does not specify when these additional populations were defined. The statistical and analytical plan does not mention them. In addition, their intent is not clear. In fact, they are rarely used in presenting results of the study. The study report implies that they were defined post-hoc because of the protocol amendments that liberalized the addition and continued use of ICS and anti-inflammatory medications during the study. Possibly the Sponsor anticipated that the frequency of exacerbations would be related to the use of concomitant medications, and because of the substantive changes made in the study allowing anti-inflammatory medications, the sub-populations were devised to address that. This had some legitimacy, but when the results of the study showed few exacerbations overall, as described below, the sub-populations possibly proved to be unnecessary.*

7.2.2 Baseline Safety Characteristics

Section 6.1.3.2 Baseline and Demographic Characteristics above identified some of the demographic and disease severity characteristics of the study population. The next Table summarizes some other historical characteristics of the patients' diseases at baseline that are more specifically relevant to the study's SAE endpoints.

Table 11: Baseline Characteristics of Asthma History in Study Population

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
No. of non-scheduled MD visits – N(%)				
None	429 (81.4)	402 (76.3)	412 (80.2)	410 (79.3)
1-2	77 (14.6)	94 (17.8)	80 (15.6)	80 (15.5)
3-4	13 (2.5)	21 (4.0)	19 (3.7)	17 (3.3)
>4	7 (1.3)	8 (1.5)	3 (0.6)	7 (1.4)
Missing	1 (0.2)	2 (0.4)	0	3 (0.6)
No. of oral steroid courses – N(%)				
None	438 (83.1)	432 (82.0)	432 (84.0)	430 (83.2)
1-2	79 (15.0)	76 (14.4)	77 (15.0)	77 (14.9)
>2	10 (1.9)	17 (3.2)	5 (1.0)	8 (1.5)
Missing	0	2 (0.4)	0	2 (0.4)
No. of emergency room visits – N(%)				
None	493 (93.5)	487 (92.4)	480 (93.4)	481 (93.0)
1-2	29 (5.5)	31 (5.0)	33 (6.4)	28 (5.4)
>2	5 (0.9)	7 (1.3)	1 (0.2)	6 (1.2)
Missing	0	2 (0.4)	0	2 (0.4)
No. of hospitalizations – N(%)				
None	517 (98.1)	518 (98.3)	508 (98.8)	506 (97.9)
1-2	10 (1.9)	7 (1.3)	6 (1.2)	7 (1.4)
>2	0	0	0	2 (0.4)
Missing	0	2 (0.4)	0	2 (0.4)
No. of ICU admissions – N(%)				
None	524 (99.4)	524 (99.4)	514 (100.0)	514 (99.4)
1-2	3 (0.6)	1 (0.2)	0	1 (0.2)
>2	0	0	0	0
Missing	0	2 (0.4)	0	2 (0.4)
No. of hospitalizations w/ mech. Ventilation – N(%)				
None	524 (99.4)	524 (99.4)	514 (100.0)	514 (99.4)
1-2	3 (0.6)	1 (0.2)	0	1 (0.2)
>2	0	0	0	0
Missing	0	2 (0.4)	0	2 (0.4)

Source: 2307.pdf, August 12, 2004, pp 220-221

7.2.3 Exposure

The duration of exposure in each treatment group and summary statistics of exposure are shown in Table 12 below.

Table 12: Drug Exposure During the Study

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Days of Exposure N(%)				
1-28	29 (5.5)	37 (7.0)	25 (4.9)	23 (4.4)
>28-56	20 (3.8)	18 (3.4)	27 (5.3)	20 (3.9)
>56-84	14 (2.7)	9 (1.7)	12 (2.3)	11 (2.1)
>84-112	121 (23.0)	143 (27.1)	133 (25.9)	134 (25.9)
>112	342 (64.9)	320 (60.7)	317 (61.7)	328 (63.4)
Missing	1 (0.2)	0	0	1 (0.2)
Statistics for Days of Exposure				
N	526	527	514	516
Mean (SD)	104.6 (27.60)	103.0 (30.14)	103.6 (28.19)	105.8 (25.81)
Median	113.0	113.0	113.0	113.0
Range	1-148	1-135	1-149	1-144

Source: 2307.pdf, August 12, 2004, p 49

Within the formoterol open-label group of 517 patients, the following numbers and proportions of patients required the use of extra on-demand rescue formoterol doses:

- At week 4: 289 patients (55.9%)
- At week 8: 235 (45.5%)
- At week 12: 226 (43.7%)
- At week 16: 209 (40.4%)

The average number of capsules inhaled during each 4-week period between visits ranged from 4 to 5 over the course of the study. [2307.pdf, August 12, 2004, p 384]

Patients also used albuterol for rescue during the study. Table 13 shows the numbers and proportions of patients at each visit who took albuterol since the previous visit. The figures for the formoterol open-label group represent albuterol use, not rescue formoterol doses.

Table 13: Use of Rescue Albuterol During the Study

	Formoterol 12 mcg BID	Formoterol 24 mcg BID	Placebo	Formoterol Open-label
Visit	N (%)			
Screening	8/527 (1.5)	7/527 (1.3)	10/514 (1.9)	4/517 (0.8)
First dose	0/527	0/527	0/514	0/517
Week 4	62/522 (11.9)	72/524 (13.7)	88/511 (17.2)	55/506 (10.9)
Week 8	55/488 (11.3)	60/476 (12.6)	68/473 (14.4)	47/480 (9.8)
Week 12	46/469 (9.8)	53/467 (11.3)	61/457 (13.3)	42/466 (9.0)
Week 16	46/457 (10.1)	55/458 (12.0)	68/438 (15.5)	44/453 (9.7)

Source: 2307.pdf, August 12, 2004, p 383

7.2.4 Deaths

There were no deaths during this study. One patient in the placebo group died of metastatic colon cancer approximately 3 months after the last dose of study medication. The patient had had ulcerative colitis for many years and had a bout of severe colitis toward the end of the study, which was possibly attributed to study drug. An abdominal CT scan and colonoscopy after completing the study diagnosed the colon cancer and metastases. [2307.pdf, August 12, 2004, p 81]

7.2.5 Other Serious Adverse Events

The Table below summarizes all the categories of AEs that were considered for this review. The population of analysis is the Safety/ITT Population. As previously noted, serious asthma exacerbations were not addressed by the Sponsor, but were the outcome that generated the Phase 4 commitment. The information about the serious asthma exacerbation category shown in Table 14 was generated by FDA reviewers, not by the Sponsor. Each category of the AEs will be detailed in the sections following. Serious and non-serious, and asthma-related and non-asthma-related AEs will be considered separately.

Table 14: Categories of Adverse Events

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
	N (%)			
Deaths	0	0	0	0
Total AEs	279 (52.9)	321 (60.9)	291 (56.6)	285 (55.1)
Total asthma-related AEs	74 (14.0)	72 (13.7)	81 (15.8)	53 (10.3)
Serious asthma-related AEs	5 (0.9)	2 (0.4)	1 (0.2)	1 (0.2)
Serious asthma exacerbations ^a	3 (0.6)	2 (0.4)	1 (0.2)	1 (0.2)
Asthma exacerbations	53 (10.1)	56 (10.6)	68 (13.2)	39 (7.5)
“Significant” asthma exacerbations ^b	31 (5.9)	33 (6.3)	45 (8.8)	23 (4.4)

^aPer FDA review

^bRequired use of oral or parenteral steroids

7.2.5.1 Serious asthma-related adverse events

AEs were determined to be asthma-related if the verbatim events fit the MedDRA preferred terms chest discomfort, asthma, cough, wheezing, dyspnea, dyspnea exacerbated, status asthmaticus, respiratory distress, bronchospasm, acute respiratory failure, or hypoxia.

As Table 14 showed, only nine patients (<1%) in the study had serious asthma-related AEs. All were serious by virtue of requiring hospitalization. The specific MedDRA terms associated with the events are displayed in Table 15 below, and Table 16 following gives summary information about each patient. Because the SMART study suggested there might be different risks in black and Caucasian patients, races of the patients are noted in the Tables. Two of the nine patients were black, seven were Caucasian.

Table 15: Serious Asthma-related Adverse Events by Preferred Term

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
	N (%)			
Patients with Events	5 (0.9)	2 (0.4)	1 (0.2)	1 (0.2)
Caucasian	4/430	2/411	1/402	0/401
Black	1/59	0/75	0/61	1/73
No. of Events	8	2	1	1
Respiratory distress	2 (0.4)	0	0	0
Status asthmaticus	2 (0.4)	0	0	0

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Asthma	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Bronchospasm	1 (0.2)	0	0	0
Cough	1 (0.2)	0	0	0
Dyspnea	1 (0.2)	0	0	0
Acute respiratory failure	0	1 (0.2)	0	0

Source: 2307.pdf, August 12, 2004, p 55

Table 16: Patients with Serious Asthma-related Adverse Events

Patient ID	Description of Event	Outcome/Attribution
Formoterol 12 mcg BID		
0525/00002	Status asthmaticus, cough, dyspnea, bronchospasm. 53 y/o black male in motor vehicle accident on study day 56 after syncopal episode. Study medication discontinued. Status asthmaticus on study day 61 was life-threatening, required mechanical ventilation and steroids. Recovered on day 64	Discharged from hospital. Continued on study. No subsequent AEs Not related to study medication (Note: this pt's status asthmaticus does not appear to be included in the events shown in Table 15 because the investigator believed that event was due to discontinuation of study medication following the auto accident)
0631/00018	Respiratory distress 78 y/o Caucasian female fell and fractured humerus on study day 12. On study day 41, she had an MI and respiratory distress.	Discontinued from the study. Note: the investigator attributed respiratory distress to the MI but the pt is included here because respiratory distress was a pre-defined criterion for asthma-related AE
0719/00001	Respiratory distress 37 y/o Caucasian female with PAR. Several non-serious, severe asthma exacerbations during study. On day 63, pt experienced bronchitis, pneumonia and respiratory distress requiring hospitalization.	Discontinued from the study. Respiratory distress attributed to pneumonia which was attributed to gastric reflux
0745/00004	Status asthmaticus 29 y/o Caucasian female developed status asthmaticus, narcolepsy and pneumonia requiring hospitalization on day 32	Discharged from hospital on day 36 and continued in study Not related to study medication
0767/00009	Status asthmaticus 28 y/o Caucasian female hospitalized on day 2 for asthma exacerbation. Recovered after 8 days	Study medication discontinued. New medications initiated Not related to study medication
Formoterol 24 mcg BID		
0539/00005	Acute respiratory failure 51 y/o Caucasian male experienced asthma exacerbation on day 3 requiring intubation and IV steroids. Respiratory failure resolved in day 6, asthma exacerbation resolved on day 8	Study medication discontinued. New medications initiated Not related to study medication
0589/00018	Asthma	Discontinued from study on day 92

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Patient ID	Description of Event	Outcome/Attribution
	54 y/o Caucasian female hospitalized for asthma exacerbation on day 92.	Not related to study medication
Placebo		
0535/00027	Asthma 72 y/o Caucasian male with allergies had exacerbation on day 74 preceded by 2 weeks of dyspnea. Hospitalized day 75, treated with IV steroids, antibiotics – discharged day 80. Also, previous non-serious exacerbation days 16-23.	Study medication discontinued. Second serious exacerbation w/ hospitalization day 87, after discontinuation. Suspected to be study drug related
Formoterol Open-Label		
0544/00010	Asthma 53 y/o black female hospitalized day 66 for asthma exacerbation w/ probably pneumonia, treated with IV fluids, antibiotics. Study medication interrupted days 66-67, resumed day 68. Discharged day 72	Full recovery, continued in study. No relationship to study drug suspected
Source: 2307.pdf, August 12, 2004, pp 82-87		

The SAEs in the study that were not considered asthma-related by the Sponsor are discussed in Section 7.2.5.2 Serious, non-asthma-related adverse events below. This reviewer agrees that none of them could be considered asthma-related, save possibly one. Patient 0766/00004 in the Formoterol 12 mcg group experienced a pneumonia SAE requiring hospitalization on day 72 of the study, but the patient narrative includes asthma among the admitting diagnoses and bronchodilators among the treatments. Without additional information, however, the investigator’s report that the serious event was pneumonia - not asthma - must be honored.

7.2.5.1.1 Serious asthma exacerbations

Serious asthma exacerbations are subsumed in the serious asthma-related AE category. Seven of the nine patients described in Table 16 had serious asthma exacerbations, and represent the only such events that occurred in this study. The two patients whose SAEs were not asthma exacerbations (0631/00018, 0719/00001) were both in the formoterol 12 mcg group. When they are removed from consideration, the incidence of serious asthma exacerbations is virtually the same among the four treatment groups.

Some patients had asthma exacerbations that did not rise to the regulatory criteria of “serious,” but led to their discontinuation from the study. Those events can reasonably be considered clinically meaningful. It was of interest for this review to determine how many patients either had a serious asthma exacerbation or had a non-serious exacerbation significant enough for the patient or investigator to lead to premature discontinuation from the study. The numbers of patients who had either event – asthma-related SAE or discontinuation because of asthma-related non-serious AE – are shown in the next Table. The patients who discontinued prematurely

because of non-serious AEs are considered in more detail in Section 7.2.6.1.1 Asthma-related adverse events associated with dropouts below.

Table 17: Patients with Serious Asthma Exacerbations or Premature Study Discontinuation Because of Non-serious Asthma Exacerbation

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Number of Patients	8	13	12	8

This study was performed to follow up on the findings of concern in the Phase 3 program. The next Table displays the results from all four studies. The most notable finding when all studies are examined is the much higher rate of serious exacerbations in the pediatric study. The second finding of interest is that the rates of events in the Foradil 24 mcg BID groups were similar in the two Phase 3 adult studies, but much lower in the Phase 4 study. It is possible this reflects the more common use of anti-inflammatory medications in the Phase 4 study.

Table 18: Serious Asthma Exacerbations in Foradil Studies

Study	Treatment				
	Foradil 12 mcg BID	Foradil 24 mcg BID	Albuterol	Formoterol Open-label	Placebo
	N (%)				
040 N=541	0/136 (0)	4/135 (3.0)	2/134 (1.5)	N.A.	0/136 (0)
041 N=554	1/139 (0.7)	5/136 (3.7)	0/138 (0)	N.A.	2/141 (1.4)
049^a N=518	8/171 (4.7)	11/171 (6.4)	N.A.	N.A.	0/176 (0)
2307 N=2085	3/527 (0.6)	2/527 (0.4)	N.A.	1/517 (0.2)	1/514 (0.2)

^aPediatric study

7.2.5.1.2 Use of inhaled corticosteroids

The FDA review of the SMART study included attention to whether concomitant use of inhaled corticosteroids (ICS) provided protection from the risks seen in that study. As noted, the population in this Foradil study was subdivided and analyzed according to their use of anti-inflammatory medications including ICS. The Sponsor analyzed the occurrence of all asthma-related AEs accordingly. The results are summarized in the next Table.

These results from this study must be interpreted cautiously because the approach to use of ICS changed during the course of the study, as explained in Section 6.1.2.8 Changes to the study protocol or plan above. Therefore, patients at the beginning of the study had different access to ICS than patients enrolled after the protocol was amended. With that caveat, the results shown in the Table below do not suggest a protective effect of ICS; indeed, the rates of AEs tended to be higher in the patients receiving regular ICS, perhaps reflecting worse underlying disease in patients for whom ICS were prescribed.

The Sponsor did not perform similar analyses for patients with asthma-related SAEs, presumably because there were so few such patients. Of the seven patients who had serious asthma

exacerbations, four had no regular ICS during the study, including the two patients whose exacerbations required intubation. Two patients were on regular ICS throughout the study, and one had ICS added after baseline.

Table 19: Occurrence Of Asthma-related Adverse Events According to Inhaled Corticosteroid Use

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
N (%) of patients with asthma-related AE – Total population	74 (14.0)	72 (13.7)	81 (15.8)	53 (10.3)
N (%) of patients with asthma-related AE at any time				
Sub-populations 1&2^a	49 (15.9)	46 (14.1)	54 (17.0)	32 (10.6)
Sub-population 3^b	25 (11.5)	26 (13.0)	27 (13.8)	21 (9.7)
N (%) of patients with asthma-related AE while on regular ICS				
Sub-populations 1&2	47 (15.2)	44 (13.5)	50 (15.7)	29 (9.6)
N (%) of patients with asthma-related AE while not on regular ICS				
Sub-populations 2&3	29 (12.7)	28 (13.4)	32 (15.0)	24 (10.4)

^aPatients who had regular ICS throughout study (sub-population 1) or added after baseline (sub-population 2)
^bPatients who had no regular ICS use during the study
 Source: 2307.pdf, August 12, 2004, pp 58-60

7.2.5.2 Serious, non-asthma-related adverse events

The Table below shows the numbers of patients with serious, non-asthma-related SAEs, and the specific events for each patient. Some patients had both asthma-related and non-asthma-related SAEs.

Table 20: Serious, Non-asthma-related Adverse Events

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
N (%) of Patients with Non-asthma SAE	9 (1.7)	4 (0.76)	4 (0.78)	7 (1.4)
Pt Number: SAE(s)				
	0525/00002: Motor vehicle accident, syncope, ventricular ectopy, EEG disturbance	0563/00030: elevated CK, non-specific acute chest pain	0509/00010: motor vehicle accident	0510/00032: cholelithiasis
	0543/00016: Right lower lobe pneumonia	0600/00011: fractured clavicle, fractured ribs, motorcycle accident	0550/00003: chest pain, numbness left arm	0544/00010: bacterial infection, syncope
	0607/00022: Prostate cancer	0648/00007: chronic pelvic pain	0632/00003: rheumatoid arthritis	0576/00039: cystocele
	0631/00018: Black out, fractured right humerus, inferior myocardial infarction	0670/00064: herniation of cervical disc	0755/00022: right internal carotid artery aneurysm	0629/00019: third degree burns
	0678/00008: Fall, fractured right femur			0647/00010: worsening congenital right ankle tarsal coalition
	0710/00008: Arrhythmia, chest pain			0678/00007: abdominal pain, nausea, vomiting
	0719/00001: worsening of stomach acid reflux			0685/00004: gallstones
	0745/00004: narcolepsy, right middle lung pneumonia			

Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
0766/00004: pneumonia			0722/00017: syncope
Source: 2307.pdf, August 12, 2004, p 528ff			

7.2.6 Dropouts and Other Significant Adverse Events

7.2.6.1 Asthma-related adverse events – Non-serious

The next Table shows the non-serious asthma-related AEs, and the preferred terms used by the Sponsor to define asthma-related. The data are those provided by the Sponsor. This reviewer inspected the patient data listings of adverse events. The Sponsor's categorization of verbatim terms into MedDRA terms was judged to be appropriate and suitable.

The figures in Table 21 represent patients. Some patients had multiple events, so the number of total events is displayed also. Comparisons were made between the treatments and between the treatments and placebo in total asthma-related AEs. The only significant difference, noted in the Table, was fewer events in the formoterol open-label group than in the placebo group. [2307.pdf, August 12, 2004, p 58]

Table 21: Asthma-related Adverse Events

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
	N (%)			
Total Patients with Asthma-related AEs	74 (14.0)	72 (13.7)	81 (15.8)	53 (10.3) ^a
Total Number of Events	83	82	84	61
Asthma	53 (10.1)	56 (10.6)	68 (13.2)	39 (7.5)
Cough	15 (2.8)	10 (1.9)	7 (1.4)	13 (2.5)
Wheezing	5 (0.9)	5 (0.9)	1 (0.2)	4 (0.8)
Dyspnea	4 (0.8)	5 (0.9)	3 (0.6)	4 (0.8)
Status asthmaticus	2 (0.4)	1 (0.2)	1 (0.2)	0
Respiratory distress	2 (0.4)	0	0	0
Chest discomfort	1 (0.2)	4 (0.8)	2 (0.4)	1 (0.2)
Bronchospasm	1 (0.2)	0	0	0
Acute respiratory failure	0	1 (0.2)	0	0
Dyspnea exacerbated	0	0	1 (0.2)	0
Hypoxia	0	0	1 (0.2)	0

^ap=0.0094 vs. placebo
 Source: 2307.pdf, August 12, 2004, p 57

7.2.6.1.1 *Asthma-related adverse events associated with dropouts*

The patients who discontinued the study because of an asthma-related AE are shown in the next Table. There were few such patients and although a relatively high rate in the placebo group is not unexpected, it is notable that an equal rate occurred in the high-dose formoterol group and more significantly, most of those dropouts were because of asthma.

Table 22: Study Discontinuation Because of Asthma-related Adverse Events

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Patients with asthma-related AE causing premature discontinuation N(%)	7 (1.3)	13 (2.5)	12 (2.3)	7 (1.4)
Total no. of events	7	14	12	8
AEs associated with premature discontinuation				
Asthma	5 (0.9)	12 (2.3)	10 (1.9)	6 (1.2)
Respiratory distress	2 (0.4)	0	0	0
Dyspnea	0	1 (0.2)	1 (0.2)	1 (0.2)
Cough	0	0	0	1 (0.2)
Dyspnea exacerbated	0	0	1 (0.2)	0
Wheezing	0	1 (0.2)	0	0

Source: 2307.pdf, August 12, 2004, p 67

7.2.6.2 *Asthma exacerbations – Non-serious*

Asthma exacerbations that were not serious are not specifically discussed or presented in the study report, but they can be inferred to some extent from the tabulation of asthma-related adverse events shown in Table 21. Inspection of the adverse event data listings shows that the reported term “asthma exacerbation” was coded under the preferred term “asthma”. Similarly, other reported terms like “asthma flare” or “worsening of asthma” were captured under the “asthma” preferred term. “Increased wheezing,” on the other hand, was coded under the preferred term “wheezing.” Some reported terms could represent an exacerbation of asthma (e.g., respiratory distress), but it cannot be determined without more information.

Of the AEs listed in Table 21, all except possibly “cough” could legitimately indicate an asthma exacerbation. Considering these uncertainties in the data set, for practical purposes the asthma-related events displayed in Table 21 can reasonably be considered synonymous with asthma exacerbations.

7.2.6.2.1 *Significant asthma exacerbations*

The Sponsor designated asthma exacerbations that required oral or parenteral steroids as “significant,” regardless of whether hospitalization was required. It does not appear that this categorization was discussed beforehand with the Division, nor does it represent a categorization commonly accepted in the medical community.

The rates of significant asthma exacerbations are shown in Table 14. All the patients who had serious asthma exacerbations were included among those in the significant asthma exacerbation category.

There were other patients in the study who used systemic corticosteroids (oral and/or parenteral) for allergy or other respiratory conditions, as well. They are shown in the next Table. Contrasting the results in Table 23 with those in Table 14 indicates that most systemic corticosteroid use in the study was for asthma exacerbations.

Table 23: Use of Systemic Corticosteroids

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Any systemic corticosteroids N(%)	39 (7.4)	41 (7.8)	49 (9.5)	35 (6.8)

Source: 2307.pdf, August 12, 2004, p 51

7.2.6.3 Adverse events associated with dropouts

The asthma-related AEs that led to study dropout were discussed in Sections 7.2.5.1.1 Serious asthma exacerbations and 7.2.6.1.1 Asthma-related adverse events associated with dropouts above. The next Table summarizes the numbers of patients who prematurely discontinued from the study because of non-asthma-related adverse events. For context, the numbers of asthma-related dropouts are shown again in Table 24 below. The Table also lists the SOCs of the events that led to discontinuations.

Patients in the two formoterol groups appear to have dropped out more commonly because of infectious events. The data listings show these events to be distributed evenly among various respiratory tract infections (bronchitis, sinusitis, pharyngitis). The higher rate of cardiac events reflects more reports of palpitations and tachycardia. The high rate of general disorders events in the high dose formoterol group represents reports of jitteriness. That is consistent with the expected high rate of events associated with β -agonist use that is also shown in the nervous system and psychiatric categories (e.g., nervousness, insomnia, anxiety).

Table 24: Study Dropout Because of Non-asthma-related Adverse Events

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
N (%) of patients discontinued because of AE	20 (3.8)	38 (7.2)	21 (4.1)	20 (3.9)
No. of events leading to discontinuation	38	54	21	30
N (%) of patients discontinued because of asthma-related AE	7 (1.3)	13 (2.5)	12 (2.3)	7 (1.4)
No. of asthma-related events leading to discontinuation	7	14	12	8
Primary system organ class – N (%) of patients				
Respiratory, thoracic, mediastinal	9 (1.7)	13 (2.5)	12 (2.3)	7 (1.4)
Infections and infestations	5 (0.9)	4 (0.8)	1 (0.2)	0
Cardiac	4 (0.8)	4 (0.8)	0	2 (0.4)
Nervous system	3 (0.6)	10 (1.9)	2 (0.4)	2 (0.4)
Gastrointestinal	2 (0.4)	1 (0.2)	0	5 (1.0)
General disorders	2 (0.4)	6 (1.1)	1 (0.2)	1 (0.2)
Injury, poisoning, procedural complications	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Psychiatric	2 (0.4)	6 (1.1)	2 (0.4)	1 (0.2)

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Metabolism	1 (0.2)	0	0	0
Renal and urinary	1 (0.2)	0	0	0
Investigations	0	2 (0.4)	1 (0.2)	1 (0.2)
Musculoskeletal	0	2 (0.4)	0	4 (0.8)
Skin and subcutaneous	0	1 (0.2)	0	1 (0.2)
Vascular	0	0	1 (0.2)	1 (0.2)

Source: 2307.pdf, August 12, 2004, p 66

The Applicant analyzed the time to premature withdrawal and found no differences between the treatment groups. The mean times for the groups were 104.2 days (formoterol 12 mcg BID); 108.3 days (formoterol 24 mcg BID); 101.6 days (placebo); and 131.2 days (formoterol open-label).

7.2.7 Other Adverse Events

More than half of all patients had at least one treatment-emergent AE. The next Table shows the summary data for AEs of any kind.

Table 25: Summary of Adverse Events

	Formoterol 12 mcg BID	Formoterol 24 mcg BID	Placebo	Formoterol Open-label
	N (%)			
Total patients	527 (100)	527 (100)	514 (100)	517 (100)
Total patients with AE	279 (52.9)	321 (60.9)	291 (56.6)	285 (55.1)
Total number of events	630	674	552	530

Source: 2307.pdf, August 12, 2004, p 61

Table 27 in the 9 Appendix lists the rates of AEs in each treatment group by MedDRA system organ class (SOC). By far, the SOC most commonly affected was infections and infestations, followed by the respiratory, thoracic and mediastinal disorders SOC. Each of the other SOCs had fewer than 10% of the AEs reported. The specific events that occurred in $\geq 2\%$ of patients in any group are shown by MedDRA preferred term in Table 26 below.

Reviewer's Comment: *It would be ideal to contrast the rates of events in this Phase 4 study with those in the overall Phase 3 experience. Most of the events in Table 26, however, do not appear in the NDA summary tables because they did not occur at rates above 2%. Of the few events in common (cough, upper respiratory infection, and insomnia), the rates were lower in both formoterol groups in this study than in the Phase 3 studies.*

Table 26: Adverse Events Occurring in At Least 2% of Patients

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Adverse Event (Preferred Term) – N (%) of Patients				
Asthma	53 (10.1)	56 (10.6)	68 (13.2)	39 (7.5)

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Upper respiratory tract infection	49 (9.3)	49 (9.3)	63 (12.3)	59 (11.4)
Sinusitis	32 (6.1)	25 (4.7)	22 (4.3)	24 (4.6)
Nasopharyngitis	28 (5.3)	32 (6.1)	25 (4.9)	39 (7.5)
Headache	23 (4.4)	18 (3.4)	23 (4.5)	20 (3.9)
Pharyngolaryngeal pain	17 (3.2)	15 (2.8)	11 (2.1)	10 (1.9)
Nasal congestion	17 (3.2)	9 (1.7)	5 (1.0)	13 (2.5)
Bronchitis	16 (3.0)	11 (2.1)	8 (1.6)	9 (1.7)
Cough	15 (2.8)	10 (1.9)	7 (1.4)	13 (2.5)
Tremor	5 (0.9)	25 (4.7)	3 (0.6)	6 (1.2)
Viral upper respiratory tract infection	5 (0.9)	12 (2.3)	6 (1.2)	3 (0.6)
Feeling jittery	2 (0.4)	16 (3.0)	2 (0.4)	3 (0.6)
Insomnia	2 (0.4)	14 (2.7)	4 (0.8)	3 (0.6)

Source: 2307.pdf, August 12, 2004, p 63

7.2.8 Laboratory Findings

Laboratory testing was performed at screening to determine the patients' suitability for the study, but was not among the study evaluations.

7.2.9 Vital Signs

Blood pressure and pulse were measured at each study visit. There was a statistically significant difference in diastolic blood pressure at week 4 between the formoterol 12 mcg BID and placebo groups; however, the difference was only 1 mm Hg and not clinically significant. Pulse rates in the formoterol 24 mcg group were significantly different from the other groups; however, the differences were small (1.2-1.6 bpm) and would be expected in the high dose group.

7.2.10 Electrocardiograms (ECGs)

ECGs were obtained at screening but not thereafter in this study.

7.2.11 Special Safety Studies

The Applicant examined the frequency of asthma-related emergency room (ER) visits as a Special Safety Topic. In all treatment groups, 97-98% of patients did not require ER visits, and about 2% in all groups required one visit. Only three patients, all in the placebo group, required more than one visit.

8 OVERALL ASSESSMENT

8.1 Conclusions

Generally speaking, the Phase 4 study conducted with Foradil Aerolizer and reviewed here did not contribute important new information to the understanding of possible adverse outcomes associated with use of long-acting beta-agonists. Specifically, the signal for *dose-related* serious asthma exacerbations observed in all three pivotal Phase 3 studies was not substantiated here. That may reflect a true, different finding, but it could also reflect a significant difference between the studies. In the time between the Phase 3 and Phase 4 studies, the standard of asthma care changed to increase the use of anti-inflammatory medications. That might have altered the clinical courses of the patients. In addition, unfortunately, the Phase 4 study did not prospectively define or specifically solicit serious asthma exacerbations. Whether that factor had a true impact on the study outcomes is difficult to assess, however, because the occurrence of those events could be determined from the study data in any case.

Although the higher dose of Foradil in this study did not appear to be associated with more serious asthma exacerbations than the lower dose, there were more patients in the higher dose group than in the lower dose group who had either a serious exacerbation or who dropped out of the study because of an asthma-related AE (13 vs. 8). This may indicate a differently defined but clinically similar phenomenon; i.e., patients whose exacerbations are clinically worse than those with the lower dose.

This study can neither substantiate nor refute the findings of the SMART study. Even assuming that formoterol and salmeterol would have similar effects, this study has too few patients to comparably evaluate the same kind of events that were of concern in the SMART study. The rate of asthma-related deaths or life-threatening experiences in SMART (37/13,176) would have predicted only 1-2 such patients in each treatment group in the Foradil study. In fact, there were no deaths in the Foradil study and two life-threatening experiences: one each in the formoterol 12 mcg BID and 24 mcg BID groups.

In conclusion, this Foradil Phase 4 study was too small to be definitive, but the results were generally compatible with the decision not to approve the higher 24 mcg BID dose.

9 APPENDIX

Table 27: Number of Patients with Adverse Events by System Organ Class

	Formoterol 12 mcg BID N=527	Formoterol 24 mcg BID N=527	Placebo N=514	Formoterol Open-label N=517
Primary system organ class – N (%) of Patients				
Infections and infestations	164 (31.1)	153 (29.0)	165 (32.1)	158 (30.6)
Respiratory, thoracic, mediastinal	119 (22.6)	113 (21.4)	109 (21.2)	79 (15.3)
Nervous system	36 (6.8)	52 (9.9)	36 (7.0)	36 (7.0)
Gastrointestinal	35 (6.6)	31 (5.9)	37 (7.2)	28 (5.4)
Injury, poisoning, procedural	23 (4.4)	20 (3.8)	26 (5.1)	21 (4.1)
Musculoskeletal	22 (4.2)	30 (5.7)	22 (4.3)	33 (6.4)
General disorders	18 (3.4)	41 (7.8)	22 (4.3)	16 (3.1)
Psychiatric	12 (2.3)	31 (5.9)	7 (1.4)	4 (0.8)
Skin	9 (1.7)	18 (3.4)	15 (2.9)	15 (2.9)
Cardiac	6 (1.1)	7 (1.3)	4 (0.8)	5 (1.0)
Eye	6 (1.1)	9 (1.7)	5 (1.0)	5 (1.0)
Investigations	6 (1.1)	10 (1.9)	4 (0.8)	7 (1.4)
Metabolism and nutrition	6 (1.1)	6 (1.1)	2 (0.4)	3 (0.6)
Reproductive and breast	6 (1.1)	5 (0.9)	2 (0.4)	4 (0.8)
Vascular	6 (1.1)	1 (0.2)	5 (1.0)	3 (0.6)
Renal and urinary	5 (0.9)	1 (0.2)	4 (0.8)	2 (0.4)
Ear and labyrinth	4 (0.8)	4 (0.8)	4 (0.8)	3 (0.6)
Immune system	4 (0.8)	6 (1.1)	5 (1.0)	4 (0.8)
Neoplasms	4 (0.8)	2 (0.4)	3 (0.6)	1 (0.2)
Surgical and medical procedures	4 (0.8)	3 (0.6)	0	3 (0.6)
Blood and lymphatic	3 (0.6)	1 (0.2)	0	4 (0.8)
Congenital, familial, and genetic	2 (0.4)	0	0	1 (0.2)
Hepatobiliary	0	0	0	3 (0.6)

Source: 2307.pdf, August 12, 2004, p 61

REFERENCES

¹ Castle W, Fuller R, Hall J, Palmer J, 1993, Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment, *BMJ*, 306:1034-1037.